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RESEARCH**

APPLICATION NUMBER:

219249Orig1s000

MULTI-DISCIPLINE REVIEW

NDA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Disclaimer: FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. FDA collaborated with Australia’s Therapeutic Goods Administration (TGA), Health Canada (HC), and Switzerland’s Swissmedic (SMC). While the conclusions and recommendations expressed herein reflect FDA’s completed review of the application, the applications may still be under review at the other regulatory agencies.

Application Type	NDA
Application Number(s)	219249
Priority or Standard	Priority
Submit Date(s)	March 27, 2024
Received Date(s)	March 27, 2024
PDUFA Goal Date	November 27, 2024
Division/Office	DO1/OOD
Review Completion Date	<i>Electronic Stamp Date</i>
Established Name	Inavolisib
(Proposed) Trade Name	Itovebi
Pharmacologic Class	Kinase inhibitor
Other name(s)	RO7113755, GDC-0077
Applicant	Genentech Inc.
Formulation(s)	3mg and 9mg tablets
Dosing Regimen	9mg once daily orally
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Inavolisib, in combination with palbociclib and fulvestrant, is indicated for the treatment of adults with endocrine-resistant, <i>PIK3CA</i> -mutated, hormone receptor (HR)-positive, human

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	epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.

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Reviewers of Multi-Disciplinary Review and Evaluation**Additional Reviewers of Application**

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	Risk Management Assessor Peer	(b) (6)
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	SMC Project Orbis coordinators	
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OPQ=Office of Pharmaceutical Quality
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DEPI= Division of Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis

Glossary

AAG	α -1-acid glycoprotein
AC	advisory committee
ADA	American Diabetes Association
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AEGT	adverse event group term
AESI	adverse events of special interest
AI	aromatase inhibitor
AKT	protein kinase B
ASCO	American Society of Clinical Oncology
AUC	area under the concentration-time curve
AUC ₀₋₂₄	area under the concentration-time curve from 0 to 24 hours
AUC _{0-t}	area under the concentration-time curve from Time 0 to Time t
BCRP	breast cancer resistance protein
BDC	bile-duct cannulated
BICR	blinded independent central review
BLA	biologics license application
BMI	body mass index
BOR	best overall objective response
BPCA	Best Pharmaceuticals for Children Act
BPI-SF	Brief Pain Inventory-Short Form
BRF	Benefit Risk Framework
BSV	between-subject variability
CAP	College of American Pathologists
CBER	Center for Biologics Evaluation and Research
CBR	clinical benefit rate
CDER	Center for Drug Evaluation and Research
CDK4/6	cyclin-dependent kinase 4/6
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CL	clearance
C _{max}	maximum concentration observed
CMC	chemistry, manufacturing, and controls
C _{min}	minimum plasma concentration observed
CNS	central nervous system

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COA	clinical outcome assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CT	computed tomography
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DDI	drug-drug interactions
DMC	data monitoring committee
DOR	duration of response
EC ₅₀	half-maximal effective concentration
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
ER	estrogen receptor
ET	endocrine therapy
ETASU	elements to assure safe use
FAS	full analysis set
FBG	fasting blood glucose
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	Good Clinical Practice
GHS/HRQoL	Global Health Status/Health-Related Quality of Life
GLP	good laboratory practice
GMR	geometric mean ratio
GRMP	good review management practice
HER2-	human epidermal growth factor receptor 2-negative
hERG	human ether-à-go-go-related gene
HR+	hormone receptor positive
HSA	human serum albumin
IC ₅₀	half-maximal inhibitory concentration
ICE	intercurrent event
ICF	informed consent form

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ICH	International Conference on Harmonization
iDCC	independent data coordinating center
iDMC	independent Data Monitoring Committee
ILD	interstitial lung disease
IND	Investigational New Drug
iPSP	Initial Pediatric Study Plan
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
LA/mBC	locally advanced/ metastatic breast cancer
LHRH	luteinizing hormone–releasing hormone
LPI	Last Patient In
LTL	less-than-lifetime
MAA	market authorization application
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MN	mobile nursing
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NGS	next-generation sequencing
NME	new molecular entity
NOAEL	no-observed-adverse-effect level
NPT	non-protocol anti-cancer therapy
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBPK	physiologically-based pharmacokinetic
PBRER	Periodic Benefit-Risk Evaluation Report
PCR	polymerase chain reaction
PD	pharmacodynamics
PF	physical functioning
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform

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	(gene name/acronym)
PO	oral
popPK	population pharmacokinetics
PP	per protocol
PPI	patient package insert
PR+	progesterone receptor positive
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PRO-CTCAE	Patient-Reported Outcomes Common Terminology Criteria for Adverse Events
PSUR	Periodic Safety Update report
PT	preferred term
QD	once a day
QTc	corrected QT
QW	once weekly
QWBA	Quantitative Whole Body Autoradiography
RED	rapid equilibrium dialysis
REMS	risk evaluation and mitigation strategy
RF	role functioning
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety set analysis
SC	subcutaneous
SCID	severe combined immunodeficient
SCP	summary of clinical pharmacology
SD	stable disease
SERD	selective estrogen-receptor degrader
SGE	special government employee
SMQ	standardised MedDRA query
SOC	system organ class
SRE	skeletal related event
$t_{1/2}$	half-life
TEAE	treatment emergent adverse event
TFST	time to first subsequent therapy
TGI	tumor growth inhibition
TK	toxicokinetic
T_{max}	time to maximum observed concentration
TTCD	time to confirmed deterioration
V_c	central volume of distribution
VHP	voluntary harmonization procedure
WT	wild type

1 Executive Summary

1.1. Product Introduction

Inavolisib (Itovebi) is a small molecule kinase inhibitor of the phosphatidylinositol 3-kinase (PI3K) with inhibitory activity predominantly against PI3K α . Inavolisib is a new molecular entity. It does not have an approval for any indication worldwide. Itovebi film-coated tablets are supplied for oral administration with two strengths that contain 3 mg and 9 mg of inavolisib.

The Applicant proposed the following indication for NDA 219249:

(b) (4)

The recommended indication for regular approval is:

Inavolisib, in combination with palbociclib and fulvestrant, is indicated for the treatment of adults with endocrine-resistant, PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.

The recommended dose for inavolisib is 9 mg taken orally once daily in combination with palbociclib and fulvestrant until disease progression or unacceptable toxicity. The recommended dosage of palbociclib is 125 mg taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a cycle of 28 days. The recommended dosage of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, and 29, and once monthly thereafter.

For premenopausal and perimenopausal women, a luteinizing hormone releasing hormone (LHRH) agonist should be administered in accordance with local clinical practice.

For men, administration of an LHRH agonist should be considered in accordance with local clinical practice.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends granting regular approval for inavolisib, in combination with palbociclib and fulvestrant, for the treatment of adults with endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy in accordance with 21 Code of Federal Regulations (CFR) 314.126(a)(b).

The basis for recommendation for regular approval of inavolisib is the efficacy and safety results obtained from INAVO120, an ongoing, randomized, placebo-controlled, double-blind, multicenter trial in 325 patients with endocrine resistant, PIK3CA-mutated, HR-positive, HER2-negative (defined as IHC 0 or 1+, or IHC 2+/ISH-), advanced or metastatic breast cancer, following recurrence on or within 12 months of adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. Patients were randomized 1:1 to receive either inavolisib 9 mg or placebo orally once daily, in combination with palbociclib 125 mg orally once daily for 21 consecutive days followed by 7 days off treatment, and fulvestrant 500 mg administered intramuscularly on Cycle 1, Days 1 and 15, and then on Day 1 of every 28-day cycle. The primary efficacy endpoint was PFS as assessed by investigator. Key secondary endpoints included OS and ORR. DOR was a secondary endpoint.

Presence of a PIK3CA mutation was determined through testing of blood plasma-derived ctDNA with a next-generation sequencing (NGS) assay performed at a designated central laboratory, or through local testing of ctDNA or tumor tissue with an appropriately validated NGS or PCR assay. Randomization was stratified by presence of visceral disease (yes or no), endocrine resistance (primary or secondary), and geographic region (North America/Western Europe, Asia, other). Primary endocrine resistance in the trial was defined as relapse while on the first 2 years of adjuvant endocrine therapy (ET) and secondary endocrine resistance was defined as relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.

INAVO120 demonstrated a statistically significant and clinically meaningful improvement in the primary endpoint of PFS based on investigator assessment. The median PFS was 15 months (95% CI 11.3, 20.5) vs. 7.3 months (95% CI: 5.6, 9.3) favoring inavolisib + palbociclib + fulvestrant (HR 0.43, 95% CI: 0.32, 0.59; p-value <0.0001). PFS by blinded independent central review (BICR) was prospectively planned and was supportive of the primary endpoint. At the planned interim analysis for OS, a total of 97 events had occurred (63% of planned OS events) and did not reach statistical significance based on the interim analysis stopping boundary. Interim OS results showed a HR of 0.64 (95% CI: 0.43, 0.97) with median OS not estimable (95% CI: 27.3, NE) on the inavolisib + palbociclib + fulvestrant arm and 31.1 months (95% CI: 22.3, NE) on the placebo + palbociclib + fulvestrant arm. Thus, there appears to be no detriment in OS at this time. The final analysis of OS is expected in the second quarter of 2025 and a postmarketing commitment (PMC) has been issued for the final OS.

Results from secondary endpoints of ORR, and DOR appeared to be supportive of the primary endpoint results. However, since the interim analysis of OS at the time of PFS analysis was not statistically significant, none of the remaining secondary endpoints in the pre-specified testing hierarchy were formally tested at this time. The ORR was 58% (95% CI: 50-66%) for the inavolisib + palbociclib + fulvestrant arm vs. 25% (95% CI: 19-32%) for the placebo + palbociclib + fulvestrant arm and median DOR was 18.4 months (95% CI: 10.4-22.2) vs. 9.6 months (7.4, 16.6), respectively.

Data from a phase 1 trial, GO39374, was submitted by the Applicant

(b) (4)

GO39374 is an ongoing, open-label, multicenter, trial designed to evaluate the safety, tolerability, and PK of inavolisib administered orally as a single agent in patients with locally advanced or metastatic PIK3CA-mutated solid tumors, including breast cancer, and in combination with standard-of-care endocrine and/or targeted therapies in patients with PIK3CA-mutated locally advanced and metastatic breast cancer. The Applicant submitted data from 3 cohorts. Arm B (N=33; inavolisib in combination with palbociclib and letrozole), Arm E (N=20; inavolisib in combination with palbociclib and fulvestrant), and Arm F (N=21; inavolisib in combination with palbociclib, fulvestrant, and metformin). Arms B, E and F did not require that patients have endocrine resistant breast cancer. The confirmed ORR results in patients with measurable disease in Arm B (N=25), Arm E (N=15), and Arm F (N=18) were 52% (95% CI: 31%, 72%), 40% (95% CI: 16%, 68%), and 17% (95% CI: 0%, 41%), respectively. While activity was observed across the three treatment arms based on the confirmed ORR and DOR, given the small sample sizes and wide CI of ORR, the contribution of inavolisib to efficacy was unclear in these single arm cohorts.

(b) (4)

Patients treated with inavolisib + palbociclib + fulvestrant experienced more toxicities than those treated with palbociclib + fulvestrant. The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were decreased neutrophils, decreased hemoglobin, increased fasting glucose, decreased platelets, decreased lymphocytes, stomatitis, diarrhea, decreased calcium, fatigue, decreased potassium, increased creatinine, increased ALT, nausea, decreased sodium, decreased magnesium, rash, decreased appetite, COVID-19 infection, and headache. A higher proportion of patients experienced serious adverse events (SAEs) in the inavolisib arm (24.1% vs. 10.5%), Grade ≥ 3 adverse events (86% vs. 82%), and dose discontinuation (6% vs. 1%). Fatal adverse reactions occurred in 3.7% of patients receiving inavolisib. Hyperglycemia, stomatitis, and diarrhea are included as Warnings and Precautions, as these were considered severe, and occurred in a significant proportion of patients as noted in labeling.

In addition, the Applicant further explored safety and tolerability through assessment of patient-generated data. A list of expected symptomatic adverse events from the combination of inavolisib, palbociclib, and fulvestrant (diarrhea, nausea, vomiting, fatigue, mouth sores, decreased appetite, and rash), was selected from the patient reported outcome (PRO)-CTCAE item library, along with an additional single item assessing bother due to side-effects of treatment. These PRO data were assessed appropriately with acceptable data quality. Analysis of patient-reported symptoms that worsened from baseline were generally observed to be worse in the inavolisib arm, with the greatest difference observed for diarrhea, mouth sores, decreased appetite, and rash. The patient-reported data provide additional insight into the safety and tolerability of the approved regimen and were included in section 6 of the USPI to further inform patients and providers.

Overall, results from INAVO120 showed a statistically significant and clinically meaningful improvement for the primary endpoint of PFS when inavolisib was added to palbociclib and fulvestrant for the population enrolled. Results for secondary endpoints of ORR and OS were supportive of the primary endpoint. The addition of inavolisib to palbociclib and fulvestrant resulted in increased toxicity that was appropriately characterized by both clinician- and patient-reported assessment. Overall, the safety profile was acceptable for a patient population with a serious and life-threatening condition and is manageable with appropriate monitoring, dose modifications, and/or supportive care as described in the labeling.

Therefore, the review team recommends granting regular approval to inavolisib + palbociclib + fulvestrant for endocrine-resistant, PIK3CA-mutated, HR-positive, HER2-negative, locally advanced or metastatic breast cancer. This represents a new therapeutic option in combination with palbociclib + fulvestrant for an endocrine resistant population. The indication for approval is:

Inavolisib (ITOVEBI), in combination with palbociclib and fulvestrant, is indicated for the treatment of adults with endocrine-resistant, PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.

A supplemental Pre-Market Approval (PMA) Application (sPMA P190032-S023) was submitted to CDRH for the FoundationOne Liquid CDx (F1LCDx) The sPMA will receive contemporaneous approval with this NDA as a companion diagnostic device for inavolisib. A PMC has been issued for tissue testing, as the PMA is planned to be submitted at the end of 2024.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Breast cancer is the second most common cancer in women worldwide after skin cancer. In the U.S., 310,720 new cases of breast cancer and 42,780 deaths from breast cancer are estimated for 2024. Histopathological subtypes of breast cancer are defined by expression of the estrogen receptor (ER), progesterone receptor (PR), and/or human epidermal growth factor receptor 2 (HER2). Approximately 70% of patients with breast cancer will have hormone receptor (HR)-positive, HER2-negative disease. Although associated with a better prognosis than the other breast cancer subtypes, if HR-positive, HER2-negative breast cancer is advanced or metastatic, it is incurable and associated with a limited life expectancy.

Endocrine therapy is the mainstay for HR-positive breast cancer. However, resistance may occur to endocrine therapy and a major challenge to treating HR-positive breast cancer is overcoming endocrine resistance. Activation of the PI3K/AKT pathway may lead to endocrine resistance. Endocrine resistant breast cancer is not uniformly defined but generally refers to cancer that grows in the presence of endocrine therapy (ET) or soon after completing ET. Endocrine resistant breast cancer is considered to be a negative prognostic factor as these patients tend to have worse survival outcomes compared to patients with endocrine sensitive breast cancer.

While there are no specific therapies approved by FDA for treatment of patients with ET resistant HR-positive advanced or metastatic breast cancer, generally the treatment options after first line therapy can be considered for this population.

The preferred first-line treatment for patients with HR-positive, HER2-negative advanced or metastatic breast cancer in the U.S. is a CDK4/6 inhibitor in combination with endocrine therapy (an aromatase inhibitor [AI] or fulvestrant). At disease progression, FDA-approved options for second and later-line treatment include endocrine monotherapy with fulvestrant, an AI, or tamoxifen (if not received as first-line treatment); everolimus in combination with exemestane; alpelisib in combination with fulvestrant in patients with a PIK3CA mutated tumor; capivasertib in combination with fulvestrant for patients with tumors that have a PIK3CA/AKT1/PTEN alteration, and chemotherapy such as capecitabine. Sequential endocrine based therapy is preferred because it is typically associated with less toxicity than chemotherapy. Endocrine monotherapy is also associated with less toxicity than combinations with targeted agents. In addition to these therapies, the antibody-drug-conjugate, fam-trastuzumab deruxtecan, is now available for patients with unresectable or metastatic HER2-low (IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant therapy. At the time of design of INAVO120 (2019), palbociclib plus fulvestrant appeared to be an acceptable control arm

for patients with HR-positive, HER2-negative metastatic breast cancer (with or without a PIK3CA mutation). This combination is still an option for first-line treatment; however, based on results from the MONALEESA-2 and MONARCH 3 trials which showed overall survival improvement, ribociclib and abemaciclib are now used more commonly than palbociclib in the first line setting in the US.

Approximately 35-40% of patients with HR-positive breast cancer have tumors that harbor mutations in PIK3CA, the gene encoding the catalytic subunit of the alpha isoform of PI3K. PIK3CA mutations result in upregulation of PI3K pathway and are considered a negative prognostic factor. Alpelisib (PI3K α inhibitor) plus fulvestrant and capivasertib (AKT inhibitor) plus fulvestrant are two treatment regimens approved by the FDA for use in patients with PIK3CA-mutated advanced breast cancer. However, both are for second line and later treatment and are not specifically for patients with endocrine resistant breast cancer.

The efficacy and safety assessment for inavolisib in combination with palbociclib and fulvestrant is primarily based on data from INAVO120, a randomized (1:1), placebo-controlled, double-blind, multicenter trial in 325 patients with PIK3CA mutated, HR-positive, HER2-negative (defined as IHC 0 or 1+, or IHC 2+/ISH-), advanced or metastatic breast cancer, following recurrence on or within 12 months of adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. PIK3CA mutation was determined through testing of blood plasma-derived ctDNA with a next-generation sequencing (NGS) assay performed at the Sponsor-designated central laboratory, or through local testing of ctDNA or tumor tissue with an appropriately validated NGS or PCR assay. Randomization was stratified by presence of visceral disease (yes or no), endocrine resistance (primary or secondary), and geographic region (North America/Western Europe, Asia, other). Primary endocrine resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy and secondary endocrine resistance was defined as relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. Patients were required to have a HbA1c<6% and fasting blood glucose<126 mg/dL. The study excluded patients with Type 1 diabetes mellitus or Type 2 diabetes mellitus requiring ongoing systemic therapy at the start of study treatment.

Patients received either inavolisib 9 mg (n=161) or placebo (n=164) orally once daily, in combination with palbociclib 125 mg orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a cycle of 28 days and fulvestrant (500 mg) administered intramuscularly on Cycle 1, Days 1 and 15, and then on Day 1 of every 28-day cycle. Patients received treatment until disease progression or unacceptable toxicity. The primary efficacy endpoint for INAVO120 was PFS as assessed by investigator. A prospectively planned sensitivity analysis of PFS by BICR assessment was also performed on all patients. Key secondary endpoints included OS and ORR. DOR was a secondary endpoint.

INAVO120 met its primary endpoint with a median PFS of 15 months (95% CI 11.3, 20.5) vs 7.3 months (95% CI: 5.6, 9.3) favoring inavolisib arm

(HR 0.43, 95% CI: 0.32, 0.59; p-value <0.0001). PFS by BICR results were supportive of the primary endpoint. At the planned interim analysis for OS, a total of 97 events had occurred (63% of planned OS events) and did not reach statistical significance based on the interim analysis stopping boundary [HR of 0.64 (95% CI: 0.43, 0.97)]. The final analysis of OS is expected in the second quarter of 2025. Results for the secondary endpoints of ORR and DOR appear to support the primary endpoint results. However, since the interim analysis of OS at the time of PFS analysis was not statistically significant, none of the remaining secondary endpoints in the pre-specified testing hierarchy were formally tested at this time.

Racial and ethnic minorities reflective of the U.S. population of patients with breast cancer were significantly underrepresented in INAVO120. INAVO120 was a multinational trial with just 16 patients (4.9%) enrolled from the US. Almost all patients were female (98%) and the median age of enrolled patients was 54 years. The majority of patients on study were White, with only two Black patients and 20 Hispanic/Latino patients enrolled on study. Due to the lack of diversity in the enrolled population, a Post Marketing Commitment (PMC) is being issued to further characterize the efficacy and safety of inavolisib for the treatment of breast cancer in study populations whose demographics are more representative of the population of U.S. patients for the proposed indication.

Data from a phase 1 trial GO39374 was submitted by the Applicant

(b) (4)

GO39374 is an ongoing, open-label, multicenter, trial designed to evaluate the safety, tolerability, and PK of inavolisib administered orally as a single agent in patients with locally advanced or metastatic PIK3CA-mutated solid tumors, including breast cancer, and in combination with standard-of-care endocrine and/or targeted therapies in patients with PIK3CA-mutated locally advanced and metastatic breast cancer. The applicant submitted data from 3 cohorts. Arm B (N=33; inavolisib in combination with palbociclib and letrozole), Arm E (N=20; inavolisib in combination with palbociclib and fulvestrant), and Arm F (N=21; inavolisib in combination with palbociclib, fulvestrant, and metformin). Arms B, E and F did not require that patients have endocrine resistant breast cancer. The confirmed ORR results in patients with measurable disease in Arm B (N=25), Arm E (N=15), and Arm F (N=18) were 52% (95% CI: 31%, 72%), 40% (95% CI: 16%, 68%), and 17% (95% CI: 0%, 41%), respectively. While activity was observed across the three treatment arms based on the confirmed ORR and DOR, given the small sample sizes and wide CI of ORR, the contribution of inavolisib to efficacy was unclear in these single arm cohorts.

(b) (4)

The overall safety profile for the triplet combination was consistent with the anticipated safety profile for inavolisib and the known safety

profile for palbociclib and fulvestrant. Adverse events known to occur with PI3K inhibitors include hyperglycemia, stomatitis, diarrhea, and rash. Hyperglycemia occurred at much higher rates on the inavolisib treatment arm (85%) compared to the placebo arm (43%). There were no grade 4-5 cases of hyperglycemia or cases of DKA and HHNK. However, patients that enrolled on the trial were required to fasting blood glucose (FBG) <126 and HBA1c<6%. Stomatitis occurred at higher rates in the inavolisib treatment arm (51%) compared to the placebo arm (27%), including 6% of patients on the inavolisib arm having grade 3 events. There were no grade 4-5 events or SAEs. Diarrhea occurred at higher rates in the inavolisib treatment arm (48%) compared to the placebo arm (16%), including 4% of patients on the inavolisib arm having grade 3 events. There were two SAEs and no grade 4-5 events or colitis. Rash occurred in 27% of patients treated with inavolisib compared to 19% of patients on the placebo arm. There were no grade 3-5 events or SAEs. Ocular toxicity occurred in 22% of patients treated with inavolisib compared to 13% on the placebo arm. The most common toxicity was dry eye (9%). There were no grade 3-5 events, no SAEs and ocular toxicity did not lead to dose modifications (discontinuation, reduction, or interruption).

Hematologic toxicities were seen in both treatment arms and are known toxicities with palbociclib. Neutropenia and anemia were seen in a similar proportion of patients regarding all grade toxicity; however, grade 3-4 toxicity was slightly higher in the inavolisib treatment arm. Thrombocytopenia (including platelet count decreased) was higher in the inavolisib treatment arm compared to the placebo treatment arm. Other adverse events (including laboratory abnormalities) noted in >20% of patients treated with inavolisib + palbociclib + fulvestrant include decreased calcium, fatigue, decreased potassium, increased creatinine, increased ALT, nausea, decreased sodium, decreased magnesium, decreased albumin, decreased appetite, Covid-19, and headache.

In addition, the Applicant evaluated expected symptomatic adverse events using patient-reported outcomes. Symptomatic adverse events related to likely toxicity from the combination of inavolisib, palbociclib, and fulvestrant (diarrhea, nausea, vomiting, fatigue, mouth sores, decreased appetite, and rash), were selected and assessed from the patient reported outcome (PRO)-CTCAE item library, along with an additional single item assessing bother due to side-effects of treatment. In general, these patient-reported symptoms were observed to be worse in the inavolisib arm, with the greatest difference observed for diarrhea, mouth sores, decreased appetite, and rash. Although the PRO data collection was considered exploratory, these symptoms were considered supportive of the clinician reported safety information and informative for labeling and were included in Section 6 of the USPI.

The addition of inavolisib to standard of care treatment with palbociclib and fulvestrant resulted in a statistically significant and clinically meaningful improvement in PFS for the patient population enrolled on INAVO120. Results for secondary endpoints were supportive of the primary endpoint. The addition of inavolisib to palbociclib and fulvestrant resulted in increased toxicity. However, the median relative dose

intensity of palbociclib and fulvestrant was similar between the two treatment arms of the INAVO120; therefore, the triplet combination therapy including inavolisib did not have a significant impact on the ability to administer full dose palbociclib + fulvestrant. The most notable increase in adverse events were observed in hyperglycemia, stomatitis, and diarrhea, including severe cases. Therefore, hyperglycemia, stomatitis and diarrhea will be labeled under warnings and precautions in the USPI to better inform providing physicians and to provide guidance for dose modifications. These adverse events could be managed with dose interruptions and dose reductions in most cases.

Overall, the benefit-risk assessment is favorable for the triplet combination treatment with inavolisib + palbociclib + fulvestrant in adult patients with PIK3CA mutated, HR-positive, HER2-negative, locally advanced, or metastatic breast cancer, following recurrence on or within 12 months of adjuvant endocrine therapy. There is not adequate data to support a benefit for use of the triplet combination in patients that do not have PIK3CA mutated advanced breast cancer that is not considered endocrine resistant or for use of a different endocrine therapy other than fulvestrant.

Based on the overall benefit-risk assessment, the review team recommends regular approval for the following indication:

Inavolisib (ITOVEBI), in combination with palbociclib and fulvestrant, is indicated for the treatment of adults with endocrine-resistant, PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.

Inavolisib will be the first FDA-approved treatment to be used in a triplet combination, specifically for the first line treatment of patients with PIK3CA mutated locally advanced or metastatic HR positive, HER2 negative breast cancer considered to have endocrine resistant disease. Patients should be selected for treatment using the FoundationOne Liquid CDx (F1LDx). The sPMA P190032-S023 will be contemporaneously approved with this NDA for inavolisib. A PMC has been issued for tissue testing, as the PMA is planned to be submitted at the end of 2024.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Breast cancer is the most common cancer in women, with 310,720 new cases estimated and 42,780 deaths estimated from breast cancer in the U.S. in 2024. Although rare breast cancer does occur in male patients.	Endocrine resistant, PIK3CA mutated, HR-positive, HER2-negative advanced or metastatic breast cancer is a serious and life-threatening condition.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• About 70% of breast cancers are hormone receptor (HR) positive. • Approximately 35-40% of patients with HR-positive breast cancer have tumors that harbor mutations in PIK3CA. • Endocrine resistant breast cancer is considered to be a negative prognostic factor as these patients tend to have worse survival outcomes compared to patients with endocrine sensitive breast cancer. • Advanced or metastatic HR-positive, HER-negative breast cancer remains incurable.	
<u>Current Treatment Options</u>	• Treatment for advanced or metastatic breast cancer is palliative in intent with the goals to prolong survival, delay progression, and reduce symptoms from cancer. • Treatment with a CDK 4/6 inhibitor plus endocrine therapy (fulvestrant or aromatase inhibitor) is considered standard of care first line treatment for patients with advanced or metastatic HR-positive, HER-negative breast cancer. • For patients that have progression of disease with/after CDK4/6 inhibitor + endocrine therapy, treatment options include endocrine monotherapy or combination endocrine therapy + targeted agents (alpelisib, capivasertib, elacestrant, everolimus) depending on the presence or absence of specific genetic alterations. Second line treatment with CDK 4/6 inhibitor + endocrine therapy may be considered for patients that did not receive it in the first line. Other options include chemotherapy (capecitabine, eribulin, ixabepilone, paclitaxel protein-bound, gemcitabine), and/or an antibody-drug conjugate fam-trastuzumab-deruxtecan, for patients with HER2 low (IHC1+ or IHC2+/ISH-) advanced or metastatic breast cancer	There are no FDA approvals specifically for the first line treatment of patients with endocrine resistant, PIK3CA mutated, HR-positive, HER-negative advanced or metastatic breast cancer. These patients are treated with currently available options for HR-positive, HER2 negative breast cancer. All treatment options are palliative and there is an unmet medical need to improve outcomes in these patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	developing recurrence during or within 6 months of adjuvant therapy.	
Benefit	• INAVO120 enrolled 325 patients with PIK3CA-mutated, HR-positive, HER2-negative (defined as IHC 0 or 1+, or IHC 2+/ISH-), advanced or metastatic breast cancer, following recurrence on or within 12 months of adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. • Patients were randomized 1:1 to either inavolisib + palbociclib + fulvestrant or placebo + palbociclib + fulvestrant. • The median PFS by investigator was 15 months in the inavolisib arm and 7.3 months in the placebo arm (HR 0.43, 95% CI: 0.32, 0.59; p-value <0.0001). • PFS by BICR results were supportive of the primary endpoint. • At the planned interim analysis for OS, a total of 97 events had occurred (63% of planned OS events) and did not reach statistical significance based on the interim analysis stopping boundary.	Inavolisib + palbociclib + fulvestrant demonstrated a statistically significant and clinically meaningful improvement in PFS for endocrine resistant, PIK3CA mutated, HR-positive, HER2-negative advanced or metastatic breast cancer, which was supported by a favorable trend in OS and secondary endpoints such as ORR and DOR.
Risk and Risk Management	• Serious adverse reactions occurred in 24% of patients who received inavolisib with palbociclib and fulvestrant. Serious adverse reactions in ≥ 1% of patients included anemia (1.9%), diarrhea (1.2%), and urinary tract infection (1.2%). • Fatal adverse reactions occurred in 3.7% of patients who received inavolisib with palbociclib and fulvestrant, including (0.6% each) acute coronary syndrome, cerebral hemorrhage, cerebrovascular accident, COVID-19 infection, and gastrointestinal hemorrhage.	Safe use of inavolisib with palbociclib plus fulvestrant can be managed with labeling. Hyperglycemia, stomatitis, diarrhea, and embryo-fetal toxicity are included under Warnings and Precautions. There is no indication for a REMS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- The most common ($\geq 20\%$) adverse reactions, including laboratory abnormalities, were decreased neutrophils, decreased hemoglobin, increased fasting glucose, decreased platelets, decreased lymphocytes, stomatitis, diarrhea, decreased calcium, fatigue, decreased potassium, increased creatinine, increased ALT, nausea, decreased sodium, decreased magnesium, rash, decreased appetite, COVID-19 infection, and headache. - PRO-CTCAE data was collected by the Applicant to further inform on tolerability. In general, these patient-reported symptoms were observed to be worse in the inavolisib arm, with the greatest difference observed for diarrhea, mouth sores, decreased appetite, and rash.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
	X Clinical outcome assessment (COA) data, such as	
	X Patient reported outcome (PRO)	Section 8.1.1 Efficacy Results – Secondary and exploratory COA (PRO) endpoints
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerFO)	

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☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Cross-Disciplinary Team Leader

Preeti Narayan, MD

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position: Breast cancer is the most commonly diagnosed cancer in women, with an estimated global incidence of 2.2 million new cases and almost 700,000 deaths reported in 2020 ([Sung et al. 2021](#)). Breast cancer in men is rare; accounting for less than 1% of all breast cancer cases in the US. Hormone receptor positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) breast cancer is the most common subtype accounting for approximately 70% of all breast cancers ([Breast Cancer, Facts and Figures 2022-2024](#)).

In the U.S., the median age at diagnosis for HR+, HER2- breast cancer patients is 64.0 years. For metastatic HR+, HER2- breast cancer, the annual incidence was observed to be highest for non-Hispanic Blacks (5.1 per 100,000 women), followed by non-Hispanic Whites (4.0 per 100,000), Hispanics (3.0 per 100,000), and Asian/Pacific Islanders (2.8 per 100,000 women) ([SEER 2023](#)).

Locally advanced and metastatic breast cancer (LA/mBC) remains a virtually incurable disease, with 29.2% of these patients likely to survive at least 5 years from the time of diagnosis. The 5-year survival of distant disease also remains low for HR+, HER2- LA/mBC at 34% ([SEER 2023](#)).

Approximately 35-40% of patients with HR+ breast cancer have tumors that harbor mutations in *PIK3CA*, the gene encoding the catalytic subunit of the alpha isoform of PI3K (i.e., p110 α) ([Fillbrunn et al. 2022](#)). There are mixed reports on whether there are differences in *PIK3CA* mutation prevalence in HR+ breast cancer by race. In studies of Asian and Hispanic patients, the mutation prevalence range (i.e., 35-40%) was similar to non-Hispanic Whites, while for African American women and those with African ancestry, some data suggest *PIK3CA* mutation prevalence may be up to 10% lower ([Li et al. 2021](#); [Blesinger et al. 2018](#); [Chen et al. 2022](#); [Pitt et al. 2018](#); [Baselga et al. 2017](#)).

PIK3CA mutations result in upregulation of PI3K pathway activity ([Saal et al. 2005](#); [Stemke-Hale et al. 2008](#)) and are a negative prognostic factor ([Fillbrunn et al. 2022](#)). Specifically, it has been estimated that patients with HR+, HER2- mBC whose tumors harbor one or more *PIK3CA* mutations exhibit approximately 2 months shorter progression-free survival (PFS) and 8 months shorter overall survival (OS), when treated with standard of care options compared with their wildtype counterparts ([Fillbrunn et al. 2022](#)).

The FDA's Assessment:

FDA agrees with the Applicant's assessment. FDA considers advanced and metastatic HR-positive, HER2-negative breast cancer that is endocrine resistant to be incurable, and the goal of therapy is palliative.

Endocrine therapy is the mainstay for HR-positive breast cancer. However, resistance may occur to endocrine therapy and a major challenge to treating HR-positive breast cancer is overcoming endocrine resistance. Activation of the PI3K/AKT pathway may lead to endocrine resistance. Endocrine resistant breast cancer is not uniformly defined but generally refers to cancer that grows in the presence of endocrine therapy (ET) or soon after completing ET. Endocrine resistant breast cancer is considered to be a negative prognostic factor as these patients tend to have worse survival outcomes compared to patients with endocrine sensitive breast cancer.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Treatment Options in HR-positive, HER2-negative LA/mBC

Endocrine therapy (ET) remains the cornerstone of treatment for patients with HR+ breast cancer. The current treatment paradigm for advanced HR+, HER2– breast cancer is sequential endocrine-based therapies to control the disease and delay chemotherapy in the majority of cases. For patients considered endocrine-resistant/refractory or with visceral crisis (imminent organ failure), chemotherapy is recommended ([NCCN 2024](#)).

The combination of a cyclin dependent kinase 4/6 (CDK4/6) inhibitor with either fulvestrant or an aromatase inhibitor (AI) is considered the standard of care first- and/or second-line treatment for LA/mBC; endocrine monotherapy may be considered appropriate for frail patients with comorbidities ([ESMO 2023](#); [NCCN 2024](#)). Endocrine-based therapy is recommended for both post- and pre-/peri-menopausal patients, though pre-/peri-menopausal women are recommended to have ovarian function suppression or ablation. In men, the treatment approach is similar to that of women ([ESMO 2023](#); [NCCN 2024](#); [Vasconcelos de Matos et al. 2023](#)).

In patients who relapse after ET plus a CDK4/6 inhibitor, several treatment options are available, which 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. As such, the treatment options range from endocrine monotherapy (e.g. elacestrant for *ESR1* mutated tumors) to combinations with targeted agents, like alpelisib plus fulvestrant (for *PIK3CA*-mutated tumors), everolimus plus ET, and caviplasertib plus fulvestrant (for *PIK3CA/AKT/PTEN* altered tumors), and in some cases, second-line CDK4/6 inhibitor plus an endocrine agent ([ESMO 2023](#); [NCCN 2024](#)).

In addition to these therapies, particularly in cases of endocrine resistance and/or rapid disease progression and significant visceral disease, chemotherapy-based may be used at physician's clinical discretion ([Guiliano et al. 2019](#)). Current guidelines recommend the use of sequential single-agent chemotherapy. However, in patients with visceral crisis, combination chemotherapy regimens are recommended on the basis of improved response rates and longer time to progression compared to single agents, but at the expense of increased toxicity and suboptimal quality of life ([ESMO 2023](#); [NCCN 2024](#)). There are several chemotherapy agents considered appropriate as monotherapy or in combination, including taxanes (most commonly weekly paclitaxel), capecitabine and eribulin. ([Seidman et al. 2008](#); [Jäger et al. 2010](#); [Kaufmann et al. 2010](#); [Cortes et al. 2011](#); [Stockler et al. 2011](#); [O'Shaughnessy et al. 2012](#); [Rugo et al. 2015](#); [Harbeck et al. 2017](#)). There is no clear recommendation for one over the other, and the treatment decision is individualized after taking into consideration factors such as previous therapies, co-morbidities, and patient preference ([ESMO 2023](#); [NCCN 2024](#)). Recently, the antibody-drug-conjugate (ADC), fam-trastuzumab deruxtecan has been approved for patients with HER2-low (IHC 1+ or IHC 2+/ISH-) LA/mBC, who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant therapy.

Treatment Options in PIK3CA-mutated, HR-positive, HER2-negative LA/mBC

Currently, patients with HR+, HER2– LA/mBC whose tumors harbor a *PIK3CA* mutation can be treated with any standard-of-care therapy for HR+, HER2– LA/mBC since these therapies have been approved without a specific biomarker requirement. However, as none of these treatment options target the PI3K pathway directly, patients with *PIK3CA*-mutated tumors may derive less benefit compared to patients whose tumors do not harbor a *PIK3CA* mutation ([Fillbrunn et al. 2022](#)). This has been observed with both endocrine-based ([Fillbrunn et al. 2022](#)) and chemotherapy-based options ([Mosele et al. 2020](#)).

Because *PIK3CA* mutations are a known predictive biomarker of response to PI3K α AKT inhibitors ([André et al. 2019](#); [Turner et al. 2023](#)), there are additional treatment options for patients with *PIK3CA*-mutated tumors ([André et al. 2019](#); [Turner et al. 2023](#)). Alpelisib (PI3K α inhibitor) plus fulvestrant is a preferred second/later line option for patients with *PIK3CA*-mutated, HR+, HER2– LA/mBC ([André et al. 2019](#); [Rugo et al. 2020](#)). The challenging safety and tolerability of alpelisib has affected its adoption in clinical practice and is a key reason it is not recommended as a first-line treatment option ([ESMO 2023](#); [NCCN 2024](#)). In addition, everolimus (an mTOR inhibitor) in combination with exemestane is recommended as second/later line option, regardless of *PI3KCA* mutation status.

Recently, capivasertib (AKT inhibitor) plus fulvestrant was approved for patients with HR+, HER2– LA/mBC that harbors a *PIK3CA/AKT1/PTEN* alteration following recurrence or progression on an endocrine-based regimen and is a preferred second/later -line option ([NCCN 2024](#)).

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The FDA’s Assessment:

FDA agrees with the Applicant’s assessment.

Currently, there are no FDA approved treatments specifically for the first line treatment of patients with PIK3CA mutated locally advanced or metastatic HR-positive, HER2-negative breast cancer considered to have endocrine resistant disease.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant’s Position: Inavolisib is not currently marketed in the US or in any other country.

The FDA’s Assessment:

FDA agrees with the Applicant’s assessment.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant’s Position: For more detailed regulatory history, please see Module 1.6.3 Correspondence regarding meetings.

Table 1: Applicant – Regulatory History of Key FDA interactions

Date	Type of FDA Interaction	Purpose of FDA Interaction
11 July 2019	Type B Pre-Phase III meeting	To seek FDA’s feedback on key design elements of the proposed Phase III Study WO41554, proposed companion diagnostic plan, acceptability of the nonclinical toxicology package, and proposed clinical pharmacology program. FDA agreed with the Sponsor’s proposals overall and made additional recommendations regarding QTc and drug-drug interaction (DDI) assessments.
14 July 2023	Type C NDA Format & Content interaction Written Response	To obtain FDA feedback on the acceptability of the proposed contents and format of the NDA to support inavolisib in combination with palbociclib and fulvestrant for the treatment of adult patients with <i>PIK3CA</i> -mutated, HR+, HER2– LA/mBC. Overall, FDA found the proposed contents and format acceptable with the final determination to be made at the time of submission and review. FDA made additional recommendations to provide supporting justification for the proposed indication and commented on the clinical pharmacology strategy.
05 February 2024	Type B Pre-NDA meeting	To obtain feedback on the acceptability of the study results from the Phase III WO41554 study and supporting Phase I GO39374 study to support an NDA for the proposed indication. FDA indicated that whether the data would support the proposed indication would be a review issue. FDA agreed with the proposed stability data package and provided

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		additional recommendations with regard to DDI data, diversity, the dose justification, and the content and format of the Clinical Pharmacology section.

The FDA's Assessment:

In general, FDA agrees with the Applicant's assessment, with the following caveats. At the July 2019 meeting, FDA recommended further dose optimization for inavolisib, as limited data had been generated at doses less than 9mg. At the July 2023 meeting, FDA stated that supporting data and adequate justification must be provided for the proposed indication as it was broader than the patient population enrolled into the INAVO120 trial. At the February 2024 meeting, FDA stated that adequate justification for dose selection needs to be provided and reiterated that adequate justification must be provided for the proposed indication.

In addition, Breakthrough Therapy Designation (BTD) was granted on May 20, 2024, for the following indication *"inavolisib is in combination with palbociclib and fulvestrant 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."* Of note, the indication granted BTD is slightly different than the Applicant proposed indication in this NDA application.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was consulted to perform site inspections as part of the review for this NDA. Reference is made to the Clinical Inspection Summary by Dr. Elena Boley dated 8/29/2024. The following three clinical sites were chosen as they were high enrolling sites for the INAVO 120 Trial (WO41554), and the clinical investigators had not been inspected previously:

1. Dr. Seock Ah Im (Site #323897; Seoul National University Hospital, Seoul, South Korea)
 - 35 patients screened; 16 patients consented; 8 patients enrolled and randomized.
2. Dr. Antonino Musolino (Site #323146; Universitaria Di Parma, Parma, Italy)
 - 22 patients screened; 7 patients consented; 6 patients enrolled and randomized.
3. Dr. Florence Dalenc (Site #323629; Institut Universitaire Du Cancer De Toulouse-Oncopole, Toulouse, France)
 - 32 patients screened; 9 patients consented; 5 patients enrolled and randomized.

The OSI inspections did not find any evidence of under-reporting of adverse events and no discrepancies were noted at the three clinical sites. OSI concluded that based on these inspections, Study WO41554 appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the proposed indication.

4.2. Product Quality

The FDA Office of Product Quality (OPQ) review team recommended approval for inavolisib. The review team assessed the drug substance, the drug product, quality labeling, manufacturing, biopharmaceutics, and microbiology for inavolisib and concluded that the Applicant provided sufficient information to assure the identity, strength, purity, and quality of the proposed product. The review team also concluded that all associated manufacturing, testing, and packaging facilities were deemed acceptable based on prior history, file review and district recommendation.

For details, please refer to the Product Quality review by Drs. Payal Agarwal, Anitha Govada, and Xing Wang dated 8/28/24.

4.3. Clinical Microbiology

No Microbiology issues were reported in the OPQ review referenced above for this NDA application.

4.4. Devices and Companion Diagnostic Issues

CDRH received a supplemental PMA Application (P190032/S023) from Foundation Medicine Inc. (FMI) for the FoundationOne Liquid CDx (F1CDx). CDRH considers this sPMA approvable as a companion diagnostic device for inavolisib in combination with palbociclib and fulvestrant.

FoundationOne Liquid CDx is a qualitative next generation sequencing based in vitro diagnostic test that uses targeted high throughput hybridization-based capture technology to detect and report substitutions, insertions and deletions (indels) in 311 genes, including rearrangements in eight (8) genes and copy number alterations in three (3) genes. FoundationOneLiquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood of cancer patients collected in FoundationOneLiquid CDx cfDNA blood collection tubes included in the FoundationOneLiquid CDx Blood Sample Collection Kit. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with targeted therapies in accordance with the approved therapeutic product labeling.

The FoundationOne Liquid CDx assay was initially approved in November 2017 under P190032. Foundation Medicine, Inc. has since submitted multiple supplements expanding the indications of the device, including expansions for CDx indications, as well as updates to the assay.

This PMA supplement for F1CDx was primarily comprised of results from the INAVO120 clinical study. Analytical study data were leveraged with data from P190032 (this was agreed to in CDRH's written response to Q232680 provided to FMI on December 18, 2023).

A patient whose tumor harbors any of the following 62 alterations listed below is defined as *PIK3CA*-mutation positive by F1LCDx.

R88Q	N345D	E453G	E542V	Q546H	H1047L	G1049R
G108A	N345H	E453K	E545A	Q546K	H1047N	G1049S
G108D	N345I	E453Q	E545D	Q546L	H1047P	
G108R	N345K	E453V	E545G	Q546P	H1047Q	
G108S	N345S	E542A	E545K	Q546R	H1047R	
G108V	N345T	E542D	E545L	M1043I	H1047T	
K111N	N345Y	E542G	E545Q	M1043T	H1047Y	
K111R	C420R	E542K	E545R	M1043V	G1049A	
K111E	E453A	E542Q	E545V	H1047D	G1049C	
G118D	E453D	E542R	Q546E	H1047I	G1049D	

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Inavolisib (ITOVEBI), also known as GDC-0077, RO7113755, and G02967907, is an inhibitor of phosphatidylinositol 3-kinase (PI3K) with inhibitory activity predominantly against PI3K α , encoded by the PIK3CA gene, and belongs to the pharmacological class of kinase inhibitors. PI3K is a signal transducer downstream of cell surface receptors and regulator of cell metabolism and survival. The PI3K signaling pathway has been reported to be dysregulated in hormone receptor (HR)-positive breast cancer, often due to activating PIK3CA mutations. In this NDA submission, the Applicant submitted nonclinical pharmacology (primary, secondary, safety), ADME/PK, and toxicology (general, developmental, genetic) data to support the approval of inavolisib in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, *PIK3CA*-mutated, HR-positive, human epidermal growth-factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy. The proposed recommended dosage and administration of inavolisib is 9 mg taken orally once daily.

In an in vitro biochemical assay, inavolisib inhibited PI3K α with higher potency compared to the other PI3K isoforms including PI3K β , PI3K δ , and PI3K γ with inhibitory constant (K_i) values of 0.038 nM, 101.7 nM, 12.8 nM, and 21.8 nM, respectively. The steady-state C_{max} for inavolisib is 69 ng/mL (169 nM or ~ 107 nM unbound) at the recommended dose of 9 mg/day. In a kinase panel of 224 kinases, inavolisib only inhibited 3 kinases (defined as $> 80\%$ inhibition at 1 μ M) – PI3K α , PI3K γ , and PI3K δ (96.4%, 96.2%, and 81.7% inhibition at 1 μ M, respectively). Inavolisib treatment of a human breast cancer cell line (HCC1954) reported to contain the hotspot H1047R *PIK3CA* alteration, led to proteasome-dependent depletion of the PI3K catalytic subunit alpha isoform (p110 α) protein but not in a human breast cancer cell line (HDQ-P1) reported to be *PIK3CA* wild type. Similarly, inavolisib treatment resulted in greater increases in apoptosis, as measured by cleaved PARP protein, and decreases in downstream signaling, as measured by pAKT⁴⁷³, in the *PIK3CA*-mutated breast cancer cell line (HCC1954) than in the *PIK3CA*-WT breast cancer cell line (HDQ-P1). Inavolisib treatment of the MCF-7 breast cancer cell line (estrogen receptor [ER]-positive, HER2-negative, and *PIK3CA*^{E545K}-mutated) resulted in reduced in vitro cell viability alone and a synergistic effect in combination with fulvestrant or palbociclib. Inavolisib showed anti-tumor effects in xenograft mouse models of human breast cancer using KPL-4, HCC1954X1, and MCF7 cell lines. KPL-4 and HCC1954X1 are reported to be ER-negative/HER2-positive and to harbor a hotspot alteration in the p110 α catalytic domain (H1047R), resulting in elevated levels of pAKT and constitutive PI3K pathway activation. The antitumor effect of inavolisib (% tumor growth inhibition [TGI] = 61) was increased when administered in combination with palbociclib (%TGI = 102), fulvestrant (%TGI =

79), or palbociclib plus fulvestrant (%TGI = 119) in mice bearing MCF-7 tumors.

Inavolisib did not show significant inhibition of cardiac human ether-à-go-go-related gene (hERG) channel, NaV1.5 voltage gated sodium channel, or CaV1.2 L type calcium channel, in vitro. In a GLP-compliant single dose safety pharmacology study in telemetry instrumented Beagle dogs, inavolisib-related cardiovascular effects included generally dose-dependent, reversible 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 $\geq$ 0.3 mg/kg. Overall, the findings up to 3 mg/kg (10 times the human exposure at the recommended dose of 9 mg/day based on C_{max}) were not considered adverse based on the changes being minimal in magnitude and transient. No cardiovascular, respiratory, or neurobehavioral abnormalities were detected in the rat or dog repeat-dose toxicity studies.

Nonclinical ADME/PK studies showed that exposure to inavolisib in rats and dogs increased dose proportionally and showed no significant accumulation following multiple administrations. In rats, exposure was higher (approximately 2-fold) in females than in males; however, overall, there were no significant differences in toxicities in female compared to male rats. No sex-related differences in exposure parameters were noted in dogs. Tissue distribution studies in pigmented and non-pigmented rats showed that inavolisib-related radioactivity was extensively distributed in rat tissues and organs, including the endocrine tissues (adrenal gland), excretory tissues (kidney, liver, urinary bladder wall), the gastrointestinal tract, uveal tract, and the skin. By 672 hours post-dose, levels of radioactivity in all tissues were below quantifiable levels except for the adrenal gland, medulla and cortex, and uveal tract, where concentrations remained quantifiable at 1344 hours post-dose. Following a single oral administration, inavolisib was the most abundant drug-related component in rat plasma, urine, feces, and bile. No human-specific metabolites (> 10% of total circulating radioactivity exposure) were observed. 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).

Inavolisib was evaluated in GLP-compliant, repeat-dose toxicology studies in Sprague-Dawley rats and Beagle dogs following once daily oral administration, consistent with the clinical route of administration and intended dosing schedule, for up to 3 months in duration. Rats were dosed up to 10 mg/kg and 5 mg/kg in the 4- and 13-week studies, respectively, corresponding to 6.3 times and 1.8 times the human exposure at the recommended dose of 9 mg/day based on AUC, respectively. Dogs were dosed up to 5/3 mg/kg and 1.5/1 mg/kg in the 4- and 13-week studies, respectively, corresponding to up to 6.1 times and 1.5 times the human exposure at the recommended dose of 9 mg/day based on AUC. There were no early mortalities in rats; however, dogs were dose reduced in both 4- and 13-week studies due to moribund condition associated with hypoactivity, body weight loss, hyperglycemia, reddish conjunctiva, and/or

clinical observations indicative of persistent ocular inflammation correlated with slight mixed cell endophthalmitis. Overall, the major target organs of toxicity in rats or dogs were the lymphoid tissues (thymus, gut-associated lymphoid tissue/Peyer's patch, mesenteric and mandibular lymph nodes, spleen, bone marrow), eye, pancreas, and male and female reproductive organs. Findings in the lymphoid organs consisted of decreases in erythroid or lymphoid cellularity which correlated with decreases in red or white blood cell parameters at ≥ 1.5 mg/kg/day in rats (≥ 0.3 times the human exposure at the recommended dose of 9 mg/day based on AUC). Hyperglycemia was observed in both rats and dogs at ≥ 1 mg/kg/day (≥ 0.1 times the human exposure at the recommended dose of 9 mg/day based on AUC) and ≥ 0.5 mg/kg/day (≥ 0.8 times the human exposure at the recommended dose of 9 mg/day based on AUC), respectively. Hyperglycemia was reversible and was correlated with histopathology findings in the pancreas which included islet hypertrophy with vascular ectasia (angiectasia) in rats and diffuse hypertrophy/vacuolation of islet cells in dogs. Ocular findings were noted in rats and dogs. In rats, minimal to mild lens degeneration of the eye was observed at 10 mg/kg/day (6.3 times the human exposure at the recommended dose of 9 mg/day based on AUC) at terminal and recovery necropsy in the 1-month study only. In dogs, bilateral, reversible, very slight swelling of the fibers at the equatorial region of the lens and lens cortex vacuolation were observed at ≥ 0.3 mg/kg/day (≥ 0.5 times the human exposure at the recommended dose of 9 mg/day based on combined male and female AUC value of 485 ng·h/mL) and ≥ 1 mg/kg/day (≥ 1.2 times the human exposure at the recommended dose based on combined male and female AUC value of 1250 ng·h/mL), respectively, in the 3-month study. Hyperglycemia of any grade occurred in 60% of patients treated with ITOVEBI and is included in the Warnings and Precautions of the label. Ocular toxicities were limited to grades 1-2 adverse reactions in patients, with dry eye, blurred vision, and increased lacrimation as the most frequently reported adverse reactions. Findings of ocular toxicity were included in section 13.2 of the Prescribing Information (PI) based on distribution of inavolisib in the eye and dose-related findings in rats and dogs, suggesting that the ocular toxicities may be a direct effect of inavolisib administration.

In GLP-compliant genetic toxicology studies, inavolisib was not mutagenic in the bacterial reverse mutation assay. Inavolisib was clastogenic in an in vitro human lymphocyte micronucleus assay. In an in vivo rat bone marrow micronucleus assay, female rats were administered vehicle control or 5, 15, or 40 mg/kg inavolisib orally, once daily for three days. Inavolisib treatment did not cause a significant increase in micronucleus frequency in polychromatic erythrocytes of the bone marrow and did not induce DNA strand breaks in the liver above the historical control range when evaluated by the alkaline Comet assay. Carcinogenicity studies were not conducted, nor warranted, with inavolisib to support the proposed indication in patients with advanced cancer in accordance with ICH S9 guidance.

In a GLP-compliant preliminary embryo-fetal development study, pregnant rats received oral doses of inavolisib up to 6 mg/kg/day during the period of organogenesis from gestational day

(GD)7 to GD17. Administration of inavolisib resulted in dose dependent effects on embryo-fetal development at ≥ 2 mg/kg (≥ 0.9 times the human exposure at the recommended dose of 9 mg/day based on AUC) that included decreases in fetal body weight and placental weight, post-implantation loss, lower fetal viability, fetal malformations (including kyphosis of vertebral column, fused thoracic arch, microphthalmia) and variations (including dilated renal pelvis, short supernumerary rib, and wavy rib).

Fertility and early embryonic development studies were not conducted nor are warranted to support the proposed indication in patients with advanced cancer in accordance with ICH S9 guidance. In the 4-week and 13-week repeat-dose toxicology studies with inavolisib in rats and dogs, histopathology changes observed in reproductive organs suggest that inavolisib has the potential to impair male and female fertility. Adverse findings in animals included dose-dependent and reversible atrophy of the prostate and seminal vesicle and decreased organ weights, without microscopic correlates, in the epididymis and testis at oral inavolisib doses ≥ 1.5 mg/kg/day in male rats (≥ 0.4 times the human exposure at the recommended dose of 9 mg/day based on AUC), and focal inspissation of seminiferous tubule contents and reversible multinucleated spermatids in the testis and epithelial degeneration/necrosis in the epididymis at oral inavolisib doses ≥ 1.5 mg/kg/day in male dogs (≥ 2 times the human exposure at the recommended dose of 9 mg/day based on AUC). Findings in dogs were not observed following a recovery period. Atrophy in the uterus and vagina, decreased ovarian follicles and findings suggestive of an interruption/alteration of the estrus cycle were observed in female rats following up to 3 months of dosing at oral inavolisib doses ≥ 3 mg/kg/day (≥ 1.2 times the human exposure at the recommended dose of 9 mg/day based on AUC). Findings in the uterus, vagina, and estrous cycle observed in the 4-week toxicity study were not observed following a 4-week recovery period. Recovery was not assessed in the 3-month study in rats.

Based on animal data and its mechanism of action, ITOVEBI can cause fetal harm when administered to a pregnant woman. Inavolisib was genotoxic in vitro (clastogenic) but was not genotoxic in an in vivo rat bone marrow micronucleus test and did not induce DNA break in a liver comet assay. Therefore, overall, inavolisib is not considered genotoxic. Inavolisib has an estimated elimination half-life of 15 hours following a single 9 mg dose. Consistent with the recommendations outlined in the FDA guidance "Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry", females of reproductive potential should use effective non-hormonal contraception during treatment with ITOVEBI and for 1 week after the last dose. Male patients with female partners of reproductive potential should use effective contraception during treatment with ITOVEBI and for 1 week after the last dose. FDA recommended the use of non-hormonal contraception for females due to the potential for drug-drug interaction between inavolisib and combined oral contraceptives, which are known substrates of CYP3A. These contraceptives could reduce the effectiveness of the combined oral contraceptives and lead to unintended pregnancies. Until the drug-drug interaction potential between inavolisib and CYP3A substrates is evaluated, the concomitant

medication should be limited to non-hormonal contraceptives. There are no data on the presence of inavolisib or its metabolites in human milk, its effects on milk production, or the breastfed child. Because of the potential for serious adverse reactions in a breastfed child, lactating women should not breastfeed during treatment with ITOVEBI and for 1 week after the last dose. Because ITOVEBI is indicated in combination with palbociclib and fulvestrant, the prescribing information also includes a reference to the Full Prescribing Information of palbociclib and fulvestrant for pregnancy, contraception, infertility, and lactation information.

Recommendation:

The nonclinical data submitted to this NDA are adequate to support the approval of ITOVEBI for the granted indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position: Not applicable.

5.3. Pharmacology

Primary pharmacology

The Applicant's Position: Inavolisib is a highly selective oral small molecule inhibitor of the catalytic subunit alpha isoform protein of PI3K (p110 α ; encoded by the *PIK3CA* gene), with sub-nanomolar potency. In addition, inavolisib promotes the degradation of mutated p110 α . 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.

In *PIK3CA*-mutated breast cancer cell line-derived xenograft models, inavolisib reduced tumor growth. This anti-tumor activity was more pronounced when inavolisib was used in combination with standard-of-care therapies for breast cancer, including fulvestrant or palbociclib (CDK4/6 inhibitor). Together, these nonclinical data for inavolisib support combination therapy use as a treatment for patients with *PIK3CA*-mutated, HR+, HER2– LA/mBC.

Key In Vitro Primary Pharmacology Findings:

- Inavolisib has an *in vitro* biochemical potency (K_i) of 0.038 nM for PI3K α , which is 300-fold more selective over the other Class I PI3K isoforms ([Hanan et al. 2022](#), Study 16-1792/4.2.1.1).
- Inavolisib inhibited 3 of 224 kinases in the Invitrogen kinase panel at >80% at a concentration of 1 μ M. Two of the kinases, PI3K α and PI3K γ , are targets of inavolisib. Additionally, inavolisib inhibited PI3KC2 β , a PI3K family member, at 82%. In a subsequent

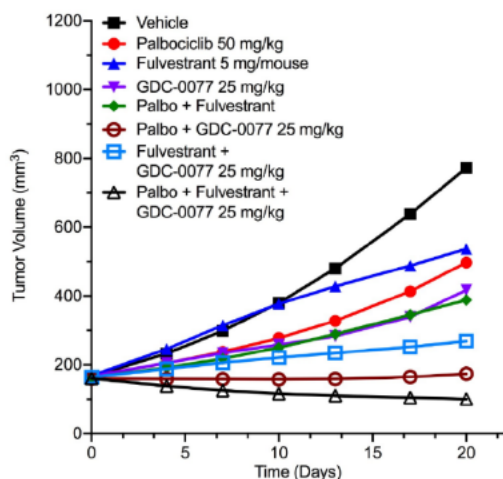
study, inavolisib was 2000-fold more selective for PI3K α relative to all other kinases tested (Study 16-1794/4.2.1.1).

- Inavolisib promotes the degradation of mutated p110 α . Treatment of cells with inavolisib leads to depletion of p110 α protein in the HCC1954 breast cancer cell line that contains mutated *PIK3CA* but not in the HDQ-P1 cell line that is wild type (WT) for *PIK3CA*. Inavolisib shows greater reduction in levels of pathway markers such as pAKT and a greater increase in apoptosis when assayed by cleaved poly (ADP-ribose) polymerase (cleaved PARP) in *PIK3CA*-mutant cell lines than in *PIK3CA* WT cancer cells (Study 16-1793/4.2.1.1, [Song et al. 2022](#)).
- Inavolisib inhibits cellular proliferation of *PIK3CA*-mutated breast cancer cells *in vitro*, with mean half-maximal effective anti-proliferative concentrations (EC₅₀) in the nanomolar range ([Hanan et al. 2022](#), [Song et al. 2022](#)).

Key *In Vivo* Primary Pharmacology Findings:

- PI3K pathway markers pAKT, pPRAS40, and pS6 were reduced for up to 8 hours in response to a single dose of 5 or 50 mg/kg inavolisib, and reduction of pathway markers was both dose- and time-dependent in the HCC1954X1 breast cancer xenograft model (Study 15-0797-B/4.2.1.1).
- Inavolisib inhibited tumor growth of KPL-4 *PIK3CA*-mutated human breast cancer xenograft tumors grown orthotopically in severe combined immunodeficient (SCID) beige mice. Treatment at the highest dose of inavolisib at the maximum tolerated dose (MTD) of 50 mg/kg resulted in a maximal response of 153% tumor growth inhibition (TGI) and 100% objective response rate (ORR) (9 partial responses [PR] and 1 complete response [CR] out of 10 animals) (Study 13-3399-L/4.2.1.1).
- Inavolisib inhibited tumor growth in a nude mouse HCC1954X1 *PIK3CA*-mutated human breast cancer xenograft model. Treatment at the highest dose of inavolisib (50 mg/kg) resulted in 149% TGI and 60% ORR (6 PRs out of 10 animals) (Study 13-3399-O/4.2.1.1).
- The combination of inavolisib with palbociclib and fulvestrant resulted in greater TGI than inavolisib, palbociclib, or fulvestrant administered as single agents or doublet combinations in a nude mouse MCF7 *PIK3CA*-mutated breast cancer xenograft model. 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 (Study 16-2204/4.2.1.1, **Figure 1**).

Figure 1: Applicant - Response of MCF7 *PIK3CA*-Mutated Breast Cancer Xenografts to Combination Therapy with Inavolisib, Palbociclib, and Fulvestrant (Study 16-2204 / 4.2.1.1 Primary Pharmacodynamics)



MCT = 0.5% methylcellulose/0.2% Tween 80; Palbo = palbociclib; *PIK3CA* = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform; PO = oral; QD = once daily; QW = once weekly; SC = subcutaneous.
 Notes: Inavolisib is also known as GDC-0077. Vehicle was MCT; or corn oil (for fulvestrant only). Tumor volumes after PO QD administration of inavolisib or palbociclib, SC QW administration of fulvestrant, or double or triple combination for 20 days is depicted by dose group.

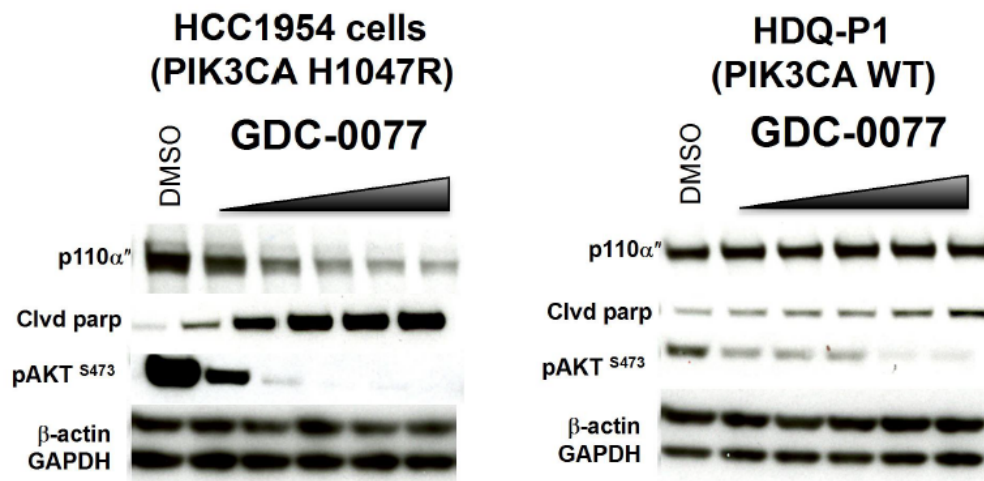
The FDA’s Assessment:

In general, FDA agrees with the Applicant’s position. Authors in the publications discussed above and used to support labeling are affiliated with Genentech (the Applicant). Select data discussed by the Applicant are shown below.

Table 2: Biochemical Potency of Inavolisib Against PI3K Isoforms (Study 16-1792)

	PI3K α	PI3K β	PI3K δ	PI3K γ
Mean Ki (nM)	0.038 ± 0.003	101.7 ± 12.1	12.8 ± 2.15	21.8 ± 1.16
Fold Selectivity (relative to PI3K α)	N/A	2676	337	574

Figure 2: Inavolisib-Induced Depletion of p110 α Protein in a *PIK3CA*-Mutated, but Not in a *PIK3CA*-Wild Type, Cell Line (Study 16-1793)

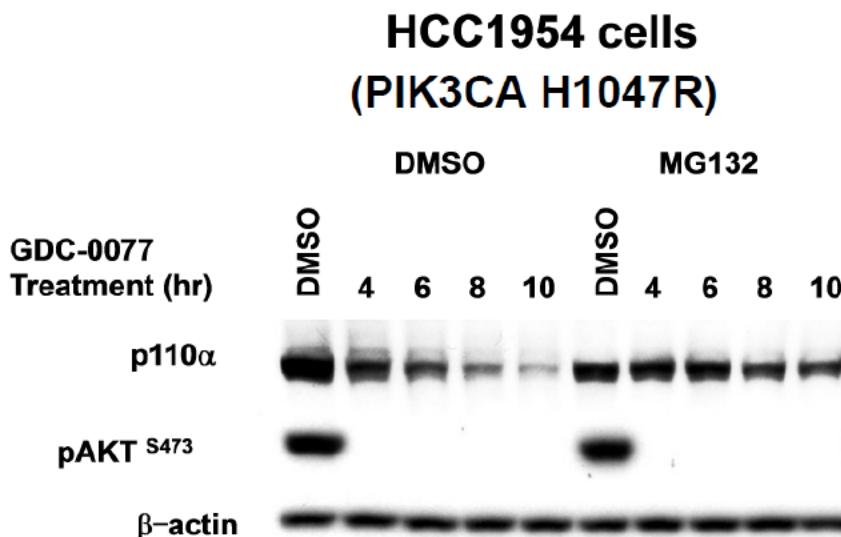


Clvd = cleaved; DMSO = dimethyl sulfoxide; GAPDH = glyceraldehyde 3-phosphate dehydrogenase; pAKT^{S473} = protein kinase B phosphorylated at Serine 473; parp = poly (ADP-ribose) polymerase; *PIK3CA* = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform; p110 α = catalytic subunit alpha isoform protein; WT = wild type.

Notes: Inavolisib is also known as GDC-0077. Dose titration 0, 37 nM, 111 nM, 333 nM, 1 μ M, 3 μ M. The HCC1954 cell line contains an H1047R *PIK3CA* alteration. The HDQ-P1 cell line is wild type for *PIK3CA*.

(Excerpted from the Applicant's submission)

Figure 3: Effect of Proteasome Inhibition on p110 α Protein Depletion by Inavolisib in a PIK3CA-Mutated Cell Line (Study 16-1793)



DMSO = dimethyl sulfoxide; hr = hour; pAKT^{S473} = protein kinase B phosphorylated at Serine 473; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform; p110 α = catalytic subunit alpha isoform protein.

Notes: Inavolisib concentration = 1.6 μ M. MG132 concentration = 10 μ M.

MG132 is a specific inhibitor of the proteasome.

(Excerpted from the Applicant's submission)

Secondary Pharmacology

The Applicant's Position: No 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 μ M against 88 targets (including those associated with abuse liability), including major classes of biogenic amine receptors, neuropeptide receptors, ion channels, neurotransmitter transporters, and enzymes (Studies 15-0292 and 15-1941/4.2.1.2).

The FDA's Assessment:

FDA agrees with the Applicant's position.

Safety Pharmacology

Inavolisib does not show significant inhibition of cardiac human ether-à-go-go-related gene (hERG) channel (Study 15-3355/4.2.1.3), Nav1.5 voltage-gated sodium channel (Study 15-0486/4.2.1.3), or Cav1.2 L-type calcium channel (Study 15-0487/4.2.1.3) in *in vitro* assays. The 50%

inhibitory concentration (IC₅₀) for inhibition of hERG current was > 1700 × higher than the human plasma maximum concentration observed (C_{max}) [unbound] (0.116 μM) at the 9 mg dose.

In the single-dose telemetry-instrumented dog safety pharmacology study (Study 15-3293/4.2.1.3), 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 QT (QTc) interval (+ 11 msec/+ 5%) at doses ≥ 0.3 mg/kg (Study 15-3293). 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).

No cardiovascular, respiratory, or neurobehavioral abnormalities were detected in rat or dog repeat-dose toxicity studies.

The FDA's Assessment:

FDA agrees with the Applicant's position. To calculate the exposure multiples, FDA used the C_{max} of 69 ng/mL at the recommended dose of 9 mg/day human dose described in the PI for ITOVEBI.

5.4. ADME/PK

The Applicant's Position: The nonclinical PK and toxicokinetic (TK) studies demonstrate that inavolisib has a favorable absorption, distribution, metabolism, excretion (ADME) profile and characteristics consistent with a compound that can be delivered orally to achieve the targeted clinical exposure. Inavolisib was well absorbed across preclinical species, with bioavailability ranging from 57.5% to 100%. Metabolism of inavolisib was minimal and no human-specific metabolites were observed in *in vitro* studies and in plasma. *In vitro* studies suggested a low potential for drug-drug interaction (DDI) involving cytochrome P450s (CYPs) or drug transporters at clinically relevant concentrations.

See Table 3 and Table 4 for integrated summaries of area under the concentration-time curve (AUC) and C_{max} parameters of toxicology studies. See Table 5 for exposure multiples from toxicology studies.

Absorption <i>Determination of Mass Balance and Pharmacokinetics Following a Single Oral Administration of [¹⁴C]Inavolisib in Male and Female Sprague Dawley Rats. Study 17-2251/4.2.2.5 Excretion.</i>
Inavolisib was absorbed relatively slowly following PO dosing of 3 mg/kg (200 μCi/kg), with a T _{max} of 4h for total radioactivity. Absorption was estimated to be 45.3% and 50.7% in male and female rats, respectively. The systemic half-life of total radioactivity was 17.8 and 26.6h for male and female rats, respectively.
Distribution <i>Tissue Distribution Following a Single Oral Dose of [¹⁴C]Inavolisib in Male and Female Long-Evans and Male Sprague Dawley Rats Using Quantitative Whole Body Autoradiography (QWBA). Study 18-2298/4.2.2.3 Distribution.</i> <i>Determination of In Vitro Protein binding of Inavolisib in CD-1 Mouse, Sprague Dawley Rat, New Zealand Rabbit, Beagle Dog, Cynomolgus Monkey, and Human Plasma, and Human α1-Acid Glycoprotein (AAG) and Human Serum Albumin (HSA) Solutions Using Rapid Equilibrium Dialysis (RED). Study 15-3820/4.2.2.3 Distribution.</i>

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Following PO administration of 3 mg/kg (200 µCi/kg) ¹⁴C-inavolisib to Sprague-Dawley (albino) rats, the absorption and distribution were rapid, with the majority of peak tissue radioactivity concentrations observed 1 hour post dosing. The endocrine tissues (adrenal gland), excretory tissues (kidney, liver, urinary bladder wall) and GI tract contained the highest distribution of [¹⁴C]inavolisib-derived radioactivity. In pigmented rats, distribution of inavolisib-derived radioactivity was comparable to that in albino rats, with the exception of melanin containing tissues, such as uveal tract and skin that presented higher levels of radioactivity. Radioactivity levels were below the quantitation limit at 1344 h post-dose in all tissues, except in the adrenal gland, eye and kidney. No or minimal radioactivity could be detected in the brain and spinal cord throughout the study. Plasma protein binding in rank order of highest overall average binding: mouse (25.2% unbound) > rabbit (53.1% unbound), rat (59.8% unbound), and human (63.3% unbound) > dog (69.2% unbound) and monkey (73.4% unbound). The binding to HSA was 74.0% unbound and binding to AAG was 98.2% unbound.
Metabolism Metabolite Identification for Inavolisib.1.5 in Rat, Dog, and Human Liver Microsomes. Study 16-0871/4.2.2.4 Metabolism. Metabolite Profiling and Identification of Inavolisib in Plasma, Bile, Urine, and Feces from Intact and Bile Duct Cannulated Male and Female Sprague Dawley Rats Following a Single Oral Dose of [¹⁴C]Inavolisib. Study 18-0814/4.2.2.4 Metabolism
After 1 hour incubation, more than 98.8% of inavolisib was recovered in all LMs tested. Three minor metabolites were detected: M1, M2, and M3 (1% of total UV response). Based on structurally informative fragments ions, the following 3 minor metabolites were tentatively identified in human, rat, and dog: oxidative metabolite (M1, + 16 amu), oxidative ring opened metabolite (M2, + 32 amu), and dealkylated and oxidative metabolite (M3, -55 amu). No human unique metabolites were detected. <i>In vivo</i>, following PO administration of 3 mg/kg (200 µCi/kg) ¹⁴C-inavolisib to rats, GDC-0077 was the most abundant drug-related material in plasma and accounted for an average of 80.6% of extractable radioactivity from plasma. Circulating metabolites were M5 (imidazole ring cleavage) and M27 (- 29 Da) which accounted for an average of 7.3% and 3.6% of extractable radioactivity from plasma, respectively.
Excretion Determination of Mass Balance and Pharmacokinetics Following a Single Oral Administration of [¹⁴C]Inavolisib in Male and Female Sprague Dawley Rats. Study 17-2251/4.2.2.5 Excretion.
A PO dose of 3 mg/kg (200 µCi/kg) ¹⁴C-inavolisib was administered to rats. In intact rats, the primary route of elimination of radioactivity was in the feces (61.9% and 60.5% of the administered dose in male and female rats, respectively). A mean of 25.5% and 32.0% of the administered dose was recovered in the urine of male and female rats, respectively. In bile-duct cannulated (BDC) rats, the primary route of elimination of radioactivity was fecal (43.6% of the administered dose in males and an average of 37.7% in females). An average of 13.1% and 10.8% of the administered dose was recovered in the bile of BDC male and female rats, respectively. An average of 32.2% and 39.9% of the administered dose was recovered in the urine of BDC male and female rats, respectively. The sum of radioactivity recovered in urine and bile from BDC rats indicated that at least 45.3% and 50.7% of the oral dose had been absorbed in male and female rats, respectively.
Pharmacokinetic Drug-Drug Interactions In Vitro Evaluation of GDC-0077.1-5 as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes. Study 15-2967/4.2.1.4 PK Drug Interactions. In Vitro Evaluation of GDC 0077.1-5 as an Inhibitor of Cytochrome P450 (CYP) Enzymes in Human Liver Microsomes and Human Hepatocytes. Study 16-0806/4.2.1.4 PK Drug Interactions In Vitro Interaction Studies of GDC-0077 with human BCRP and MDR1 Efflux (ABC) Transporters and with human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 Uptake Transporters Interaction Studies of inavolisib with human BCRP and MDR1 Efflux (ABC) Transporters and with human MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 Uptake Transporters. Study 18-2263/4.2.1.4 PK Drug Interactions. Evaluation of inavolisib as a Substrate of human ABC Transporters MDR1 and BCRP and Human Solute Carriers (SLC) OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1 and MATE2K / 19-1182 / 4.2.2.6 Pharmacokinetic Drug Interactions OATP1B3, OCT1, OCT2, MATE1 and MATE2K. Study 19-1182/4.2.1.4 PK Drug Interactions.
Inavolisib was not a reversible inhibitor of any of the CYPs tested. It displayed mild metabolism-dependent inhibition of CYP3A4 and weak induction of CYP3A4. These results suggested a low likelihood of CYP-related DDI at clinically relevant concentrations. Inavolisib did not inhibit any of the transporters tested at clinically relevant concentrations. It was substrate of P-gp and BCRP but not a substrate of any of the other transporters tested.
TK data from general toxicology studies 4-week and 13-week repeat dose toxicology and toxicokinetic studies in rats (Studies 15-3303, 18-2456); and in dogs (Studies 15-3288, 18-2455)/4.2.3.2 Repeat-Dose Toxicity.
In general, exposures of inavolisib in dog and rat increased dose proportionally and were similar on Day 1 and after multiple administrations. In rats, exposure was approximately 2-fold higher in females than in males, whereas there were no sex-related differences in exposure in dogs.

Table 3: Applicant - Integrated Summary Table of AUC Parameters from GLP Toxicology Studies

		(ng · h/mL) RD (Study 15-3303) D1/D28		(ng · h/mL) RD (Study 18-2456) D1/D43/D86		(ng · h/mL) pEFD (Study 19-0593) GD7/GD17	(ng · h/mL) Genotox (Study 16-0989) D1	(h · ng/mL) Pig-a IMP (Study 21-1488) D29
Rat		M	F	M	F	F	F	F
		(1)	(1)	(1.5)	(1.5)	(0.6)	(5)	(5)
		98.9/152	333/338	288/375/325	537/568/545	246/256	2210	2220
(mg/kg dose)		(3)	(3)	(5)	(5)	(2)	(15)	(10)
AUC ₀₋₂₄		376/815	1250/1220	902/1300/1260	1700/2150/1790	1010/892	7620	3480
		(10)	(10)			(6)	(40)	(20)
		1290/3850	5480/6320			2020/2500	17100	8680
		(ng · h/mL) RD (Study15-3288) D1/D28		(ng · h/mL) RD (Study 18-2455) D1/D46/D91		(ng · h/mL) CV SPH (Study15-3293) Day 29		
Dog		M	F	M	F	M	F	
		(0.5)	(0.5)	(0.3)	(0.3)	(1)	(1)	
		828/837	900/956	439/403/456	514/567/670	1670	1230	
(mg/kg dose)		(1.5)	(1.5)	(1.5/1.0 ^a)	(1.5/1.0 ^a)	(3)	(3)	
AUC ₀₋₂₄		2380/2130	2770/1970	2470/1720/1100	2460/2870/1560	3420	6630	
		(5/3 ^b)	(5/3 ^b)					
		10,300/4750	11,900/6130					

AUC₀₋₂₄ = area under the concentration-time curve from Time 0 to 24 hours; CV = cardiovascular; D = day; F = female; GD = gestation day; Genotox = *in vivo* genotoxicity (4.2.3.3.2); IMP = impurities (4.2.3.7.6); pEFD = preliminary embryo-fetal development (4.2.3.5.2); M = male; PK = pharmacokinetic; RD = repeat dose (4.2.3.2); SPH = safety pharmacology (4.2.1.3); TK = toxicokinetic.

^a The dose for this group was lowered from 1.5 mg/kg to 1.0 mg/kg on Study Day 58 for males and Study Day 60 for females.

^b The dose for this group was lowered from 5 mg/kg to 3 mg/kg on Study Day 10, and TK samples were collected from this group on Study Days 1 and 21.

Table 4: Applicant - Integrated Summary Table of C_{max} Parameters from GLP Toxicology Studies

		(ng · h/mL) RD (Study 15-3303) D1/D28		(ng · h/mL) RD (Study 18-2456) D1/D43/D86		(ng · h/mL) pEFD (Study 19-0593) GD7/GD17	(ng · h/mL) Genotox (Study 16-0989) D1	(h · ng/mL) Pig-a IMP (Study 21-1488) D29
Rat		M	F	M	F	F	F	F
		(1)	(1)	(1.5)	(1.5)	(0.6)	(5)	(5)
(mg/kg dose)		33.1/41.3	92.9/94.9	62.6/68.8/63.3	94.5/106/150	43.4/46.3	481	419
		(3)	(3)	(5)	(5)	(2)	(15)	(10)
C _{max}		91.4/163	440/295	212/244/275	257/454/281	173/128	1480	632
		(10)	(10)			(6)	(40)	(20)
		213/793	1140/1500			389/432	1740	1270
		(ng · h/mL) RD (Study15-3288) D1/D28		(ng · h/mL) RD (Study 18-2455) D1/D46/D91		(ng · h/mL) CV SPH (Study15-3293) Day 29		
Dog		M	F	M	F	M	F	
		(0.5)	(0.5)	(0.3)	(0.3)	(1)	(1)	
(mg/kg dose)		148/170	177/184	82.5/72.4/74.6	84.3/99.7/93.9	335	263	
		(1.5)	(1.5)	(1.5/1.0 ^a)	(1.5/1.0 ^a)	(3)	(3)	
C _{max}		549/416	581/336	413/332/147	401/535/269	573	785	
		(5/3 ^b)	(5/3 ^b)					
		1860/1140	1940/1440					

C_{max} = maximum concentration observed; CV = cardiovascular; D = day; F = female; GD = gestation day; Genotox = *in vivo* genotoxicity (4.2.3.3.2); IMP = impurities (4.2.3.7.6); pEFD = preliminary embryo-fetal development (4.2.3.5.2); M = male; PK = pharmacokinetic; RD = repeat dose (4.2.3.2); SPH = safety pharmacology (4.2.1.3); TK = toxicokinetic.

^a The dose for this group was lowered from 1.5 mg/kg to 1.0 mg/kg on Study Day 58 for males and Study Day 60 for females.

^b The dose for this group was lowered from 5 mg/kg to 3 mg/kg on Study Day 10, and TK samples were collected from this group on Study Days 1 and 21.

Table 5: Applicant - Exposure Multiples in Pivotal Toxicology Studies

Species	Study Number	NOAEL, STD ₁₀ , HNSTD as Indicated	Dose (mg/kg)	AUC (ng • hr/mL)	Exposure Multiple ^a
Sprague-Dawley rat	18-2456	NOAEL	1.5	443	0.42 ×
	15-3303	STD ₁₀	10	3850 (M), 6320 (F)	3.6 × 6.0 ×
Beagle dog	18-2455	NOAEL	0.3	563	0.53 ×
	15-3288	HNSTD	1.5	2050	1.9 ×
Sprague-Dawley rat	19-0593	NOAEL (embryo-fetal development)	0.6	256	0.24 ×

AUC = area under the concentration-time curve; hr = hour; M = male; F = female; NOAEL = no-observed-adverse-effect level; STD₁₀ = Severely Toxic Dose in 10% of the animals; HNSTD = Highest Non-Severely Toxic Dose.

^a Based on AUC = 1060 ng • hr/mL at the 9 mg human dose (Study G039374).

The FDA's Assessment:

Overall, FDA agrees with the Applicant's interpretation of the ADME/PK data. To calculate the exposure multiples, FDA used the AUC of 1010 ng•h/mL at the recommended dose of 9 mg/day described in the PI for ITOVEBI. Exposure multiples used to support labeling are discussed in the relevant sections of this review.

See the clinical pharmacology Section 6 for information regarding human data and drug interaction studies.

5.5. Toxicology

5.5.1. General Toxicology

The nonclinical safety of inavolisib has been assessed in a comprehensive battery of toxicology studies, including single dose and repeat-dose general toxicology studies (once daily [QD] oral [PO] dosing) of up to 3 months duration in rats and dogs. The majority of findings identified in nonclinical toxicology studies were consistent with the anticipated pharmacologic effects of PI3K inhibition, including hyperglycemia 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 fibers in the eye in dogs. Findings were generally dose-dependent and reversible, and considered to be clinically monitorable and/or manageable. Lens fiber degeneration observed in some rats (≥ 3.6 times clinical AUC exposure of 1060 ng • hr/mL at 9 mg [determined from PK samples from Study G039374]) was considered irreversible.

A 4-Week Good Laboratory Practice (GLP) Toxicity Study of Inavolisib via Oral Administration in Sprague Dawley Rats with a 4 Week Recovery Period (Study 15-3303 / 4.2.3.2 Repeat Dose Toxicity):

Drug-related Findings:

- ≥ 1 mg/kg: Dose-dependent $\downarrow$ in body weight gain; mild $\downarrow$ monocytes (females), transient $\uparrow$ glucose with minimal-mild $\uparrow$ cholesterol; $\downarrow$ organ weights in pituitary gland, salivary gland, spleen, and liver; microscopic atrophy of mammary gland (minimal-moderate), pituitary gland (pars distalis, minimal), and mandibular salivary gland (minimal)
- ≥ 3 mg/kg: mild $\downarrow$ reticulocytes; minimal-mild $\uparrow$ creatinine, total bilirubin, globulins, and $\downarrow$ phosphorus, ALP; $\downarrow$ organ weights in thymus, prostate gland, uterus, thyroid gland, and kidney; minimal-mild $\downarrow$ hematopoiesis and minimal $\uparrow$ pigment-laden macrophages in spleen; minimal atrophy of Harderian gland (females), uterus, and vagina

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10 mg/kg: body weight loss and thin appearance; ↓platelets and eosinophils, ↑lymphocytes (males only); ↑ fibrinogen (males only); transient hyperglycemia and glucosuria; minimal-mild ↑BUN, ALT, AST and ↓potassium; ↓ organ weights in seminal vesicles, testes, epididymis, ovary, lung, and heart; microscopic atrophy in the exocrine pancreas (minimal-mild), prostate and seminal vesicles (minimal); minimal pancreatic islet hypertrophy and angiectasia; adverse bone marrow hypocellularity and eye lens fiber degeneration.

- At recovery necropsy, all findings had fully or partially recovered, except eye lens degeneration at 10 mg/kg.

13-Week GLP Multiple Dose Oral Gavage Toxicity and Toxicokinetic Study of Inavolisib in Sprague Dawley Rats with No Recovery (Study 18-2456 / 4.2.3.2 Repeat Dose Toxicity):

Drug-related Findings:

- Well tolerated up to 5 mg/kg.
- ≥ 1.5 mg/kg: dose-dependent ↓ in body weight gain; mild ↓ decreased red cell mass, leukocytes, lymphocytes, neutrophils; slight ↑ APTT; ↓ organ weights in the pituitary, prostate, thyroid, mandibular gland, spleen, and epididymis; very slight atrophy of pituitary gland (pars distalis), prostate gland; very slight ↑ in pigmented macrophages in the spleen
- 5 mg/kg: hyperglycemia and glucosuria; ↓ basophils and eosinophils; ↓ organ weights in the adrenal gland, liver, kidney (males), testis; very slight bone marrow hypocellularity; very slight-slight atrophy of exocrine pancreas and vagina; very slight ↓ in ovarian follicles; very slight ↓ cellularity of splenic red pulp; adverse interruption/alteration of estrus cycle in females

4-Week GLP Multiple Dose Oral Gavage Toxicity and Toxicokinetic Study of Inavolisib in Dogs with a 4-Week Recovery Phase (Study 15-3288 / 4.2.3.2 Repeat Dose Toxicity):

Drug-related Findings:

- Tolerated up to 1.5 mg/kg; Intolerability at 5/3 mg/kg due to multi-organ, ocular inflammation.
- ≥ 0.5 mg/kg: Dose-dependent body weight loss; abnormal feces; transient hyperglycemia; minimal-mild ↓ BUN; ↓ thymus weight; minimal mixed cell inflammation in the esophagus and rectum and ↑ incidence of neutrophils in mandibular lymph node with correlating minimal-mild ↑ neutrophils, fibrinogen; slight-moderate lymphoid depletion.
- ≥ 1.5 mg/kg: vomitus, thin appearance; glucosuria; mild ↓ reticulocytes; minimal ↓ creatinine; minimal-mild ↑ cholesterol; ↓ phosphorus; ↑ liver weights (males); minimal-marked multi-organ inflammation (gastrointestinal tract, mandibular lymph node, eyes, blood vessels, gall bladder, urinary bladder), with correlating ↑ cellularity of the bone marrow and minimal-mild ↑ monocytes; slight ↑ in the liver; minimal-slight inspissation of seminiferous tubules in the testis.
- 5/3 mg/kg: ophthalmic anterior segment inflammation; ↑ body temperature; minimal ↑ AST, minimal-moderate ↑ ALT, ALP, GGT; mild ↑ bilirubin; minimal ↓ red cell mass, RDW; minimal-mild ↑ WBC, lymphocytes, platelets; ↓ albumin, albumin:globulin ratio, ↑ globulin; morbidity due to multi-organ inflammation (eyes, lung, heart, liver); multinucleated spermatids in testis and epididymal degeneration and necrosis.
- At recovery necropsy, all findings exhibited reversibility with the exception of inspissation of seminiferous tubules in the testis

13-week GLP Multiple Dose Oral Gavage Toxicity and Toxicokinetic Study of GDC-0077 in Dogs with 12-Week Recovery (18-2455 / 4.2.3.2 Repeat Dose Toxicity):

Drug-related Findings:

- Intolerability at 1.5/1.0 mg/kg due to body weight loss and marked hyperglycemia.
- 0.3 mg/kg: mild ↑ platelets (females); very slight lens fiber swelling in the eye.
- 1.5/1.0 mg/kg: reddish conjunctiva; body weight loss; ophthalmologic opacity at posterior capsule/cortex of the lens of the eye without microscopic correlates; hyperglycemia with associated glucosuria, ↑ urine volume, hypertrophy/vacuolation of pancreatic islet cells, and, in one animal, centrilobular vacuolation/degeneration in the liver, tubular vacuolation in the kidney, and vacuolation of the lens of the eye; mild ↑ ALP, mild ↓ BUN, creatinine; mild-moderate platelets; and very slight-slight focal inflammation in tongue, rectum, and eyes accompanied with clinical pathology changes consistent with inflammation (↑ globulins, WBC, neutrophils, monocytes, fibrinogen and ↓ albumin/globulin ratio, albumin).
- At recovery necropsy (males only), all inavolisib-findings demonstrated full reversibility

The FDA's Assessment:

In general, FDA agrees with the Applicant's summary of the results from the toxicology studies. Additional data and discussions are provided below.

4-Week rat study (Study 15-3303):

The histopathology finding in the eye included minimal lens degeneration in 2/10 female rats and retina rosette in 1/10 female rats at 10 mg/kg/day (6.3 times the human exposure at the recommended dose of 9 mg/day based on AUC). At the recovery necropsy, mild lens

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degeneration in the eye was observed in 1/4 male rats at 10 mg/kg/day (3.8 times the human exposure at the recommended dose of 9 mg/day based on AUC on Day 28).

13-Week rat study (Study 18-2456)

Study initiation date: January 29, 2019
 Duration: 13 Weeks
 GLP compliance: Yes
 Drug, lot#, and % purity: GDC-0077, lot # 68878-287, 98.9% purity

Methods

Doses: 0, 1.5, 5 mg/kg/day GDC-0077
 Frequency of dosing: Once daily
 Number/Sex/Group: 10
 Dose volume: 5 mL/kg
 Formulation/Vehicle: 0.5% w/v Methylcellulose (MC) in water for injection
 Route of administration: Oral gavage
 Species/Strain: Rat/ Crl:CD(SD)
 Age: 9 Weeks (at dosing)
 Comment on Study Design and Conduct: Recovery groups were not included in the study.
 Dosing Solution Analysis: Acceptable for concentration and homogeneity.

Observations and Results (Necropsy)

Parameters	Major Findings						
Organ Weights	≥ 1.5 mg/kg/day: statistically significant decreases in organ weights (relative to brain weights) were noted in the pituitary, mandibular gland, spleen, kidney, epididymides, prostate, and thyroid. 5 mg/kg/day: statistically significant decreases in organ weights (relative to brain weights) were noted in the adrenal, liver, and testis.						
Gross Pathology	Unremarkable						
Histopathology Adequate Battery: Yes	Terminal Necropsy						
	N=10/group	Males (mg/kg/day)			Females (mg/kg/day)		
		0	1.5	5.0	0	1.5	5.0
	Aorta Inflammation, chronic, adventitia <i>Slight</i>						1
Bone marrow, femur Decreased cellularity <i>Very slight</i>			5			8	
Bone marrow, sternum Decreased cellularity <i>Very slight</i>						2	

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	Esophagus Fibrosis, submucosa <i>Slight</i>						1
	Inflammation, chronic, serosa <i>Slight</i>						1
	Inflammation, granulomatous, serosa <i>Very slight</i>						1
	Heart Inflammation, chronic, epicardium <i>Slight</i>						1
	Kidneys Basophilia <i>Very slight</i>		1	1			
	Ovaries Decreased, follicle <i>Very slight</i>						3
	Pancreas Depletion, zymogen granule, diffuse <i>Very slight</i> <i>Slight</i>	1	1	1 2			3 1
	Pituitary Decreased cell cytoplasm, pars distalis <i>Very slight</i>		1	5		4	7
	Prostate gland Decreased size/secretion, lobular <i>Very slight</i>		2	5	N/A	N/A	N/A
	Spleen Decreased cellularity, red pulp, erythroid <i>Very slight</i> Increased pigmented macrophage, brown, red pulp <i>Very slight</i>					7	5 10
	Vagina Atrophy, mucosal epithelium <i>Very slight</i>	N/A	N/A	N/A			3
	Estrous cycle stage						
	Diestrus	N/A	N/A	N/A	2	4	4
Estrus				2			
Metestrus				3			
Proestrus				3	6	3	
Undetermined						3	
N/A: Not applicable							

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- Histopathology findings in the bone marrow and splenic red pulp correlated with changes in hematology parameters in clinical pathology. Findings in the pituitary and prostate correlated with decreases in organ weights. Other histopathology findings were of unknown significance based on minimal change, low incidence, or possible relationship to dosing procedure (e.g., findings in esophagus).
- All the female rats at 5 mg/kg/day were either in diestrus or proestrus, suggesting an interruption or alteration in the estrus cycle.

13-Week dog study (Study 18-2455)

Study initiation date: January 25, 2019
Duration: 13 Weeks
GLP compliance: Yes
Drug, lot#, and % purity: GDC-0077, lot # 68878-287, 98.9% purity

Methods

Doses: 0, 0.3, 1.5/1.0 mg/kg/day
Frequency of dosing: Once daily
Number/Sex/Group: 3 (terminal); 3 (recovery at 0 and 1.5/1.0 mg/kg/day only)
Dose volume: 5 mL/kg
Formulation/Vehicle: 0.5% w/v Methylcellulose (MC) in water for injection
Route of administration: Oral gavage
Species/Strain: Dog/Beagle
Age: 11 to 14 Months old (at initiation of acclimation)
Comment on Study Design and Conduct: Based on findings of body weight loss, marked hyperglycemia, and reddish conjunctiva in one female animal, the dose for Group 3 was reduced from 1.5 mg/kg/day to 1.0 mg/kg/day beginning on Study Day 58 for males and Study Day 60 for females.
Recovery was limited to males only to evaluate testicular findings that were observed in the previously conducted 28-day toxicity study in dogs.
Dosing Solution Analysis: Acceptable for concentration and homogeneity (except for the 0.3 mg/kg/day formulation on Day 91 [76.6% - 80.6% of nominal which was outside the acceptance criteria of 100.0% ± 15.0%]).

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Select Observation and Results							
Parameters	Major Findings						
Semen Analysis	1.5/1.0 mg/kg/day: reversible decreased mean sperm count (0.2x) compared to control group at the end of dosing period.						
Organ Weights	Unremarkable						
Gross Pathology	1.5/1.0 mg/kg/day: reversible white discoloration of the external medulla of kidneys and enlarged liver.						
Histopathology Adequate Battery: Yes	Terminal Necropsy						
	N=3/group	Males (mg/kg/day)			Females (mg/kg/day)		
		0	0.3	1.5/1.0	0	0.3	1.5/1.0
	Adrenals Vacuolation, zona glomerulosa cell, diffuse <i>Very slight</i>						1
	Vacuolation, zona reticularis cell, diffuse <i>Very slight</i>						1
	Eyes Infiltrate, neutrophil, stroma, corneal-limbal junction, unilateral <i>Very slight</i>			2			
	Swelling, lens fiber, equatorial region, bilateral <i>Very slight</i>		1	1		1	1
	Vacuolation, lens cortex, equatorial region, bilateral <i>Slight</i>						1
	Lacrimal glands Vacuolation, acinar cell, diffuse <i>Slight</i>						1
	Liver Vacuolation/degeneration, hepatocyte, centrilobular <i>Moderate</i>						1
	Pancreas Hypertrophy/vacuolation, islet cell, diffuse <i>Very slight</i> <i>Slight</i>			1 1			1
	Prostate Gland Atrophy, acinus, focal/multifocal <i>Very slight</i> <i>Slight</i>		2	2 1	N/A	N/A	N/A
	Testes Hypoplasia, seminiferous tubule, focal <i>Very slight</i>		1	1	N/A	N/A	N/A
Thymus Cyst Decreased size, cortex/medulla <i>Slight</i> <i>Moderate</i> <i>Marked</i>	2 1 1	1 3	3 1 2		1 2	3 1 1	

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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	Thyroid Carcinoma, squamous cell			1		
	N/A: Not applicable					
	Recovery Necropsy					
			Males (mg/kg/day)		Females (mg/kg/day)	
	N=3/group		0	1.5/1.0	0	1.5/1.0
	Epididymides Arteriolitis/periarteriolitis chronic, focal <i>Very slight</i>			1	N/A	N/A
	Prostate gland Dilatation, cystic, acinus <i>Very slight</i>			2	N/A	N/A
	Testes Arteriolitis/periarteriolitis chronic, focal <i>Very slight</i>			1	N/A	N/A
	Hypoplasia, seminiferous tubule, focal <i>Very slight</i>			1		
	N/A: Not applicable					

5.5.2. Genetic Toxicology

The Applicant's Position: Inavolisib was considered not mutagenic in *S. typhimurium* strains (TA98, TA100, TA1535, and TA1537) or *E. coli* (WP2 uvrA) in the absence or presence of an exogenous metabolic activation system (S-9) (GLP Studies 15-3356 and 16-1286/4.2.3.3.1 *In Vitro* Genotoxicity).

Inavolisib induced micronuclei *in vitro* in human peripheral blood lymphocytes (via a clastogenic mechanism) at concentrations $\geq 180 \mu\text{g/mL}$ in the absence of a rat liver metabolic activation system (S-9) when tested for 24 + 24 hours (incubation plus recovery), with the no-effect level between 120 and 180 $\mu\text{g/mL}$. Inavolisib did not induce micronuclei when tested up to the limit of solubility (350 $\mu\text{g/mL}$) for 3 + 21 hours in the absence or presence of S-9 (GLP Study 15-3357/4.2.3.3.1 *In Vitro* Genotoxicity).

There was no evidence of inavolisib-induced clastogenicity or aneugenicity in polychromatic erythrocytes of the bone marrow, or DNA damage in the liver of female Sprague-Dawley rats (which showed higher exposure than males) up to the MTD of 40 mg/kg, with a corresponding Day 1 C_{max} of 1740 ng/mL and area under the concentration–time curve from 0 to 24 hours (AUC_{0-24}) of 17,100 ng hr/mL ($\sim 16.1\times$ clinical exposure at 9 mg) (GLP Study 16-0989/4.2.3.3.1 *In Vivo* Genotoxicity).

The FDA's Assessment:

FDA agrees that inavolisib was not mutagenic in the Ames Assay. In Study 15-3356, inavolisib showed weak evidence of inducing mutation in strain TA98 of *Salmonella typhimurium* only in the presence of S-9. Treatment of strain TA98 in the presence of S-9 at 1600 $\mu\text{g/plate}$ and

above resulted in an increase in revertant numbers that was 2.1-fold the concurrent control in Experiment 1 and up to 1.9-fold the concurrent control in Experiment 2. The increase in revertant numbers in Experiment 2 did not reach 2.0-fold but was concentration-related and reproducible and is, therefore, considered evidence of weak mutagenic activity in this strain. As a follow-up, the Applicant conducted another Ames assay (study 16-1286) with inavolisib in strain TA98 in the presence of S-9 using lots G02967907.1-20 (same lot as in study 15-3356, purity 98.1%) and 60470-32 (purified lot, purity 100%) in both plate incorporation and pre-incubation methodologies. No increase in revertant numbers $\geq 2x$ the concurrent vehicle control was observed using either the plate incorporation or pre-incubation method for either lot of inavolisib.

FDA agrees that inavolisib was clastogenic in an in vitro human lymphocyte micronucleus assay and that inavolisib was not genotoxic in an in vivo rat bone marrow micronucleus assay and did not induce DNA break in a liver comet assay.

5.5.3. Carcinogenicity

The Applicant's Position: Inavolisib is intended for the treatment of patients with advanced cancer. In accordance with ICH S9 guidance on the Nonclinical Evaluation for Anticancer Pharmaceuticals ([ICH 2009](#)), no carcinogenicity studies were conducted.

The FDA's Assessment:

FDA agrees that carcinogenicity studies are not warranted to support the proposed indication in patients with advanced cancer in accordance with ICH S9 guidance.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position: The embryo-fetal development study in rats identified inavolisib-related dose dependent effects on embryo-fetal development ($\geq 0.8 x$) that included decreases in fetal body weight and placental weight, post-implantation loss, lower fetal viability, and teratogenicity (fetal external, visceral, and skeletal malformations) (Study 19-0593).

The ICH S9 guidance ([ICH 2009](#)) states that studies on (1) fertility and early embryonic development and (2) pre- and postnatal toxicology are not warranted to support marketing authorization applications for pharmaceuticals intended for the treatment of patients with advanced cancer, such as inavolisib. Accordingly, such studies were not performed.

Assessment of male and female reproductive organ was conducted as a part of the 4- and 13-week toxicity studies in rats and dogs (Studies 15-3303, 15-3288, 18-2456, and 18-2455/4.2.3.2 Repeat Dose Toxicity). 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 ($\geq 0.4 x$, Study 15-3303). In the 1-month toxicity study in dogs, focal

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inspissation of seminiferous tubule contents and multinucleated spermatids in the testis and epithelial degeneration/necrosis in the epididymis were observed (≥ 2.0 x, Study 15-3288). However, there were no inavolisib-related microscopic findings in the testes or epididymides or effects on sperm concentration, motility, or morphology in the 3-month dog toxicity study at similar exposures (Study 18-2455). In female rats, minimal to mild and reversible atrophy in the uterus and vagina and decreased ovarian follicles were observed (≥ 1.1 x) in the 4-week rat toxicity study (Study 15-3303); and findings suggestive of an interruption/alteration of the estrus cycle were observed (≥ 1.5 x) in the 3-month rat toxicity study (Study 18-2456).

<u>A GLP Preliminary Embryo-fetal Development Study of GDC-0077 by Oral Gavage in Sprague Dawley Rats (19-0593 / 4.2.3.5.2 Embryo-fetal Development):</u> Drug-related Findings: • Maternal ≥ 2 mg/kg: non-adverse lower body weight gain and transient glucose increases. • Embryo-fetal development: ○ ≥ 2 mg/kg: adverse decreases in fetal body weight and placental weight ○ 6 mg/kg: higher post-implantation loss, lower fetal viability, and teratogenicity (external, visceral, and skeletal malformations, increased skeletal and visceral variations, delayed skeletal ossifications).

The FDA’s Assessment:

FDA agrees with the Applicant’s summary of the study results described above.

FDA also agrees that fertility and early embryonic development and pre- and postnatal toxicology studies are not warranted to support the proposed indication in patients with advanced cancer in accordance with ICH S9 guidance.

Additional study results are included in the table below.

Parameters	Major Findings																																																																					
Maternal Body Weights	<u>2 mg/kg/day</u>: statistically significant decreases in group mean body weight gain (-21.5% of control on GDs 0 - 20) and group mean body weights (-8% of control on GD 20) were noted. <u>6 mg/kg/day</u>: statistically significant decreases in group mean body weight gain (-37.6% of control on GDs 0 - 20) and group mean body weights (-14% of control on GD 20) were noted.																																																																					
Litter Data (GD20)	<table border="1"> <thead> <tr> <th>Dose</th> <th>Control</th> <th>0.6</th> <th>2</th> <th>6</th> </tr> </thead> <tbody> <tr> <td>No. of Dams</td> <td>9</td> <td>9</td> <td>8</td> <td>8</td> </tr> <tr> <td>Embryo/Fetus Deaths</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>No. of embryo-fetal deaths</td> <td>0.4</td> <td>1.0</td> <td>1.8</td> <td>3.0**</td> </tr> <tr> <td>Postimplantation loss rate (%)</td> <td>2.8</td> <td>6.8</td> <td>11.8</td> <td>19.3**</td> </tr> <tr> <td>Implantation Site (%)</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> <td>1.6</td> </tr> <tr> <td>Placental Remnant (%)</td> <td>0.8</td> <td>6.8</td> <td>11.8</td> <td>16.1**</td> </tr> <tr> <td>Dead fetus (%)</td> <td>0.0</td> <td>0.0</td> <td>0.0</td> <td>1.5</td> </tr> <tr> <td>Live Fetus</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>No. of live fetuses</td> <td>14.8</td> <td>13.3</td> <td>13.8</td> <td>12.1*</td> </tr> <tr> <td>Fetal viability rate</td> <td>97.2</td> <td>93.2</td> <td>88.3</td> <td>81.0**</td> </tr> <tr> <td>Sex ratio (Male/Total)</td> <td>0.606</td> <td>0.552</td> <td>0.424*</td> <td>0.454</td> </tr> <tr> <td>Body weight (g)</td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>					Dose	Control	0.6	2	6	No. of Dams	9	9	8	8	Embryo/Fetus Deaths					No. of embryo-fetal deaths	0.4	1.0	1.8	3.0**	Postimplantation loss rate (%)	2.8	6.8	11.8	19.3**	Implantation Site (%)	0.0	0.0	0.0	1.6	Placental Remnant (%)	0.8	6.8	11.8	16.1**	Dead fetus (%)	0.0	0.0	0.0	1.5	Live Fetus					No. of live fetuses	14.8	13.3	13.8	12.1*	Fetal viability rate	97.2	93.2	88.3	81.0**	Sex ratio (Male/Total)	0.606	0.552	0.424*	0.454	Body weight (g)				
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	Male Female Placental weight (g) Male Female	3.79 3.52 0.5 0.48	3.52* 3.32 0.49 0.47	2.95** 2.78** 0.42** 0.42	2.35** 2.30** 0.40** 0.40*
* P<0.05; ** P<0.01: Significantly different from control					
External Findings in Fetus and Placental Findings	Dose	Control	0.6	2	6
	No. of Dams	9	9	8	8
	No. of fetuses	133	120	110	97
	External Findings (%)				
	Malformations	0.00 [0]	0.00 [0]	0.00 [0]	13.63 [13]*
	Anasarca	0.00 [0]	0.00 [0]	0.00 [0]	5.10 [5]
	Local edema	0.00 [0]	0.00 [0]	0.00 [0]	6.35 [6]
	Absent eye bulge	0.00 [0]	0.00 [0]	0.00 [0]	4.31 [4]
	Narrowed tail	0.00 [0]	0.00 [0]	0.00 [0]	1.04 [1]
	Short tail	0.00 [0]	0.00 [0]	0.00 [0]	0.96 [1]
No. of placentae	133	120	110	97	
Placental Findings					
Abnormalities (%)	0.00	0.00	0.00	0.00	
[]: No. of fetuses with findings * P<0.05: Significantly different from control					
Visceral Findings	Dose	Control	0.6	2	6
	No. of Dams	9	9	8	8
	No. of fetuses	64	57	53	46
	Malformations (%)				
	Mean frequencies	0.00 [0]	0.00 [0]	0.00 [0]	13.34 [6]
	Microphthalmia	0.00 [0]	0.00 [0]	0.00 [0]	9.18 [4]
	Membranous ventricular septum defect	0.00 [0]	0.00 [0]	0.00 [0]	2.09 [1]
	Persistent A-V canal	0.00 [0]	0.00 [0]	0.00 [0]	2.09 [1]
	Interrupted aortic arch	0.00 [0]	0.00 [0]	0.00 [0]	2.09 [1]
	Variations (%)				
	Mean frequencies	1.23 [1]	3.44 [2]	0.00 [0]	28.45* [42]
	Thymic remnant in neck	1.23 [1]	1.86 [1]	0.00 [0]	0.00 [0]
	Dilated renal pelvis	0.00 [0]	1.59 [1]	0.00 [0]	28.45** [13]
	Convoluted ureter	0.00 [0]	0.00 [0]	0.00 [0]	4.29 [2]
	Dilated ureter	0.00 [0]	1.59 [1]	0.00 [0]	15.00 [7]
[]: No. of fetuses with malformations/variations * P<0.05, ** P<0.01: Significantly different from control					
Skeletal Findings	Dose	Control	0.6	2	6
	No. of Dams	9	9	8	8
	No. of fetuses	69	63	57	51
	Malformations (%)				
	Mean frequencies	0.00 [0]	0.00 [0]	0.00 [0]	50.95** [26]
	Supraoccipital hole(s)	0.00 [0]	0.00 [0]	0.00 [0]	5.00 [2]
	Fused thoracic arch	0.00 [0]	0.00 [0]	0.00 [0]	11.01 [6]
	Kyphosis of vertebral column	0.00 [0]	0.00 [0]	0.00 [0]	48.45** [25]
	Variations (%)				
	Mean frequencies	10.28 [7]	17.63 [11]	25.94 [15]	83.03** [42]
	Full supernumerary rib	0.00 [0]	0.00 [0]	4.69 [3]	5.96 [3]
	Short supernumerary rib	8.89 [6]	12.08 [0]	12.50 [8]	38.34** [20]
Wavy rib	0.00 [0]	0.00 [0]	5.21 [3]	54.54** [27]	
	1.39 [1]	1.39 [1]	4.59 [2]	1.79 [1]	

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	Dumbell ossification of thoracic centrum	0.00 [0]	4.17 [3]	5.21 [3]	13.94* [7]
	Splitting of thoracic centrum				
	No. of ossified				
	Sternebrae	5.44	5.22	4.86	2.04**
	Sacral and caudal vertebrae	7.79	7.78	7.50	5.46**
[]: No. of fetuses with malformations/variations * P<0.05, ** P<0.01: Significantly different from control					
Toxicokinetics	GD	Dose Level (mg/kg/day)	C _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₂₄ (ng·h/mL)
	7	0.6	43.4	1.00	246
		2	173	1.00	1010
		6	389	1.00	2020
	17	0.6	46.3	2.00	256
2		128	2.00	892	
6		432	2.00	2500	
Animal-to-Human AUC Ratio	AUC at 2 mg/kg on GD 17 (892 ng·h/mL) was approximately 0.9 times the exposure in humans at the recommended dose of 9 mg (AUC = 962 ng·h/mL from the pivotal clinical study WO41554 in the ITT patient population).				

5.5.5. Other Toxicology Studies

Phototoxicity

The Applicant's Position: The phototoxic potential of inavolisib was assessed in a GLP neutral red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts (16-1227 / 4.2.3.7.7). Inavolisib did not reduce the viability of 3T3 cells exposed to ultraviolet radiation as compared with that in the absence of ultraviolet radiation up to the highest concentration tested of 31.6 µg/mL. Therefore, it was concluded that inavolisib did not show phototoxicity potential in this assay.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Evaluation of Degradant

The Applicant's Position: (b) (4) is a degradant (b) (4) mutagenic in the bacterial mutagenesis assay (Study 1107383). However, in the 28-day rat Pig-a gene mutation assay with inavolisib, there were no biologically relevant increases in Pig-a gene mutation in either mature erythrocytes or immature reticulocytes in the peripheral blood up to 20 mg/kg, MTD under the assay conditions employed (Study 21-1488 / 4.2.3.7.6 Impurities). The use of inavolisib in the

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rat *Pig-a* assay is justified, as the AUC ratio of (b) (4) to inavolisib was approximately 2.5% in rat plasma (Study 21-1488). In contrast, in humans, circulating metabolites were minimal with the majority (99.5%) of drug related material being inavolisib (See 2.6.4 Pharmacokinetic Written Summary, Section 5, and 2.7.2 Summary of Clinical Pharmacology Studies, Section 2.3.1.2) (Study 22-0069 [5.3.2.2, Other Human Biomaterials]; GP42652/5.3.4.1 Healthy Subject PD and PK/PD). Thus, inavolisib and (b) (4) (at clinically relevant circulating exposure) do not pose biologically relevant mutagenic risks in mammals *in vivo*.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Impurities (Including Mutagenic Impurities)

The Applicant's Position: Impurities in the drug substance (inavolisib) and drug product are controlled according to ICH Q3A and ICH Q3B, respectively. All specified and unspecified impurities in the drug substance are controlled with individual acceptance criteria lower than or equal to the ICH Q3A qualification threshold, except for impurities (b) (4) (b) (4) were qualified in a 28-day GLP toxicity study (15-3288/4.2.3.2 Repeat-Dose Toxicity) that justifies higher limits than the ICH Q3A qualification threshold. Degradation products are controlled in the drug product with individual acceptance criteria lower than or equal to the ICH Q3B qualification threshold. Refer to Module 3, 3.2.P.5.6 Justification of Specification(s).

In silico mutagenicity assessments were conducted with inavolisib and impurities of inavolisib using standard *in silico* structure–activity relationship software programs Derek for Nexus[®] (Version 6.1.0) and Leadscape Statistical bacterial mutation model (Version 2) in combination with expert review. One impurity (b) (4) was shown to be experimentally non-mutagenic in a 5-strain non–GLP compliant bacterial reverse mutation assay (Study 15-3392/4.2.3.7.6).

The FDA's Assessment:

FDA agrees with Applicant's position. Additional details are provided below.

An internal CDER (Q)SAR consult showed that (b) (4) is predicted to be negative for bacterial mutagenicity. (b) (4) was predicted to be positive for bacterial mutagenicity by Derek Nexus 6.3.0. However, it was not mutagenic in a non-GLP compliant Ames assay, and it showed a negative prediction for mutagenicity by CASE Ultra 1.9.0.8 GT1.BMUT model 1.9.0.2 and equivocal prediction by Leadscape Model Applier 2023.0.0-12 Bacterial Mut v2 model (LMA).

(b) (4) was detected in higher amounts during process development and in development

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batches. The Applicant proposed the limit of (b) (4) % w/w based on qualification of this impurity in the GLP-compliant 4-week toxicology study in dogs. (b) (4) was not mutagenic in a non-GLP-compliant Ames assay. (b) (4) was present at (b) (4) area% in inavolisib Batch G02967907.1-20 used in the 28-day GLP repeat-dose toxicology studies in rats (15-3303) and dogs (15-3288). In these studies, (b) (4) was qualified up to (b) (4) mg/kg/day ((b) (4) mg/day HED based on a 60-kg patient) and (b) (4) mg/kg/day ((b) (4) mg/day HED based on a 60-kg patient), based on the highest dose levels of 3 mg/kg/day inavolisib and 1.5 mg/kg/day inavolisib administered to rats and dogs, respectively. All finding at these dose levels were reversible except for necropsy findings of inspissation of seminiferous tubules in the testis in dogs. The maximum proposed daily dose of inavolisib is 9 mg/day and the proposed specification limit of (b) (4) % w/w is predicted to result in a maximum daily intake of (b) (4) mg/day of the impurity (b) (4). The potential maximum intake of (b) (4) is below the levels qualified in the GLP-compliant 4-week studies in dogs.

The Applicant proposed the limit of (b) (4) % w/w based on qualification of this impurity in the GLP-compliant repeat-dose toxicology study in dogs (15-3288). (b) (4) was present at (b) (4) area% in inavolisib Batch G02967901.1-20 used in the 28-day GLP repeat-dose toxicology studies in rats (15-3303) and dogs (15-3288). In these studies, (b) (4) was qualified up to (b) (4) mg/kg/day ((b) (4) mg/day HED based on a 60-kg patient) and (b) (4) mg/kg/day ((b) (4) mg/day HED based on a 60-kg patient), based on the highest dose levels of 3 mg/kg/day inavolisib and 1.5 mg/kg/day inavolisib administered to rats and dogs, respectively. The maximum proposed daily dose of inavolisib is 9 mg/day and the proposed specification limit of (b) (4) % w/w is predicted to result in a maximum daily intake of (b) (4) mg/day of the impurity (b) (4). The potential maximum intake of (b) (4) is below the levels qualified in the GLP-compliant 4-week studies in rats and dogs.

X

X

Primary Reviewer
Haw-Jyh Chiu, PhD

Acting Team Lead
Nikolett Biel, PhD

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant is seeking approval of inavolisib

(b) (4)

The proposed recommended dosage is inavolisib 9 mg orally (PO) once daily (QD) in combination with palbociclib and fulvestrant at their approved recommended dosages.

The clinical pharmacology review addressed the following three key review issues:

Dosage Acceptability: Although the clinical pharmacology review concluded that the proposed dosage is approvable from the clinical pharmacology perspective, the proposed dosage of inavolisib 9 mg PO QD may not be optimized due to 1) high rates of adverse events (AEs) and dose modifications, 2) positive exposure-response (E-R) relationships for safety, 3) limited clinical data at lower dosages, and 4) lack of E-R relationships for efficacy in patients who received the proposed dosage in combination with palbociclib and fulvestrant.

Intrinsic Factors: Dosage reduction is recommended for patients with moderate renal impairment. A postmarketing requirement (PMR) will be issued for the complete study report (CSR) and datasets for the ongoing renal impairment study to include evaluation of severe renal impairment. FDA cannot rule out >20% contribution of hepatic elimination; therefore, a PMR will be issued for a dedicated hepatic impairment study. Lastly, there was underrepresentation of patients from diverse racial and ethnic groups including Black/African American or Hispanic/Latino patients in the inavolisib development program. A postmarketing commitment (PMC) to evaluate inavolisib in a diverse patient population representative of the US population will include collection of clinical pharmacology data to assess potential impacts of race and ethnicity on inavolisib pharmacokinetics (PK) and pharmacodynamics (PD).

DDI Potential: There is low risk for CYP-based DDIs for inavolisib as an object given the lack of CYP enzyme metabolism. However, in vitro studies showed that inavolisib is a time-dependent inhibitor of CYP3A and inavolisib induces CYP3A and CYP2B6. PMCs will be issued to evaluate inavolisib clinical induction potential on CYP3A and CYP2B6. Depending on the results of the CYP3A study, additional studies may be warranted to evaluate the potential for inavolisib to induce CYP2C enzymes and interaction with combined oral contraceptives (COC).

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 219249. This NDA is approvable from a Clinical Pharmacology perspective. The key review issues with specific recommendations/comments are summarized in **Table 6**. Clinical Pharmacology PMRs and PMCs are summarized in **Table 7**.

Table 6: Key Clinical Pharmacology Review Issues, Recommendations and Comments

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
Pivotal evidence of effectiveness	The primary evidence of effectiveness comes from the Phase 3 randomized, placebo-controlled trial (WO41554) in patients with <i>PIK3CA</i> -mutant, HR+/HER2- locally advanced or metastatic breast cancer. The study met the primary endpoint for improvement in progression-free survival (PFS) with a 7.7 month improvement in median PFS (15.0 months for inavolisib + palbociclib + fulvestrant vs 7.3 months for placebo + palbociclib + fulvestrant). See Section 8.1.2 for details.
General dosing instructions	The recommended dosage is inavolisib 9 mg PO QD with or without food in combination with palbociclib and fulvestrant at their approved recommended dosages.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Renal impairment: Reduce the inavolisib starting dosage to 6 mg PO QD in patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to <60 mL/min). No dosage modification is recommended in patients with mild renal impairment (eGFR 60 to <90 mL/min). A dedicated renal impairment study is ongoing to evaluate the safety and PK of inavolisib in participants with severe renal impairment (eGFR <30 mL/min); a PMR will be issued for the CSR and datasets from this study. • Hepatic impairment: No dosage modification is recommended in patients with mild hepatic impairment (total bilirubin > upper limit of normal (ULN) to ≤ 1.5 x ULN or AST > ULN and total bilirubin ≤ ULN). The PK and safety of inavolisib in patients with moderate or severe hepatic impairment has not been characterized. A PMR will be issued for a hepatic impairment study to identify a safe dosage of inavolisib in patients with moderate or severe hepatic impairment. • Race and ethnicity: The majority of patients who received inavolisib and had PK data available were White (224/336; 66.7%), Asian (62/336; 18.5%), or Unknown (45/336; 13.4%) race. Few patients were Black/African American (4/336; 1.2%), Hispanic/Latino (14/336, 4.2%), or other underrepresented minority populations. A PMC will be issued to evaluate inavolisib in a diverse patient population more representative of the US population. Clinical pharmacology data will be collected in the PMC study (or

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	studies) to evaluate the effects of race and ethnicity on the PK and PD of inavolisib. PIK3CA mutations: The results suggested that inavolisib plus palbociclib and fulvestrant treatment is effective for patients regardless of PIK3CA mutated exon status.
Drug-drug interactions (DDI)	Two PMCs will be issued to conduct clinical study/studies to address the induction potential of inavolisib on CYP3A and CYP2B6. If the induction potential of inavolisib on CYP3A is confirmed, the Applicant may need to address the induction potential of inavolisib on CYP2C enzymes and DDI potential between inavolisib and COCs.
Bridge between the to be marketed and clinical trial formulations	The Applicant utilized dissolution studies to bridge the to-be-marketed and clinical trial formulations. Refer to the Biopharmaceutics Review for details.
Labeling	FDA labeling revisions per regulations and FDA guidances were provided. Overall, the proposed labeling language in the Clinical Pharmacology pertinent sections are generally acceptable upon the Applicant's agreement to the FDA revisions.

Table 7: Outstanding Clinical Pharmacology Issues

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMR	Dosage optimization	Dosage not optimized due to - High rates of AEs and dosage modifications - Positive E-R relationships for safety - Limited clinical data at lower dosages - Lack of E-R relationships for efficacy	Evaluate the PK/PD, safety, and efficacy of inavolisib at a lower dosage in patients with <i>PIK3CA</i> -mutant, HR+/HER2-locally advanced or metastatic breast cancer
PMR	Renal impairment	A dedicated renal impairment study is ongoing but results in patients with severe renal impairment were not available during the current review cycle. This PMR will request submission of the CSR and datasets to support dosage	Evaluate the safety and PK of inavolisib in subjects with severe renal impairment

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		recommendation in patients with severe renal impairment.	
PMR	Hepatic impairment	Cannot rule out >20% contribution of hepatic elimination and inavolisib was not studied in a sufficient number of patients with moderate or severe hepatic impairment	Evaluate the safety and PK of inavolisib in subjects with moderate and severe hepatic impairment
PMC	Diversity	Lack of representation of patients from racial and ethnic groups including Black/African American and Hispanic/Latino patients	Evaluate the PK/PD, safety, and efficacy of inavolisib in patients with <i>PIK3CA</i> -mutant, HR+/HER2- locally advanced or metastatic breast cancer that are representative of the US patient population
PMC	CYP3A induction	Inavolisib induces CYP3A in vitro. Available data cannot rule out potential induction effect of inavolisib on sensitive CYP3A substrates	Clinically evaluate the effect of repeat doses of inavolisib on the PK of a sensitive CYP3A substrate to assess for potential for reduced exposure of CYP3A substrates
PMC	CYP2B6 induction	Inavolisib induces CYP2B6 in vitro. Available data cannot rule out potential induction effect of inavolisib on sensitive CYP2B6 substrates	Clinically evaluate the effect of repeat doses of inavolisib on the PK of a sensitive CYP2B6 substrate to assess for potential for reduced exposure of CYP2B6 substrates

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data and the Applicant's Position: The clinical pharmacology evaluation of inavolisib is based on data from two clinical studies in patients: a Phase I Study GO39374 (Report 1125233) and a Phase III Study WO41554 (Report 1126696), as well as a Phase I clinical pharmacology Study in healthy subjects, GP42652 that evaluated human mass balance and absolute bioavailability (Report 1130181).

The clinical pharmacology of inavolisib has been well characterized. The data included in the dossier encompasses the following:

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- Pharmacokinetic (PK) properties following single dose and multiple doses of inavolisib administered as a single agent and with combination agents in subjects with cancer.
- PK properties following a single dose administered as a single agent in healthy subjects.
- Population PK analyses of single agent and combination studies included in the dossier.
- The results from clinical pharmacology assessments conducted in healthy subjects (mass balance and absolute bioavailability) to describe the ADME properties of inavolisib in humans.
- The results from clinical pharmacology assessments conducted in subjects with cancer to assess intrinsic (mild hepatic impairment and mild renal impairment) and extrinsic factors (food effect and effect of acid reducing agents) that may affect the PK of inavolisib.
- In addition, the outcomes of the exposure-efficacy and exposure-safety analyses conducted using data from Phase III Study WO41554 and supportive Phase I Study GO39374, which were used for the Phase III dose selection and justification in cancer subjects, support the use of the recommended dose of 9 mg inavolisib, administered orally, QD, on a continuous schedule.

The FDA's Assessment:

FDA agrees with the Applicant's summary of submitted clinical pharmacology data.

In addition, during review of NDA 219249, the Applicant submitted an interim CSR for Study GP44944, an ongoing single-dose study to evaluate the effect of renal impairment on inavolisib PK. The interim CSR included data from participants with moderate renal impairment and normal renal function.

FDA agrees that the proposed dosage of inavolisib 9 mg PO QD in combination with palbociclib and fulvestrant is approvable for the granted indication; however, FDA does not agree that the proposed dosage is optimized. See Section 6.1.2 for details on the FDA's position and recommendation for further dosage optimization of inavolisib.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data: A dose of 9 mg QD is the recommended dose for oral administration of inavolisib in combination with palbociclib and endocrine therapy in patients with *PIK3CA*-mutated, HR+, HER2– LA/mBC.

- Data from Phase I Dose Escalation/Expansion Study GO39374:
 - 9 mg QD was the MTD of inavolisib as identified during dose escalation (3 - 12 mg QD) in the dose escalation and expansion Phase 1b Study GO39374 (Stage 1 Arm A).

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- 9 mg QD showed numerically higher objective response rate (ORR) and clinical benefit rate (CBR) compared to 6 mg as a monotherapy, in doublet combination (with an endocrine agent), and in triplet combination (with a CDK4/6 inhibitor and endocrine agent) in limited number of patients evaluated (GO39374 CSR).
- Data from Phase III Study WO41554:
 - Inavolisib at a dose of 9 mg QD showed a statistically significant and clinically meaningful improvement in investigator-assessed PFS for Inavo+Palbo+Fulv versus Pbo+Palbo+Fulv in the randomized, placebo controlled Phase III Study WO41554 (Section 8.1.1).
 - Stratified HR = 0.43; 95% CI: 0.32, 0.59; log-rank p – value < 0.0001
 - Median PFS was 15.0 months in the Inavo + Palbo + Fulv arm vs. 7.3 months in the Pbo + Palbo + Fulv arm.
 - Exposure-efficacy analyses supported 9 mg QD inavolisib as an efficacious dose in the context of the positive topline efficacy results for treatment versus (vs.) placebo.
 - Inavolisib exposure was not significantly associated with ORR, best overall objective response (BOR), duration of response (DOR), CBR, PFS, or time to first subsequent therapy (TFST) based on Study WO41554, after adjustment to covariates, indicating that patients benefited similarly across the range of observed exposures following 9 mg QD.
- 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 hyperglycemia (GO39374) and anemia (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).

The Applicant's Position: At the proposed 9 mg QD dose of inavolisib, Study WO41554 demonstrated a compelling clinical benefit of inavolisib in combination with palbociclib and fulvestrant, and the treatment regimen demonstrated good tolerability. These results were further supported by the anti-tumor activity and manageable safety and tolerability in Study GO39374. Based on the totality of this information, the recommended dosing regimen for inavolisib is 9 mg QD dose, administered orally, with or without food.

The FDA's Assessment:

FDA agrees that inavolisib 9 mg PO QD in combination with palbociclib and fulvestrant is approvable in adult patients with HR+/HER2-, locally advanced or metastatic breast cancer following recurrence on or after adjuvant therapy (b) (4)

(b) (4) (i.e., inavolisib in combination with palbociclib and fulvestrant).

FDA does not consider that the Applicant has provided sufficient justification that inavolisib 9 mg PO QD is the optimized dosage for the target patient population based on the following reasons:

1) High Rate of AEs and Dosage Modifications

Multiple common AEs in the pivotal study (i.e., increase blood glucose, stomatitis/mucosal inflammation, and diarrhea) were observed at high rates in patients who received inavolisib + palbociclib + fulvestrant and at higher incidence in the treatment arm than those in the control arm (Table 8). Neutropenia, a known toxicity of palbociclib, was similar between the two arms. In addition, 69% of patients in the inavolisib + palbociclib + fulvestrant arm had at least one inavolisib interruption with 84% (595/711) of the inavolisib dose interruptions due to AEs (Table 9). These results suggest that the proposed dosing regimen for inavolisib in combination with palbociclib and fulvestrant is poorly tolerated.

Table 8: Safety Comparison between Treatment Arm and Control Arm in Study WO41554

	Inavolisib + Palbociclib + Fulvestrant (n=162)	Placebo + Palbociclib + Fulvestrant (n=162)
Common AEs		
Neutrophil decreased (lab)	95%	97%
Increased blood glucose (lab)	85%	43%
Stomatitis/mucosal inflammation	51%	27%
Diarrhea	48%	16%
Dose Interruption		
AEs leading to inavolisib or placebo interruption	69%	35%

Source: Applicant's Adapted from Table 24 of the current Assessment Aid, Response to clinical pharmacology information request (IR) dated July 3, 2024, and Reviewer's re-assessment

Table 9: Inavolisib Dose Interruption in Treatment Arm of Study WO41554

	Inavolisib + Palbociclib + Fulvestrant
Time to First Dose Interruption (days)	
Mean (SD)	90 (154)
Median (range)	27 (3 - 975)
Duration of Each Dose Interruption (days)	
Mean (SD)	4.7 (1.2)
Median (range)	1 (1 - 64)

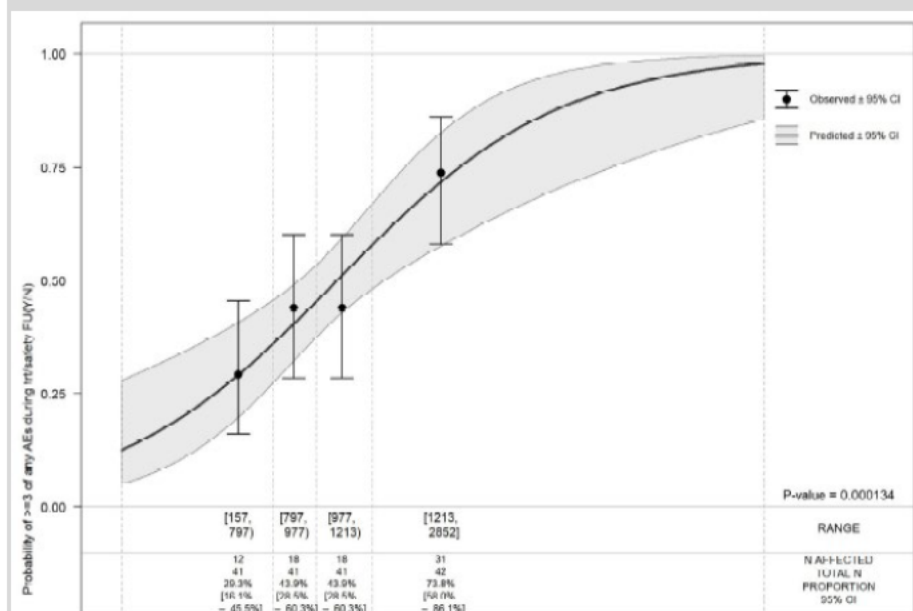
Reason for Each Dose Interruption	
AE	84% (585/711)
Medication Error	3.9% (28/711)
Other	12% (84/711)
Missing	0.6% (4/711)

Source: Applicant’s response to the clinical pharmacology IR received on July 3, 2024

2) Positive E-R Relationships for Safety

E-R analyses for safety identified positive E-R relationships for probability of any Grade ≥ 3 AEs (Figure 4), Grade ≥ 2 increased blood glucose, and dosage modification due to AE based on data from the inavolisib monotherapy dose escalation in Study G039374 at the dosage range of 6 mg PO QD to 12 mg PO QD and a positive E-R relationship for probability of Grade ≥ 2 anemia (Figure 5) based on data from inavolisib 9 mg PO QD + palbociclib + fulvestrant in Study WO41554 (See Section 19.4.2.3 Exposure Response Analysis for details).

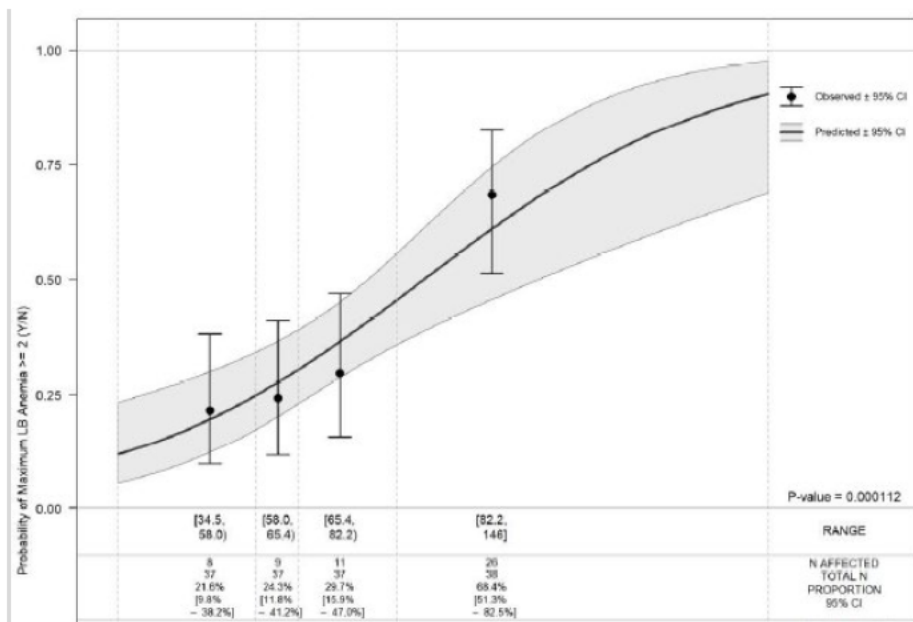
Figure 4: E-R Relationship Between the Probability of Grade ≥ 3 AEs and Quartile of inavolisib AUC



Source: Exposure-response analysis of Inavolisib (Report No. 1129439); Figure 11

Figure 5: E-R Relationship Between the Probability of Grade ≥ 2 Anemia and Quartiles of Inavolisib Cmax

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Source: Exposure-response analysis of Inavolisib (Report No. 1129439); Figure 24

3) Limited Clinical Data at Lower Dosages

In stage 1 of Arm A (inavolisib monotherapy) in Study GO39374, patients received 6, 9, and 12 mg PO QD dosage levels. There were 2 dose-limiting toxicities (DLTs) at the 12 mg PO QD dose level and therefore 9 mg PO QD was identified as the maximum tolerated dose (MTD) of inavolisib monotherapy. Only 7 patients received a starting inavolisib monotherapy dosage of 6 mg PO QD and no patients received a starting inavolisib monotherapy dosage <6 mg PO QD (Table 10). Multiple doublet and triplet combination regimens were subsequently studied in stage 1 of Study GO39374. For inavolisib in combination with palbociclib and letrozole (Arm B), there were three patients each who received inavolisib at 3 mg PO QD and 6 mg PO QD. In total, there were only 20 patients across all regimens who received inavolisib starting dosages lower than the proposed 9 mg PO QD dosage. Of note, all patients who received inavolisib in combination with palbociclib and fulvestrant received the proposed 9 mg PO QD dosage.

Table 10: Patient Enrollment by Inavolisib Dosage and Combination Partner(s) in Studies GO39374 and WO41554

Study	Combination Partners	Enrollment by Inavolisib Dosage			
		3 mg QD	6 mg QD	9 mg QD	12 mg QD
Phase 1 Study GO39374	None (Monotherapy)	-	7	9	4
	Letrozole	-	7	30	-
	Fulvestrant	-	-	59	-

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	Palbociclib + Letrozole	3	3	27	-
	Palbociclib + Fulvestrant	-	-	20	-
Pivotal Study WO41554	Palbociclib + Fulvestrant	-	-	162	-

Source: Reviewer’s analysis of Study GO39374 and Study WO41554

4) Lack of E-R Relationships for Efficacy

No apparent E-R relationships for efficacy endpoints (PFS, duration of response [DoR], time to first subsequent cancer therapy after treatment [TFST], clinical benefit rate [CBR], overall response rate [ORR], and best overall response [BOR]) were identified based on analysis of data from Study WO41554; however, the E-R efficacy results should be interpreted with caution given that the proposed triplet combination (inavolisib + palbociclib + fulvestrant) was only studied at one inavolisib dose level (9 mg PO QD). While the Applicant notes numerically higher ORR for inavolisib 9 mg PO QD compared to inavolisib 6 mg PO QD in Study GO39374, there were too few patients treated with starting dosages <9 mg PO QD to evaluate dose-activity relationships.

Taken together, the available data support approval of the proposed recommended dosage of inavolisib 9 mg PO QD but do not support the conclusion that the inavolisib dosage was optimized. A PMR will be issued to study a lower dosage of inavolisib in patients with PIK3CA-mutant, HR+/HER2-locally advanced or metastatic breast cancer to determine whether a lower dosage may improve the benefit-risk profile compared to inavolisib 9 mg PO QD.

6.2.2.2. Therapeutic Individualization

Data: Following 9 mg QD dosing, body weight, age, race (Asian vs. non-Asian), mild hepatic impairment, and mild renal impairment were not associated with clinically relevant differences in inavolisib exposure parameters. Given the totality of data, dose adjustment of inavolisib in these specific populations is not warranted.

No clinically relevant food effect (high-fat meal) was observed on inavolisib PK in Study GO39374. Hence, inavolisib can be administered with or without food. Coadministration of inavolisib with proton-pump inhibitors in Study GO39374 did not have a clinically relevant effect on the exposure of inavolisib. Hence, no dose adjustment of inavolisib is needed when it is co-administered with acid-reducing agents.

No DDIs were observed between inavolisib and combination partners used in studies GO39374 and WO41554, namely palbociclib, fulvestrant, or letrozole. Therefore, 9 mg QD inavolisib can

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be co-administered with these agents at their respective indicated dose levels. Similarly, no dose adjustment of inavolisib is needed when it is co-administered with these agents.

Nonclinical *in vitro* data, clinical endogenous biomarker data, and physiologically-based pharmacokinetic (PBPK) modeling suggest that clinically relevant DDI between inavolisib and CYP3A4 substrates is unlikely. Therefore, inavolisib can be co-administered with CYP3A4 substrates at their respective indicated dose levels.

Based on the ADME properties of inavolisib, the role of P-gp and breast cancer resistance protein (BCRP) transporters in *in vivo* disposition of inavolisib is not expected to be clinically significant. Therefore, inavolisib can be co-administered with inhibitors/inducers of P-gp and/or BCRP at their respective indicated dose levels.

Similarly, based on the ADME properties of inavolisib, hepatic impairment is considered not to have a clinically significant impact on the PK of inavolisib. Hence, dose adjustment of inavolisib in patients with hepatic impairment (including mild, moderate, and severe) is not warranted.

Population PK modeling suggested that mild renal impairment does not have a clinically significant impact on inavolisib exposure. Therefore, no dose adjustment is needed in patients with mild renal impairment. To assess if the dose of inavolisib needs to be adjusted in patients with moderate or severe renal impairment, a dedicated clinical renal impairment study is being conducted in these patients.

The Applicant's Position: No therapeutic individualization is needed in the proposed indication based on demographic factors (body weight, age, sex), lack of food effect, lack of potential DDIs, and lack of clinically relevant impact of hepatic impairment (mild, moderate, severe) or renal impairment (mild) on inavolisib PK. Moderate or severe renal impairment may affect inavolisib PK, hence a dedicated clinical renal impairment study is being conducted in these patients.

The FDA's Assessment:

FDA agrees with the Applicant that no dose adjustment is necessary in the proposed indication based on body weight (39 to 159kg), age (27 to 85 years), sex, mild renal impairment (eGFR 60 to <90 mL/min), and mild hepatic impairment. In addition, FDA agrees that neither a high-fat meal (approximately 1,000 calories with 50% from fat) nor concomitant use of a proton pump inhibitor have clinically significant effects on the PK of inavolisib (see Section 6.3.2.4 for details). FDA also assessed therapeutic individualization in the following clinical pharmacology area of interest:

1) Moderate renal impairment

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Per the population PK (popPK) analysis, moderate renal impairment (creatinine clearance [CrCL] 30 to <60 mL/min) increased inavolisib exposure ($AUC_{0-\tau,ss}$ by 42%). During review of the NDA, on August 7, 2024, the Applicant submitted the interim CSR for the ongoing clinical renal impairment study. Participants with moderate renal impairment (eGFR 30 to <60 mL/min; n=7) or normal renal function (eGFR >90 mL/min; n=7) received a single dose of inavolisib 6 mg. Inavolisib $AUC_{0-\tau}$ was 60% higher in participants with moderate renal impairment than participants with normal renal function (Table 11). The predicted median steady state $AUC_{0-\tau}$ for patients with moderate renal impairment at 6 mg PO QD dosage was similar to that for patients with normal renal function at 9 mg PO QD dosage (Table 12). Based on these results, the Applicant submitted revised labeling proposing to reduce the proposed starting dosage of inavolisib to 6 mg PO QD in patients with moderate renal impairment. FDA agrees with this recommendation.

Table 11: Dedicated Clinical Renal Impairment Study Interim Analysis Results

PK Parameter	Moderate Renal Impairment/Normal Renal Function GMR (90% CI)
$AUC_{0-\tau}$	1.6 (1.4, 1.9)
AUC_{0-INF}	1.7 (1.5, 2.0)
C_{max}	1.1 (1.0, 1.2)

AUC: Area under the concentration curve; GMR: geometric mean ratio; PK: pharmacokinetics.
Source: Adapted from Table 11-2 in Interim CSR (Report No. GP44944); dated 8/7/2024

Table 12: Estimated Steady State Exposure ($AUC_{0-\tau}$) of Inavolisib in Patients with Normal Renal Function or with Moderate Renal Impairment

Estimated Median Steady State $AUC_{0-\tau}$ (ng*hr/mL)		
Dose	Patients with Normal Renal Function	Patients with Moderate Renal Impairment
9 mg QD	1019*	1763#
6 mg QD	679**	1175#
3 mg QD	340**	586#

*popPK predicted median steady state $AUC_{0-\tau}$ based on observed data

**estimated based on dose proportionality for $AUC_{0-\tau}$ (Study GO39374)

estimated based on observed 1.73-fold higher $AUC_{0-\tau}$ in subjects with moderate renal impairment (Study GP44944)

Source: Applicant's response dated August 7, 2024; Table 1

Given that inavolisib is renally excreted and no data are available to inform the dosage of inavolisib in patients with severe renal impairment (eGFR <30 mL/min), a PMR will be issued for

the final CSR and datasets for the ongoing dedicated clinical renal impairment study, which includes participants with severe renal impairment.

2) Moderate and severe hepatic Impairment

The Applicant concluded that a dedicated clinical study of inavolisib in patients with moderate or severe hepatic impairment is not warranted due to the following:

- In vitro studies showed that inavolisib is metabolically stable in human liver microsomes (HLM). Of the metabolites recovered in excreta, the majority seem to be formed due to hydrolysis of amide and only ~2% were CYP-mediated metabolites.
- For drugs like inavolisib with low extraction ratio and low protein binding, hepatic clearance is mainly dependent on intrinsic clearance due to hepatic enzyme activity in the liver but not on the hepatic blood flow.

FDA does not agree with the Applicant's conclusion that a hepatic impairment study is not warranted based on the following reasons:

- Per the Mass Balance and Absolute Bioavailability Study GP42652, the absolute oral bioavailability of inavolisib is 76%.
- Circulating metabolites were minimal with the majority (99.5%) of drug-related material in plasma being inavolisib in the human mass balance study. Urine and feces excreta accounts for 96% of total administered dose (**Table 13**). A mean of 48% of the dose (40% as the parent drug and 8% as metabolites) was recovered in urine, and 48% (10% as the parent drug and 38% as metabolites) was recovered in feces. The amount of drug recovered as metabolites in feces and urine account for approximately 46% of the administered dose. Given the bioavailability and the percentage of inavolisib recovered as metabolites, >20% contribution of hepatic elimination cannot be ruled out. Therefore, a PMR will be issued to evaluate the PK and safety of inavolisib in patients with moderate and severe hepatic impairment.

Table 13: Inavolisib Excreta Data in Human in Mass Balance Study GP42652

	hAME (%)		
	Urine	Feces	Total
Parent	40	10	50
Metabolite	8	38	46
Total	48	48	97

Source: Reviewer compiled based on Mass Balance and Absolute Bioavailability Report No. GP42652

3) Race and ethnicity

In the popPK analysis, the majority of patients were White (n=224 [66.7%]) or Asian (n=62 [18.5%]) and there was limited representation of other racial and ethnic groups including Black

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or African American (n=4 [1.2%]) and Hispanic or Latino (n=14 [4.2%]) patients (Table 14). Based on published literature, among patients with estrogen receptor-positive (ER+)/HER2-breast cancer, the prevalence of PIK3CA mutations was around 37 – 48% across all ancestry groups, and the distributions of mutation types was also similar across all ancestry groups (Chen et al. 2022); therefore, inavolisib may be utilized in patients from racial or ethnic groups with limited current data. Due to the limited data from patients from underrepresented races and ethnicities, there are insufficient data to assess any potential differences in PK or PD for patients who were not White or Asian. A PMC will be issued to study inavolisib in a diverse patient population representative of the US population (see Section 8.1.1). Collection of clinical pharmacology data to assess potential differences in PK and PD will be included in the PMC.

Table 14: Summary of Baseline Categorical Covariates for popPK analysis

Covariate	G039374 (N=187)	WO41554 (N=149)	Overall (N=336)
Sex			
Male	1 (0.5%)	5 (3.4%)	6 (1.8%)
Female	186 (99.5%)	144 (96.6%)	330 (98.2%)
Race			
White	137 (73.3%)	87 (58.4%)	224 (66.7%)
Black or African American	3 (1.6%)	1 (0.7%)	4 (1.2%)
Asian	5 (2.7%)	57 (38.3%)	62 (18.5%)
Multiple	1 (0.5%)	0 (0%)	1 (0.3%)
Unknown	41 (21.9%)	4 (2.7%)	45 (13.4%)
Asian Patients			
Yes	5 (2.7%)	57 (38.3%)	62 (18.5%)
No	182 (97.3%)	92 (61.7%)	274 (81.5%)
Ethnicity			
Hispanic or Latino	6 (3.2%)	8 (5.4%)	14 (4.2%)
Not Hispanic or Latino	137 (73.3%)	135 (90.6%)	272 (81.0%)
Not Reported	15 (8.0%)	2 (1.3%)	17 (5.1%)
Unknown	29 (15.5%)	4 (2.7%)	33 (9.8%)
Region			
Asia	0 (0%)	54 (36.2%)	54 (16.1%)
North America/Western Europe	187 (100%)	59 (39.6%)	246 (73.2%)
Other	0 (0%)	36 (24.2%)	36 (10.7%)

Source: popPK report No. 1129436, Table 3

4) DDI – Inavolisib as an Object

i. CYP enzyme inhibitors or inducers

In the mass balance study, >99% of the drug-related material in plasma was parent inavolisib and the only CYP-mediated metabolite identified in vitro (M2) was not observed. Therefore, DDI potential between inavolisib and CYP inhibitors or inducers is considered low given the lack of CYP metabolism observed in vivo.

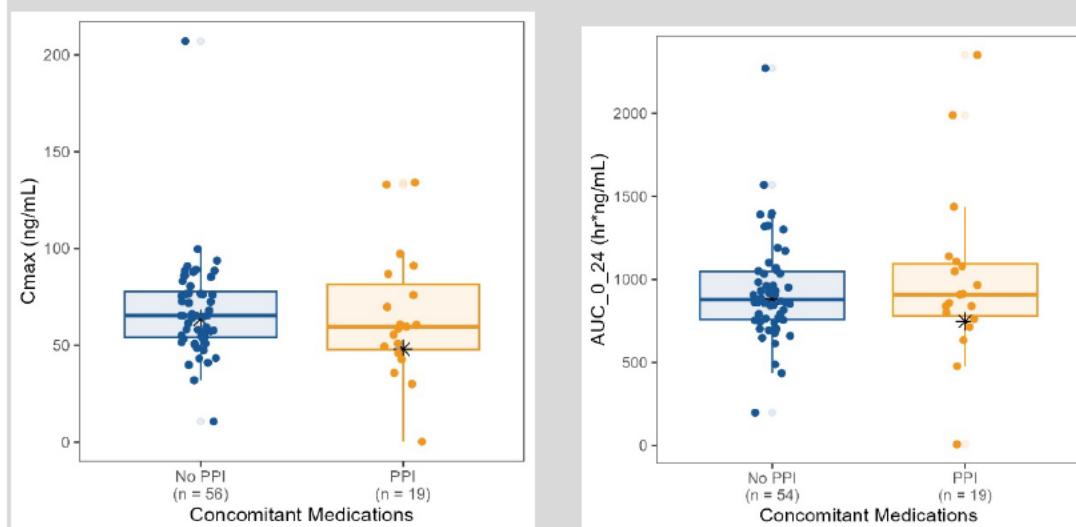
ii. Transporter inhibitors or inducers

In vitro, inavolisib is a substrate of P-gp and BCRP but not a substrate of MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2. FDA agrees with the Applicant that the DDI potential of inavolisib with P-gp or BCRP inhibitors is low given that the absolute oral bioavailability of inavolisib was 76%.

iii. Proton pump inhibitors

Inavolisib exhibits pH-dependent solubility with reduced solubility at higher pH conditions. Based on reviewer's repeat analysis, patients with self-reported concurrent proton pump inhibitor (PPI) use in Study GO339374 (n=19) showed similar inavolisib steady state C_{max} and AUC_{0-24} to patients who self-reported no PPI use (n=56 for C_{max} ; n=54 for AUC_{0-24}) (Figure 6). This analysis supports the conclusion that concomitant administration of a PPI does not have clinically meaningful impact on inavolisib PK exposure.

Figure 6: Impact of PPI on Steady State C_{max} or AUC_{0-24} of Inavolisib – FDA Analyzed



AUC_{0-24} : area under the concentration-time curve from 0 to 24 hours; C_{max} : maximum concentration observed; PPI: proton pump inhibitor.

Source: Summary of Biopharmaceutics Studies and Associated Analytical Methods; Figure 4

5) DDI – Inavolisib as a Precipitant

Per in vitro Study 16-0806, inavolisib was not a direct inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A, and was not a time-dependent inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6; however, inavolisib showed potential for time-dependent inhibition of CYP3A. Per in vitro Study 16-0131, inavolisib increased CYP3A4 mRNA up to 40-fold, CYP2B6 mRNA up to 4-fold, and CYP1A2 mRNA up to 2.5-fold at 30 µM inavolisib in each case.

The Applicant provided the following

(b) (4)

(b) (4)

Based on FDA assessment, available data cannot rule out potential induction effect of inavolisib on sensitive CYP3A substrates. See **Section 19.4.4** for details. PMCs will be issued to conduct a clinical study or studies to assess inavolisib induction potential on substrates of CYP3A and CYP2B6. If the clinical study with a CYP3A substrate identifies inavolisib as at least a weak inducer of CYP3A in vivo, additional studies may be warranted to evaluate inavolisib induction potential on CYP2C enzymes and the potential for inavolisib to interact with COCs.

6.2.2.3. Outstanding Issues

The Applicant's Position: Not applicable.

The FDA's Assessment:

The following clinical pharmacology PMRs and PMCs will be issued.

- 1) Dosage Optimization PMR: Inadequate justification and supportive data were provided to show that inavolisib 9 mg PO QD is the optimized dosage for the target patient population in combination with palbociclib and fulvestrant due to: 1) high rates of adverse events (including severe cases of hyperglycemia, stomatitis and diarrhea) and dosage modifications in patients receiving inavolisib 9 mg PO QD + palbociclib + fulvestrant, and 2) multiple positive E-R relationships for safety endpoints. In addition, there are limited clinical data at lower inavolisib starting dosages (i.e., <9 mg PO QD) and a lack of E-R relationships for efficacy using clinical data from one dose level. Additional dosage optimization is needed to identify whether an alternative inavolisib dosage would provide an improved benefit-risk profile.

- 2) Severe Renal Impairment PMR: A dedicated renal impairment study is currently ongoing. A PMR will be issued to submit the full CSR and datasets, including data from participants with severe renal impairment, after completion of the ongoing study.
- 3) Moderate and Severe Hepatic Impairment PMR: The effects of moderate and severe hepatic impairment on inavolisib safety and PK have not been characterized (see **Section 6.1.2.2**). Given the potential involvement of liver in inavolisib excretion, a PMR will be issued to evaluate the effects of moderate and severe hepatic impairment on the PK and safety of inavolisib.
- 4) Diversity PMC (see **Section 8.1.1** for additional information): Patients from different racial and ethnic groups relevant to the US patient population were not well represented in the inavolisib development program. A PMC to evaluate inavolisib in a diverse patient population will be issued. The PMC will include collection of clinical pharmacology data to evaluate any potential differences in PK and PD based on race or ethnicity.
- 5) CYP3A Induction PMC: Inavolisib increased CYP3A mRNA up to 40-fold in vitro and available data cannot rule out potential induction effect of inavolisib on sensitive CYP3A substrates in vivo. A clinical pharmacokinetic trial is needed to evaluate the effect of repeat doses of inavolisib on the single dose pharmacokinetics of a sensitive CYP3A substrate and inform appropriate management strategies for clinically relevant drug interactions.
- 6) CYP2B6 Induction PMC: Inavolisib increased CYP2B6 mRNA up to 4-fold in vitro and available data cannot rule out potential induction effect of inavolisib on sensitive CYP2B6 substrates. A clinical pharmacokinetic trial is needed to evaluate the effect of repeat doses of inavolisib on the single dose pharmacokinetics of a CYP2B6 substrate and inform appropriate management strategies for clinically relevant drug interactions.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

Absorption: Following oral administration, inavolisib was rapidly absorbed with median time to maximum observed concentration (t_{max}) of 3 hours. Administration of inavolisib in the presence of food did not impact the rate or the extent of absorption of inavolisib following a single or multiple doses of inavolisib. The absolute bioavailability of inavolisib following single oral administration of 9 mg inavolisib was 76%, demonstrating that inavolisib has a moderate to

high absolute bioavailability. With continuous QD dosing, there was approximately 2-fold accumulation, estimated based on individual exposures on Day 15 relative to Day 1 (AUC_{0-24hr}). This accumulation is consistent with the observed half-life ($t_{1/2}$) and the dosing frequency, indicating that inavolisib does not demonstrate time dependent pharmacokinetics.

Distribution: The percentage of inavolisib bound to human plasma proteins *in vitro* was low (37%) and did not appear to be concentration-dependent over the concentration range tested (0.1-10 mM). Following a single intravenous (IV) dose of 100 μ g [$^{13}C_6$]-inavolisib, the geometric mean volume of distribution was 204 L (29% CV), indicating extensive distribution into tissues.

Metabolism: Minimal metabolism of inavolisib was detected *in vitro* in rat, dog, and human liver microsome incubations. The formation of a minor oxidative metabolite was principally mediated by CYP3A4/3A5. Circulating metabolites were minimal with the majority (99.5%) of drug-related material in plasma being inavolisib in the human mass balance study. Total metabolites in the excreta accounted for 42% (35% in feces and 7% in urine) of the dose. The major metabolic pathway was hydrolysis of the primary amide to carboxylic acid; CYP-mediated metabolites were only ~2%.

Excretion: Inavolisib was eliminated to a similar extent via urinary and fecal pathways. Following oral administration of 9 mg [^{14}C]-inavolisib, a mean (SD) of 48.5% (8.18) of the dose was recovered in urine and 48.0% (7.22) of the dose was recovered in feces through the last collection interval. The overall mean recovery of total radioactivity in urine and feces samples was 96.5%, with recovery in individual volunteers that ranged from 92.6 to 99.2%. Urinary excretion represented 48.5% of the dose; unchanged inavolisib was the most prominent drug-related compound in the urine, accounting for 40.4% of the dose. Fecal excretion represented 48.0% of the administered dose. Inavolisib accounted for 10.8% of the dose in feces; metabolites M8, M14, and M15 accounted for 6.4%, 7.9%, and 6.8% of the dose, respectively. Total metabolites in the excreta accounted for 42% (35% in feces and 7% in urine) of the dose. Mean half-life ($t_{1/2}$) following a single 9 mg dose was approximately 16.4 hours (range: 14.1-21.4 hours) in patients with advanced breast cancer.

Dose Proportionality: Single agent data suggest dose proportionality within the dose range tested (6-12 mg) for C_{max} and AUC_{0-24} following single dose and at AUC_{0-24} steady state; however, for steady state C_{max} , the data suggests higher than dose proportional exposure.

Renal Impairment: Population pharmacokinetics (popPK) analysis suggested that mild renal impairment has no clinically significant impact on the exposure of inavolisib. The geometric mean ratio (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 minimum plasma concentration observed (C_{min}) is 1.11 (1.03 -1.18). A dedicated renal impairment study (GP44944) in subjects with moderate or severe renal impairment is ongoing.

Hepatic Impairment: PopPK analysis suggested no impact of mild hepatic impairment on the exposure of inavolisib. The GMR (90% CI) of inavolisib PK in patients with mild hepatic impairment (n = 111) vs. normal hepatic function (n = 224) for area under the concentration-time curve from Time 0 to Time t (AUC_{0-t}) was 0.986 (0.934 - 1.040), C_{max} is 1.010 (0.955 - 1.060), and C_{min} is 0.970 (0.902 -1.040). A dedicated study is not warranted in patients with

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moderate or severe hepatic impairment because, based on the ADME properties of inavolisib, hepatic impairment is unlikely to have a clinically significant impact on the PK of inavolisib.

Population PK: PK of inavolisib following oral administration was well-described by a population PK model consisting of a three-compartment model with first-order rate of absorption and elimination. eGFR effect on clearance (CL) and body weight and race (Asian) effects on central volume of distribution (V_c) were identified as significant with higher CL for subjects with higher eGFR, higher V_c for subjects with higher body weight and 25% lower V_c in Asian subjects compared to non-Asian subjects. However, PopPK model based simulations indicated that body weight, age, race, mild hepatic impairment, and mild renal impairment were not associated with clinically relevant differences in inavolisib exposures following 9 mg QD dosing.

The Applicant's Position: No DDIs were identified or predicted with inavolisib. Given the lack of clinically relevant impact of body weight, age, race (Asian vs. Non-Asian), hepatic impairment (mild, moderate, severe), or renal impairment (mild) on inavolisib PK, dose adjustment of inavolisib in these specific populations is not warranted.

The FDA's Assessment:

FDA generally agrees with the Applicant's summary of ADME (absorption, distribution, metabolism, and excretion) properties and dose proportionality of inavolisib. FDA disagrees with the Applicant's positions in the following areas:

- Total metabolites in the excreta accounted for 48% (38% in feces and 10% in urine) of the dose, rather than the Applicant's summarized 42%.
- Per the interim CSR of the ongoing renal impairment study submitted on August 7, 2024, inavolisib $AUC_{0-\tau}$ was 64% higher and AUC_{0-inf} was 73% higher in subjects with moderate renal impairment compared to subjects with normal renal function after a single 6 mg oral dose of inavolisib (Table 8). The C_{max} values were similar between subjects with normal renal function and subjects with moderate renal impairment.
- FDA disagrees with the Applicant's conclusion that a dedicated hepatic impairment study is not warranted (see Section 6.1.2.2). A PMR will be issued to request a dedicated clinical hepatic impairment study.
- The popPK analysis included sufficient White and Asian patients to assess for PK differences between these two racial groups only. There was limited representation of Black/African American, Hispanic/Latino, and other underrepresented minority patients in the inavolisib development program. Clinical pharmacology data will be requested to be included if a PMC on race and ethnicity to be issued by FDA.

The inavolisib steady state AUC is 1,010 h*ng/mL (25%) and C_{max} is 69 ng/mL (27%) at the recommended dosage (9 mg PO QD). Inavolisib steady state apparent (oral) volume of distribution is 155 L (3.5%). The estimated total clearance of inavolisib is 5.5 L/hr (29%).

QT Analysis:

Based on FDA's QT-IRT analysis of the clinical data from the Phase 1 Study GO39374, inavolisib is unlikely to cause ≥ 20 msec mean increase in QTc interval at the proposed recommended dosage of 9 mg PO QD. Refer to the QT-IRT review (dated 8/1/2024) for details.

Pharmacogenomics:

FDA's pharmacogenomics analysis suggested inavolisib plus palbociclib and fulvestrant treatment is effective for patients regardless of PIK3CA mutation status. See Section 6.3.2.3 for details.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data and the Applicant's Position: Yes, please refer to Section 6.2.2.1.

The FDA's Assessment:

Yes. The pivotal evidence of effectiveness is the improvement in PFS for patients who received inavolisib + palbociclib + fulvestrant compared with patients who received placebo + palbociclib + fulvestrant in Study WO51554 (refer to Section 8.1.2).

There were no apparent exposure-response (E-R) relationships for efficacy endpoints (PFS, DOR, TFST, CBR, ORR, and BOR) identified; however, this finding should be interpreted with caution because the proposed triplet combination (inavolisib + palbociclib + fulvestrant) was only studied at one dose level of inavolisib (9 mg PO QD). See Section 19.4.3.2 for details on the E-R efficacy analysis.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data and the Applicant's Position: Yes, please refer to Section 6.2.2.1.

The FDA's Assessment:

FDA agrees that inavolisib 9 mg PO QD is an effective dosage based on improved PFS for inavolisib 9 mg PO QD + palbociclib + fulvestrant compared with placebo + palbociclib + fulvestrant in patients with HR+, HER2- locally advanced or metastatic breast cancer in Study WO51554. However, it is not clear whether the proposed dosage is optimized due to:

1. High rates of AEs and dosage modification
2. Positive E-R relationships for safety
3. Limited clinical data at lower dosages

4. Lack of E-R relationship for efficacy

Given the lack of dosage optimization and potential for improved benefit-risk profile with a lower dose of inavolisib, a PMR will be issued to study a lower starting dosage. See Section 6.1.2.1 for details.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g., race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data and the Applicant's Position: No, please refer to Section 6.2.2.2.

The FDA's Assessment:

FDA disagrees with the Applicant's position.

- Renal impairment: As detailed in Section 6.1.2.2, dose reduction (to 6 mg PO QD) is recommended in patients with moderate renal impairment. Dosing recommendations for patients with severe renal impairment is not currently available and will be dependent on results of the ongoing renal impairment study.
- Hepatic impairment: A >20% contribution of hepatic elimination cannot be ruled out for inavolisib. Therefore, it is not known at this time whether an alternative dosing regimen or management strategy is required in patients with moderate or severe hepatic impairment. A PMR will be issued to evaluate the PK and safety of inavolisib in patients with moderate and severe hepatic impairment. Refer to Section 6.2.2.2 for details.
- Race and ethnicity: The available data were insufficient to determine any potential differences in PK or PD between patients of different races (other than White or Asian) and ethnicities. Clinical pharmacology data will be collected in a diversity PMC. Refer to Section 8.1.1 for details.
- *PIK3CA* mutation status and treatment effect: FDA explored the treatment efficacy by *PIK3CA* mutation status in study WO41554. *PIK3CA* mutations were detected by central laboratory using the FoundationOne® Liquid CDx assay on plasma-derived circulating tumor DNA (ctDNA), or local laboratories using various validated polymerase chain reaction (PCR) or next-generation sequencing (NGS) assays on tumor tissue or plasma. In study WO41554 (N=325), 270 patients were identified as having *PIK3CA* mutations via central testing. Consistent with literature (Martínez-Sáez et al, 2020), the majority of identified *PIK3CA* mutations were located in exon 9 (N=103, 38.1%), and exon 20 (N=119, 44.1%) (Table 15). There were 5, 8, and 10 patients with *PIK3CA* mutations that were located in exon 1, 4, and 7, respectively. Efficacy in terms of PFS was observed across patients with *PIK3CA* mutated exon 9 and exon 20 and, were consistent with the overall population (Table 16). The efficacy results for patients with "multiple exons"

and “other exons” need to be interpreted with caution due to the small sample size in those subgroups, but still showed greater PFS in the inavolisib arm versus placebo. In summary, the above results suggested inavolisib plus palbociclib and fulvestrant treatment is effective for patients regardless of *PIK3CA* mutation status.

Table 15: Listing and Frequency of Identified *PIK3CA* Mutation

EXON	MUTATION	Count (N)	Percent (%)
EXON 9	E545K	57	21.11
	E542K	39	14.44
	Q546K	5	1.85
	E545G	1	0.37
	Q546L	1	0.37
EXON 20	H1047R	98	36.3
	H1047L	15	5.56
	G1049R	3	1.11
	H1047Y	2	0.74
	M1043I	1	0.37
EXON 1	G106V	3	1.11
	G118D	1	0.37
	K111N	1	0.37
EXON 4	N345K	8	2.97
EXON 7	C420R	8	2.97
	E453Q	2	0.74
Multiple exons	E542K, H1047R	4	1.48
	G118D, H1047R	3	1.11
	E453K, H1047R	2	0.74
	E453Q, E542K	2	0.74
	E453G, E545K	1	0.37
	E453K, E542K, E545K, H1047R, M1043I	1	0.37
	E453K, E542K, E545K, M1043I	1	0.37
	E542K, E545Q, H1047R	1	0.37
	E542K, G106D, H1047R	1	0.37
	E542K, H1047Q	1	0.37

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	E542K, H1047R, K111N	1	0.37
	E545K, H1047R	1	0.37
	E545K, M1043I	1	0.37
	E545Q, H1047L	1	0.37
	E545Q, H1047R	1	0.37
	E545Q, N345K	1	0.37
	G1049R, N345K	1	0.37
	H1047R, K111N	1	0.37

Source: Reviewer's analysis. Abbreviation: PIK3CA= phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; N= Number.

Table 16. PFS by BICR Assessment in study WO41554 by PIK3CA Mutated Exon Status

PIK3CA Mutated Exon Status	Total N	Pbo + Palbo + Fulv Median (Months)	Inavo + Palbo + Fulv Median (Month)	HR (95% CI)*
All Patients	270	7.3	16.6	0.44 (0.31-0.62)
Exon Mutation				
Exon 20	119	5.9	16.6	0.50 (0.29-0.87)
Exon 9	103	7.5	18.2	0.46 (0.26-0.80)
Multiple exons [∞]	25	6.8	11.6	0.44 (0.09-2.31)
Other exons [§]	23	7.2	14.1	0.25 (0.03-2.37)

Source: Reviewer's analysis. Abbreviation: PFS = Progression Free Survival, BICR = Blinded Independent Central Review; PIK3CA= phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; N= Number; Pbo=Placebo; Palbo = Palbociclib; Fulv = Fulvestrant; Inavo = Inavolisib; HR = Hazard Ratio; CI = Confidence Interval; * Hazard ratio was estimated based on an unstratified proportional hazards model; ∞ Multiple exons were defined for patients with PIK3CA mutations detected in more than one exon; §Other exons were defined for patients with PIK3CA mutations detected in exon 1, 4, or 7.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Food-drug interaction: The GMR (90% CI) for plasma C_{max} comparing the fed to the fasted state was 0.925 (0.748-1.14) and 0.910 (0.712-1.16) after a single dose and following QD dosing, respectively. The GMR (90% CI) for AUC₀₋₂₄ comparing the fed to the fasted state was 0.895 (0.737-1.09) and 0.876 (0.701-1.09) after a single dose and following QD dosing, respectively.

Drug-drug interaction:

Effects of inavolisib on other drugs

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

CYP Substrates: *In vitro* studies suggest a low likelihood of time-dependent inhibition and induction of CYP3A4, and no potential to inhibit or induce the other CYP enzymes tested (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6) at clinically relevant concentrations. Endogenous biomarker data, palbociclib PK, and PBPK simulations together suggest that inavolisib is unlikely to have a clinically relevant impact on the exposure of CYP3A4 substrates.

Transporters: *In vitro* studies have shown that inavolisib does not appear to have the potential to inhibit any of the transporters tested (P-glycoprotein [P-gp], BCRP, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, MATE2K, OAT1, or OAT3) at clinically relevant concentrations.

Effects of other drugs on inavolisib

CYP Inhibitors/Inducers: Clinical study results show that the predominant metabolites of inavolisib are not mediated by CYP enzymes, suggesting a low likelihood of interaction between inavolisib and CYP inhibitors or inducers.

Transporters: *In vitro* studies have shown that inavolisib is not a substrate of OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT2, MATE1, or MATE2K, but is a substrate of P-gp and BCRP. However, based on the pharmacokinetic profile of inavolisib, inhibitors or inducers of P-gp and/or BCRP are not expected to have a clinically relevant DDI with inavolisib.

Acid-reducing Agents: In clinical studies, concomitant use of proton pump inhibitors did not have a clinically meaningful effect on inavolisib exposure.

The Applicant's Position:

Food-drug interaction: These data suggest that administration of inavolisib in the presence of food did not impact the rate or the extent of absorption of inavolisib following a single or multiple doses of inavolisib.

Drug-drug interactions: No clinically relevant DDIs are identified or expected with inavolisib as a victim or perpetrator.

The FDA's Assessment:

FDA agrees with the Applicant's position on food-effect on inavolisib PK. FDA does not agree with the Applicant's positions on inavolisib DDI potential. In addition, FDA agrees with the Applicant's approach of bridging different formulations using dissolution studies; refer to the Biopharmaceutics review for details.

1) Food-effect:

The effect of a high-fat meal (approximately 1,000 calories with 50% from fat) on the PK of inavolisib was evaluated after a single dose (Day 1) and following QD dosing (Day 8) in Arm D of Study GO39374 (Table 17). Study results showed that AUC₀₋₂₄ and C_{max} of inavolisib given with a high-fat meal decreased by 12% and 9%, respectively. The food effect study was conducted with the Phase 1 formulation. Subsequent trials (including Study WO51554 using the Phase 3 formulation) allowed patients to take inavolisib with or without food. Given the minor changes between formulations and the data collected in Study WO51554 in patients taking inavolisib

without regard to food, FDA agrees that inavolisib may be administered with or without food.

Table 17: Food-effect Evaluation in Study GO39374

Inavolisib Dosing	PK Parameter	N	GMR (90% CI) Test vs Reference
9 mg Single Dosing	C _{max}	Test: n = 9 Reference n = 11	0.93 (0.75 – 1.14)
	AUC ₀₋₂₄	Test: n = 9 Reference n = 9	0.90 (0.74 – 1.09)
9 mg QD Dosing	C _{max}	Test: n = 10 Reference n = 8	0.91 (0.71 – 1.16)
	AUC ₀₋₂₄	Test: n = 10 Reference n = 9	0.88 (0.70 – 1.09)

AUC: Area under the concentration curve; QD: daily; GMR: geometric mean ratio; PK: pharmacokinetic; Test: administered under fed condition; Reference: administered under fasted condition

Source: Section 2.7.2 Summary of Clinical Pharmacology, adapted from Table 10

2) PPI

As described in section 6.1.2.2, based on popPK analysis of inavolisib PK in patient with self-reported PPI use or no PPI use, no clinically significant difference in steady state inavolisib pharmacokinetics were observed based upon concomitant use of a proton pump inhibitor (lansoprazole, omeprazole, esomeprazole, pantoprazole, or rabeprazole). Refer to Section 6.2.2.2 for details.

3) DDI as an Object and Precipitant

Based on the mass balance study and in vitro evaluations, DDI potential for inavolisib as an object is low given the lack of CYP metabolism observed in vivo. Inavolisib increased CYP3A and CYP2B6 mRNA in vitro. Induction effect on CYP3A and CYP2B6 in vivo cannot be ruled out; therefore, PMCs will be issued to conduct a clinical study or studies to assess inavolisib induction potential on substates of CYP3A and CYP2B6. If inavolisib is confirmed to be at least a weak inducer of CYP3A, the induction potential on CYP2C enzymes will need to be addressed. Refer to Section 6.1.2.2.

4) DDI Potential with Combined Oral Contraceptives

In section 8.3 of the initial proposed labeling, the Applicant proposed to “advise females of reproductive potential to use effective **non-hormonal** contraception during treatment with TRADENAME”. In response to a non-clinical IR, the sponsor proposed to modify the language in section 8.3 (b) (4)

(b) (4) in their updated version of the proposed label. Co-administration of CYP3A inducers may decrease the effectiveness of oral contraceptives. Therefore, the Applicant will be informed that a clinical DDI study may be warranted if the clinical DDI study on CYP3A induction potential confirms the in vivo induction potential on CYP3A.

5) Formulation Bridging

Multiple formulations were used during the course of development, including Phase 1, Phase 1 resupply, and Phase 3 formulations. The proposed to-be-marketed formulation is identical to the Phase 3 formulation with the exception of the coating. Minor changes were made between these formulations as well as the manufacturing process. The Applicant bridged these changes by in vitro dissolution studies. Human bioequivalence studies were not needed to support the bioequivalence of these formulations, particularly the Phase 3 formulation and proposed commercial formulation. Refer to the Biopharmaceutics review for details.

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data and the Applicant's Position: All studies pertinent to the evaluation of efficacy and safety are summarized in **Table 18**. The evidence in support of the proposed indication is primarily derived from the pivotal Phase III Study WO41554 (INAVO120) (CCOD: 29 September 2023). Additional evidence is derived from the Phase I Study GO39374 (CCOD: 27 March 2023).

The FDA's Assessment:

FDA agrees that the primary efficacy and safety analyses for this application are based on results from the INAVO120 (WO41554) trial.

Data from GO39374 was submitted as supportive evidence. GO39374 was a phase 1 study with 7 different treatment arms and no comparator arm. The patient population varied in each of the 7 arms due to different eligibility criteria and differed from the patient population enrolled in INAVO120. In addition, the treatment regimen in most of the 7 arms was different than the triplet regimen from INAVO120. The Applicant submitted data from 3 of the 7 treatment arms ^{(b) (4)} that included use of any endocrine therapy for the triplet combination and to allow treatment with the triplet combination in later lines of therapy (compared to the patient population in INAVO120). The three treatment arms of focus include: Arm B (inavolisib + palbociclib + letrozole), Arm E (inavolisib + palbociclib + fulvestrant), and Arm F (inavolisib + palbociclib + fulvestrant + metformin).

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Table 18: Applicant - Listing of Clinical Trials Relevant to this NDA

Trial Identity and NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
WO41554 NCT0419149 9	Multicenter, randomized, double blinded, placebo-controlled	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 Efficacy Endpoints: OS, ORR, BOR rate, DOR, CBR, PRO Exploratory Efficacy Endpoints: Proxy for PFS2, SRE, PRO Safety, PK	Screening period: 28 days Blinded treatment period Safety follow-up: 30 days Post-treatment hyperglycemia follow-up (when applicable): up to 3 months post last treatment Survival follow-up period: until death, patient withdrawal of consent, loss to follow-up, or study termination	N = 325 (Inavo + Palbo + Fulv: 161 patients; Pbo + Palbo + Fulv: 164 patients)	Patients ≥ 18 years of age with <i>PIK3CA</i> -mutated, HR+, HER2–LA/mBC	123 sites 28 countries
Studies to Support Safety and Efficacy							
GO39374 ^a NCT0300617 2 (Arms A through F)	Multicenter, first-in-human, open-label, dose-escalation and expansion	Dose escalation (A, B, C): Escalating PO doses of inavolisib as a single agent or in combination with letrozole 2.5 mg QD PO ± palbociclib 125 mg QD PO (3 weeks on/1 week off). Expansion (B, C, D, E, F): PO inavolisib (at a dose determined from the dose-escalation phase) in combination with letrozole 2.5 mg QD PO ± palbociclib 125 mg QD PO (3 weeks on/1 week off) or in combination with fulvestrant 500 mg IM ± palbociclib 125 mg QD PO (3 weeks on/1 week off) ± metformin up to 2000 mg PO	Primary Endpoint: Safety PK Activity (Efficacy) Endpoints^d: ORR, BOR rate; DOR, CBR, PFS Exploratory: Biomarker	Screening period: 28 days Treatment period Safety follow-up period: 30 days, or until initiation of another anti-cancer therapy, whichever occurred first	Dose escalation (A, B, C): N=50 enrolled Expansion (B, C, E, D, F)^e: N=141 enrolled	Patients ≥ 18 years of age with locally advanced or metastatic <i>PIK3CA</i> -mutated solid tumors, including breast cancer	13 sites ^c 5 countries (US, Spain, Canada, UK, France)

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 negative; HR+ = hormone receptor positive; Inavo = inavolisib; IM = intramuscular; IV = intravenous; INV = investigator; LA/mBC = locally advanced/ metastatic breast cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PFS2 = proxy for time to second objective disease progression; Palbo = palbociclib; PO = oral; PRO = patient-reported outcome; Q4W = every 4 weeks; QD = once daily; SRE = Time to first skeletal-related event.

^a Phase I Study GO39374 Stage II Arm G (inavolisib in combination with trastuzumab and pertuzumab) will not be included in the dossier as this arm is still enrolling, and the treatment combination studied and the population enrolled differ from the proposed indication in the NDA.

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

^c There were 11 Principal Investigators across 13 sites.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

Pivotal Study WO41554 (INAVO120) and Supportive Study G039374

Trial Design

8.1.1.1. Pivotal Study: WO41554 (INAVO120), Phase III

The Applicant's Description: Study WO41554 is a Phase III, randomized, double-blind, placebo-controlled, multi-center, global study designed to compare the efficacy, as measured by investigator-assessed PFS, and the safety of the triplet combination of inavolisib with palbociclib and fulvestrant (Inavo+Palbo+Fulv) vs. placebo with palbociclib and fulvestrant (Pbo+Palbo+Fulv) in patients with *PIK3CA*-mutated, HR+, HER2– LA/mBC whose disease progressed during treatment or within 12 months of completing adjuvant ET and who had not received prior systemic therapy for locally advanced or metastatic disease.

Patient biomarker eligibility (i.e., positive for a study-eligible *PIK3CA* mutation) was determined through testing of blood plasma-derived circulating tumor DNA (ctDNA) with a next-generation sequencing (NGS) assay performed at the Sponsor-designated central laboratory, or through local testing of ctDNA or tumor tissue with an appropriately-validated NGS or polymerase chain reaction (PCR) assay.

Eligible patients were randomly assigned in a 1:1 ratio to one of two treatment arms: Inavo+Palbo+Fulv or Pbo+Palbo+Fulv. Inavolisib/placebo was administered at 9 mg PO 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 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. Patients were stratified by: visceral disease (yes or no), endocrine resistance (primary or secondary according to European Society for Medical Oncology Advanced Breast Cancer 4 (ESMO ABC4) guidelines and geographic region (North America/Western Europe, Asia, Other).

Patients received study treatment until unequivocal disease progression as determined by the Investigator, unacceptable toxicity, patient withdrawal of consent, loss to follow-up, death, or study termination.

After randomization, tumor assessments were performed to assess for response every 8 weeks (± 7 days) during the first 2 years of study treatment and every 12 weeks (± 7 days) thereafter.

Primary efficacy analyses were based on the tumor assessments performed by the local radiologists or Investigators. Response was assessed on the basis of physical examinations,

computed tomography (CT) scans, and other imaging modalities as clinically indicated, which could include brain imaging (CT or magnetic resonance imaging [MRI]), MRI scans, and/or bone scan, using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. A retrospective blinded independent central review (BICR) of tumor assessment data was performed to support the primary endpoint of investigator-assessed PFS.

To evaluate the PK properties of inavolisib, palbociclib, and fulvestrant administered in this triplet combination, blood samples were taken at various timepoints before and after dosing.

Patient-reported outcome (PRO) instruments, including the Brief Pain Inventory-Short Form (BPI-SF) worst pain severity item, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and its accompanying disease-specific module, the QLQ-BR23, were completed to evaluate the impact of treatment from the patient's perspective. Additionally, pre-selected symptom items from the Patient-Reported Outcomes Common Terminology Criteria for Adverse Events (PRO-CTCAE) and an overall bother item were used to assess the experience of treatment-related symptoms and their associated bother.

Patients were monitored for adverse events (AEs) throughout the study treatment, following informed consent until 30 days after the final dose of study treatment or until initiation of another anti-cancer therapy, whichever occurred first. AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. Patients who, at the 30-day safety follow-up visit, were still on anti-hyperglycemic agents for the treatment of hyperglycemia during the study treatment, and those patients with events of hyperglycemia ongoing at the 30-day safety follow-up visit, proceeded to the post-treatment hyperglycemia follow-up.

Dose Modification

The inavolisib/placebo dose reduction instructions for managing AEs are provided in the protocol. They are intended to serve as recommended guidelines to inform rather than supersede clinical judgment and the benefit-risk balance as assessed by the Investigator in managing individual cases. Dose modification for AEs was to be taken first with inavolisib rather than palbociclib unless clearly attributable to palbociclib alone based on known toxicity profile and the investigator's assessment. Interruption, but not reduction, was permitted for fulvestrant.

Blinding

Study WO41554 was a double-blind study: the Sponsor and its agents, study site personnel, and patients were blinded to treatment assignment during the study.

Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) was established to monitor safety, study conduct, and futility analysis. The iDMC reviewed unblinded safety summaries and summaries of key efficacy endpoints prepared by an independent data coordinating center (iDCC).

Trial Location: The study was conducted at 123 centers across 28 globally distributed countries, with a total of 325 patients enrolled from across Asia, Europe, Australia, North America, and Central/South America. Among them, 16 patients were enrolled from 9 U.S. sites (see **Section 8.1.1** for further details).

The FDA's Assessment:

FDA agrees with the Applicant's assessment. The control arm treatment regimen of palbociclib + fulvestrant was an appropriate regimen for the first line treatment of patients with HR positive/HER2 negative MBC when the INAVO120 trial was initiated in 2019. This combination is still an appropriate option for first line treatment; however, based on results from the MONALEESA-2 and MONARCH 3 trials, ribociclib and abemaciclib are now used more commonly than palbociclib in the first line setting in the US.

Eligibility Criteria

The Applicant's Description:

Key Inclusion Criteria

- If female, patients had to meet at least one of the following definitions:
 - Postmenopausal, as defined by criteria specified in the protocol
 - Premenopausal or perimenopausal (i.e., not meeting the criteria for postmenopausal) and meeting the following criterion:
 - Treatment with luteinizing hormone–releasing hormone (LHRH) agonist therapy (e.g., goserelin or leuprolide) beginning at least 2 weeks prior to Day 1 of Cycle 1 and continuing for the duration of study treatment
- If male, recommendation of treatment with LHRH agonist therapy beginning at least 2 weeks prior to Day 1 of Cycle 1 and continuing for the duration of study treatment
- 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 estrogen receptor (ER)–positive and/or progesterone receptor (PR)–positive tumor according to American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines
- Documented HER2–negative tumor according to ASCO/CAP guidelines
- Confirmation of biomarker eligibility: valid results from either central testing of blood or local testing of blood or tumor tissue documenting *PIK3CA*-mutated tumor status
- Patients had to have progressed during adjuvant endocrine treatment or within 12 months of completing adjuvant ET with an aromatase inhibitor or tamoxifen.
 - If a CDK4/6 inhibitor was included as part of neoadjuvant or adjuvant therapy, progression event had to be > 12 months since completion of CDK4/6 inhibitor portion of neoadjuvant or adjuvant therapy
- Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

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- Treatment with endocrine-based therapy (e.g., palbociclib and fulvestrant) was recommended at time of entry into the study, as per national or local treatment guidelines
- Adequate hematologic and organ function within 14 days prior to initiation of study treatment, including:
 - Fasting glucose < 126 mg/dL (< 7.0 mmol/L) and HbA_{1c} < 6.0% (< 42 mmol/mol)

Key Exclusion Criteria

- Any history of leptomeningeal disease or carcinomatous meningitis
- Any prior systemic therapy for metastatic breast cancer
- Prior treatment with fulvestrant or any selective estrogen-receptor degrader, with the exception of patients that had received fulvestrant or any selective estrogen-receptor degrader as part of neoadjuvant therapy only and with treatment duration of no longer than 6 months
- Prior treatment with any PI3K, AKT, or mTOR inhibitor, or any agent whose mechanism of action was to inhibit the PI3K-AKT-mTOR pathway
- Type 2 diabetes requiring ongoing systemic treatment at the time of study entry; or any history of Type 1 diabetes
- Known and untreated, or active central nervous system (CNS) metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control)
- Any active bowel inflammation (including diverticulitis)
- Symptomatic active lung disease, including pneumonitis
- Clinically significant and active liver disease, including severe liver impairment (Child-Pugh Class B/C), viral or other hepatitis, current alcohol abuse, or cirrhosis
- History of or active clinically significant cardiovascular dysfunction
- Chronic corticosteroid therapy of ≥ 10 mg of prednisone per day or an equivalent dose of other anti-inflammatory corticosteroids or immunosuppressants for a chronic disease

The FDA's Assessment:

FDA agrees with the Applicant's assessment. The criteria for fasting glucose and HbA_{1c} are stricter than the criteria in the trial leading to the approval of alpelisib and capivasertib. There were no eligibility criteria regarding body mass index (BMI).

All patients were required to have endocrine resistant HR-positive HER2-negative advanced/metastatic breast cancer. Endocrine resistance was further categorized as primary endocrine resistance or secondary endocrine resistance. Primary endocrine resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy (ET) and secondary endocrine resistance was defined as relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.

Study Endpoints

The Applicant's Description: For the primary and secondary efficacy objectives, a comparison of the treatment arms was performed in the full analysis set (FAS). The primary efficacy endpoint was PFS as assessed by the investigator according to RECIST v1.1. Secondary efficacy endpoints include: OS; ORR; BOR rate; DOR for patients with objective response; CBR; time to confirmed deterioration (TTCD) in worst pain severity; TTCD in physical functioning (PF); TTCD in role functioning (RF); and TTCD in Global Health Status/Health-Related Quality of Life (GHS/HRQoL). ORR, BOR, DOR, and CBR were based on tumor assessment by the investigator. Exploratory efficacy endpoints include time to end of next-line treatment (proxy for PFS2), time to first skeletal related event (SRE), mean and mean change from baseline scores in function (physical, role, cognitive, emotional, and social), HRQoL, and disease and treatment-related symptoms.

Safety objective of the study was to evaluate the safety of inavolisib plus palbociclib and fulvestrant compared with placebo plus palbociclib and fulvestrant (for further details see **Section 8.2.1**). PK objective of the study was to characterize the PK of inavolisib, palbociclib, and fulvestrant, when administered in combination in this population.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. The primary efficacy endpoint for the INAVO120 trial was PFS as assessed by investigator. A prospectively planned sensitivity analysis of PFS by BICR assessment was also performed on all patients.

Statistical Analysis Plan and Amendments

The Applicant's Description: The Statistical Analysis Plan (SAP) was finalized prior to the conduct of any efficacy analysis and unblinding of the database. SAP Version 1 was finalized on 25 April 2023. A subsequent amendment was finalized on 18 September 2023, to clarify the statistical testing procedure of key secondary efficacy endpoints and the power of OS analyses.

Analysis Populations

All efficacy analyses were performed in the FAS (unless otherwise specified), defined as all randomized participants; participants were included in the analyses according to the treatment they were assigned. The safety set analysis (SAS) included all participants exposed to study treatment and were analyzed according to the treatment that they actually received. The PK-evaluable population included all randomized participants in the inavolisib arm who had at least one evaluable inavolisib plasma concentration.

Hypothesis Testing

The primary analysis was a comparison of the investigator-assessed PFS between the two treatment arms using a stratified log-rank test at an overall 0.05 significance level (two-sided).

The statistical hypothesis of this study was as follows:

- H0: PFS Inavo+Palbo+Fulv = PFS Pbo+Palbo+Fulv
- H1: PFS Inavo+Palbo+Fulv $\neq$ PFS Pbo+Palbo+Fulv

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

Statistical Analysis of Efficacy Endpoints

Sensitivity analyses to the primary estimand of the primary PFS were performed by BICR-assessed PFS, investigator-assessed PFS based on unstratified analysis, investigator-assessed PFS in patients with *PIK3CA* mutation-positive status by the central test, and based on handling of missing scheduled tumor assessments.

Two supplementary analyses based on differing strategies of handling intercurrent event (ICE) were performed for investigator-assessed PFS based on hypothetical strategy and composite strategy for use of any non-protocol anti-cancer therapy (NPT) prior to disease progression.

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) OS; 2) ORR; 3) BOR; 4) CBR; 5) TTCD in pain; 6) TTCD in PF; 7) TTCD in RF; 8) TTCD in GHS/HRQoL.

The primary efficacy analysis was conducted when approximately 194 PFS events had occurred. The first interim OS analysis was planned at the time of the primary analysis of PFS. A final OS analysis was estimated to occur approximately 19 months later. With the assumptions specified in SAP Version 2, the cumulative power planned at the interim and final OS analysis was 25% and 59%, respectively.

Efficacy Subgroup Analysis

The generalizability of PFS after randomization results was investigated as a part of an exploratory analysis by estimating the treatment effect in subgroups based on baseline prognostic factors (including stratification factors) with unstratified analysis as defined in the SAP Version 2.

Safety Analysis

Safety was assessed through summaries of exposure to study treatment, AEs, changes in laboratory test results, and changes in vital signs and electrocardiograms (ECGs). All verbatim AE terms were mapped to Medical Dictionary for Regulatory Activities (MedDRA 26.1) thesaurus terms, and AE severity was graded according to NCI CTCAE v5.0. All AEs, serious adverse events (SAEs), AEs leading to death, selected AEs (including adverse events of special interest [AESIs]), and AEs leading to study treatment discontinuation or dose modification that occurred on or after the first dose of study treatment (i.e., treatment-emergent AEs) were summarized accordingly. Deaths and cause of death were summarized.

PK Analysis

Plasma concentrations of inavolisib, palbociclib, and fulvestrant vs. time data were tabulated and plotted. Inavolisib plasma concentration vs. time data, together with information on dosing

and patient characteristics, were pooled and analyzed using a popPK analysis approach, as appropriate. The PK data were combined with the safety and efficacy data for exposure-response modeling.

The FDA's Assessment:

FDA agrees with the Applicant's description of the design and protocol aspects of the INAVO120 trial as stated above.

FDA also notes that the statistical test for PFS was based on 320 patients randomized in a 1:1 ratio, where 194 PFS events would provide a power of approximately 85% to detect a hazard ratio (HR) of 0.65 with a 2-sided type I error of 5%. One interim analysis for futility was to be conducted after approximately 75 PFS events (33% of information). The futility boundary was non-binding. One interim analysis was to be performed for OS at the time of the primary endpoint analysis, when 105 OS events were expected to have occurred (68% information fraction).

Protocol Amendments

The Applicant's Description: The first version of the protocol was issued on 12 August 2019 and the protocol version in effect at the CCOD was Version 8. None of the implemented changes impacted the integrity of the trial or the interpretation of the results. The key changes relevant to the evaluation of efficacy and safety are summarized below:

Protocol Version 2 (16 October 2019) included new information about interstitial lung disease (ILD)/pneumonitis with palbociclib (IBRANCE®) based upon a label update (USPI). The pneumonitis management guidelines were updated to align with the updated label.

Protocol Version 3 (Voluntary harmonization procedure [VHP]) (4 August 2020) was amended to address feedback from VHP. Contraception requirements for women and men were amended in response to fulvestrant label change. Interim safety analysis of the first 25 enrolled patients was added.

Protocol Version 4 (Global) (3 November 2020) was primarily amended to merge the VHP and global versions and to add China-specific language. In addition,

- The exclusion criterion prohibiting prior fulvestrant or other selective estrogen-receptor degrader was modified to allow prior fulvestrant or other selective estrogen-receptor degrader only in the neoadjuvant early breast cancer setting and only if given for less than 6 months
- China-specific language was added: new inclusion criterion specified that patients enrolled in the study in China were a current resident of mainland China and of Chinese ancestry. A China-specific pharmacokinetic objective was added

Protocol Version 5 (Canada) (21 May 2021) replaced Version 4 of the protocol only in Canada. Version 5 was primarily updated to allow for mobile nursing (MN) in Canada to improve access and convenience for patients participating in the study.

Protocol Version 6 (12 August 2022) included changes from both Version 4 (Global) and Version

5 (Canada). In addition, this protocol was amended to extend participant eligibility:

- The eligible threshold for HbA_{1c} was changed from <5.7% [39 mmol/mol] to <6.0% [42 mmol/mol] to more closely align with the eligible threshold for fasting glucose of <126 mg/dL defining pre-diabetes per the American Diabetes Association (ADA)
- The eligibility criterion for measurable disease per RECIST v1.1 was extended to include bone-only disease with a measurable soft-tissue component

Protocol Version 7 (21 October 2022) was amended primarily to correct the creatinine clearance threshold in the inclusion criteria to ≥ 50 mL/min (previously ≥ 30 mL/min) to rectify an error in the previous amendment Version 6.

Protocol Version 8 (8 March 2023) was amended to redefine the study sample size due to the unanticipated slow enrollment experienced and was intended to minimize the risk of Last Patient In (LPI) occurring after the number of planned events for the primary PFS analysis was reached. The total planned enrollment of 400 participants was reduced to approximately 320. The number of PFS events to trigger primary study readout was reduced from 227 to 194, resulting in a change in the power of PFS from 90% to 85%, which was considered adequate for the primary endpoint. The impact on the power for the secondary endpoint OS was minimal.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Trial Design

8.1.1.2. Supportive Study: G039374, Phase I

The Applicant's Description: Study G039374 is an open-label, multicenter, Phase I study designed to evaluate the safety, tolerability, and PK of inavolisib administered orally as a single agent in patients with locally advanced or metastatic *PIK3CA*-mutated solid tumors, including breast cancer, and in combination with standard-of-care endocrine and/or targeted therapies in patients with *PIK3CA*-mutated LA/mBC.

Patients were enrolled in two stages: a dose-escalation stage (Stage I, Arms A, B, and C) and an expansion stage (Stage II, Arms B, C, D, E, F, and G). Patients were assigned to one of seven regimens: inavolisib as a single agent (Arm A), inavolisib in combination with palbociclib and letrozole (Arm B), inavolisib in combination with letrozole (Arm C), inavolisib in combination with fulvestrant (Arm D), inavolisib in combination with palbociclib and fulvestrant (Arm E), inavolisib in combination with palbociclib, fulvestrant, and metformin (Arm F), and inavolisib in combination with trastuzumab and pertuzumab (and letrozole or fulvestrant, if applicable) (Arm G, not included in this submission). Cycle 1 in the dose-escalation cohorts of Arm A was 35 days in length; all other cycles were 28 days in length. The study design and treatment is shown in **Section 7.1, Table 5**.

Key Inclusion Criteria:

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- Arm A enrolled patients with histologically documented *PIK3CA*-mutated, locally advanced, recurrent, or metastatic, incurable solid tumor malignancy, including breast cancer.
- Arms B, C, D, E, and F enrolled female patients with histologically documented *PIK3CA*-mutated, HR+/HER2- LA/mBC. Arms B and C enrolled postmenopausal female patients only.
- Arms A, B, C, D, and E: Fasting glucose ≤ 140 mg/dL and glycosylated hemoglobin (HbA_{1c}) $< 7\%$
- Arm F only: Patients with BMI ≥ 30 kg/m² or HbA_{1c} $\geq 5.7\%$ and $< 7\%$ at baseline
- Arms A, C, D: Absolute neutrophil count $\geq 1200/\mu\text{L}$; Arms B, E, F: Absolute neutrophil count $\geq 1500/\mu\text{L}$

Key Exclusion Criteria:

- Type 1 or 2 diabetes requiring antihyperglycemic medication
- Known and untreated, or active CNS metastases (progressing or requiring anticonvulsants or corticosteroids for symptomatic control).
- Any prior treatment with PI3K inhibitor
- Stage II, Arm B, Arm C, Arm D, and Arm E only: Prior treatment with > 1 cytotoxic chemotherapy regimen in the metastatic setting
- Stage II, Arm B and Arm E only: Any prior treatment with CDK4/6 inhibitor

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

The eligibility criteria for each arm of Study GO39374 varied and were different than that for INAVO120. Patients were not required to have endocrine resistant disease in GO39374.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data: All studies included in this submission were conducted in accordance with the principles of Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and the local laws and regulations of the countries in which the studies were conducted. Ethics Committees and Institutional Review Boards reviewed and approved all studies.

Audits and GCP compliance: See statement of GCP compliance above. An audit certificate is provided in the WO41554 CSR and GO39374 CSR, respectively.

The Roche Clinical Quality Assurance group or designee conducted 2 investigator audits, 2 study audits, 2 service provider audits, and 2 internal process audits for Study WO41554. One critical audit finding was identified during a service provider audit (b) (4) The

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outcomes of the assessments and actions completed in response to the audit are considered to demonstrate that the identified issues have been mitigated to the extent that there is no residual impact on the validity of the results obtained in Study WO41554, or on the safety of study participants. In other audits for Study WO41554, no critical audit findings were observed. The Roche Clinical Quality Assurance group or designee conducted 2 internal process audits and 1 service provider audit for Study GO39374. No critical audit findings were observed.

The Applicant's Position: For all audit findings across both studies, appropriate corrective and preventive actions were undertaken; and the studies were conducted in accordance with the GCP principles.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that studies were conducted in accordance with GCP principles.

Financial Disclosure

Data and the Applicant's Position: For financial disclosure information for both the pivotal Study WO41554 and supportive Study GO39374, please see Module 1.3.4 in the NDA and **Section 19.2.**

There are no concerns about the integrity of study data based on financial disclosures. Both the pivotal Study WO41554 and supportive Study GO39374 were conducted over multiple sites and in multiple countries, thus limiting the potential for bias on the part of a single investigator or sub-investigator to have a significant impact on the results.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. See Section 19.2 for further information.

8.1.2.1. Pivotal Study: WO41554 (INAVO120), Phase III

Patient Disposition

Data: Patients were recruited from 123 centers across 28 countries (**Table 19**).

The FAS population was comprised of a total of 325 patients: 161 patients in the Inavo + Palbo + Fulv arm and 164 patients in the Pbo + Palbo + Fulv arm. One patient was randomized to the Inavo + Palbo + Fulv arm but withdrew consent to participate in the study prior to dosing with any study drug. At the CCOD (29 Sep 2023) for the primary analysis, the median duration of follow-up for all patients was 21.3 months and was similar in both arms. A lower proportion of patients in the Inavo + Palbo + Fulv arm (58.4%) in comparison to the Pbo + Palbo + Fulv arm (70.1%) had discontinued from all study treatment. Across individual study treatments, the most common reason for study drug discontinuation was progressive disease, which occurred at higher frequency in the Pbo + Palbo + Fulv arm.

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A lower proportion of patients in the Inavo + Palbo + Fulv arm (35.4%) had discontinued from the study compared with the Pbo + Palbo + Fulv arm (40.9%). 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 Applicant's Position: The pivotal Study WO41554 enrolled a globally diverse population through the multi-center, multinational nature of the study.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. This was a multinational trial with 16 patients enrolled from the United States as outlined in Table 19 below. Refer to FDA assessment below regarding the assessment of diversity in INAVO120 below, under demographic characteristics, and the PMC issued by FDA for diversity in Section 13.

Protocol Violations/Deviations

Data: As of the CCOD (29 Sep 2023), 28.3% of patients of the FAS had at least one major protocol deviation. Overall, major protocol deviations were comparable between arms (Inavo+Palbo+Fulv: 26.1% vs. Pbo+Palbo+Fulv: 30.5%). The most common protocol deviations were procedural violations (17.8%). Major protocol deviations due to COVID-19 were comparable across arms (3.7% vs. 3.0%). The majority of major protocol deviations related to COVID-19 were medication related (3.1% vs. 2.4%). The major protocol deviations related to the Ukraine-Russia conflict were comparable across arms (1.9% vs. 1.2%), and were medication related (1.9% vs. 1.2%) or procedural related (1.2% vs. 0.6%).

The Applicant's Position: Overall, none of the major protocol deviations were considered to have impacted the monitoring of patient safety, the study outcome, or the interpretation of the study results.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that the major protocol deviations likely did not impact the outcome or interpretation of the study results.

The most common protocol deviations categorized under procedural violations were labs not done per protocol (5.0% vs 7.9%); tumor assessment not done per protocol (6.2% vs 4.3%) and ICF not signed prior to any study-specific procedure (1.9% vs 6.1%) in the inavolisib vs placebo treatment arm, respectively.

The most common protocol deviations categorized under medication were Incorrect inavolisib/placebo dose modification/interruption or delay (4.3% vs 1.8%); Incorrect palbociclib and dose modification/interruption or delay (1.2% vs 3.0%) in the inavolisib vs placebo treatment arm, respectively.

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The most common protocol deviations categorized under inclusion criteria were hemoglobin A1C greater than 6% (1.2% vs 3%) in the inavolisib vs placebo treatment arm, respectively.

The most common protocol deviations categorized under exclusion criteria were patient has received any prior systemic therapy for metastatic breast cancer (1.2% vs 0%) in the inavolisib vs placebo treatment arm, respectively.

Table of Demographic Characteristics

Data:

Table 19: Applicant - Study WO41554 Demographic Characteristics, Full Analysis Set

Demographic Parameters	Inavo+Palbo+Fulv (N=161) n (%)	Pbo+Palbo+Fulv (N=164) n (%)	All Patients (N=325) n (%)
Sex			
Male	5 (3.1%)	1 (0.6%)	6 (1.8%)
Female	156 (96.9%)	163 (99.4%)	319 (98.2%)
Age			
Mean years (SD)	53.8 (10.9)	54.1 (11.2)	54.0 (11.1)
Median (years)	53.0	54.4	54.0
Min, max (years)	27,77	29,79	27,79
Age Group			
< 18 years	0	0	0
< 65 years	136 (84.5%)	130 (79.3%)	266 (81.8%)
≥ 65 years	19 (11.8%)	28 (17.1%)	47 (14.5%)
≥ 75 years	6 (3.7%)	6 (3.6%)	12 (3.7%)
Race			
White	94 (58.4%)	97 (59.1%)	191 (58.8%)
Black or African American	1 (0.6%)	1 (0.6%)	2 (0.6%)
Asian	61 (37.9%)	63 (38.4%)	124 (38.2%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	5	3	8
Ethnicity			
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/Unknown	6 (3.7%)	5 (3.0%)	11 (3.3%)
Region			
United States	7 (4.3%)	9 (5.5%)	16 (4.9%)
Rest of the World*	1 (0.6%)	0	1 (0.3%)
Canada	10 (6.2%)	4 (2.4%)	14 (4.3%)
South America	4 (2.5%)	1 (0.6%)	5 (1.5%)
Europe	77 (47.8%)	85 (51.8%)	162 (49.8%)
Asia	58 (36.0%)	62(37.8%)	120 (36.9%)
Australia	4 (2.5%)	3 (1.8%)	7 (2.2%)

*New Zealand

Source: t_dm_FAS_29SEP2023_41554; t_dm_enrol_FAS_29SEP2023 41554; Dataset: AdaM: ADSL

The Applicant’s Position: In the FAS population, the two treatment arms were comparable with respect to demographic characteristics (**Table 19**).

Of the patients enrolled in the U.S., the majority had their ethnicity reported as “not Hispanic or Latino” (87.5%), the remainder of patients had their ethnicity reported as “Hispanic” (12.5%). With respect to race, the majority of patients were White (81.2%), with the remainder of

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patients in race categories of African American/Black (12.5%) or Asian (6.2%). This aligns well with the demographic distribution of the general population of the U.S. provided by the most recent U.S. Census (1 July 2023): White (75.5%), Black/African American (13.6%), Asian (6.3%), American Indian/Alaska Native (1.3%), Native Hawaiian/Pacific Islander (0.3%) ([U.S. Census Bureau 2023](#)).

U.S. sites participating in Study WO41554 were regionally distributed as follows: Northeast (4 sites), Southeast (18 sites), Central (1 site), and West Coast (4 sites), among which 9 sites had at least one patient enrolled. As elaborated in the Inavolisib Diversity Plan, expected incidences of HR+/HER– breast cancer of all stages, 8.9% are expected to be Hispanic (any race), 11.1% Black/African American, 0.4% to American Indian/Alaska Native, and 5.7% to be Asian/Pacific Islander. This compares favorably with the demographic distribution of US-enrolled patients described above, with the caveat that U.S. enrollment was challenging (n=16). Attempts were made to include more community-based clinical trial sites with broad patient demographics, however participation in Study WO41554 was declined.

The FDA’s Assessment:

In general, the two arms were well balanced across baseline characteristics. This was a multinational study with just 16 patients (4.9%) enrolled from the US. Almost all patients were female (98%) and the median age of 54 years for the patient population is younger than the median age (62 years old) at the time of breast cancer diagnosis in the US (cancer.org).

The majority of patients on study were White. Racial and ethnic minorities reflective of the U.S. population of patients with breast cancer were significantly underrepresented in INAVO120 (WO41554), with only two Black patients and 20 Hispanic/Latino patients enrolled on study. Due to the lack of diversity in the enrolled population, a Post Marketing Commitment (PMC) is being issued to further characterize the efficacy and safety of inavolisib for the treatment of breast cancer in study populations whose demographics are more representative of the population of U.S. patients for the proposed indication.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Baseline Characteristics

The majority of patients (60%) were post-menopausal; the remainder (38.2%) were “not post-menopausal” (i.e., pre-/peri-menopausal); six males (1.8%) enrolled and all were recorded with menopausal status of “missing”. Approximately half of patients (47.1%) had a body mass index (BMI) in the normal range (≥ 18.5 kg/m² to < 25.0 kg/m²). The majority of patients had a baseline HbA_{1c} of $< 5.7\%$ (88.0%) and fasting glucose of < 100 mg/dL (71.1%).

Baseline Disease Characteristics

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At study entry, the majority of patients had metastatic disease (99.1%) with the remainder locally advanced disease (0.9%). The majority of patients had an ER+/ PR+ hormone receptor status (69.5%). Per eCRF data, most patients had secondary endocrine resistance (65.5%) vs. primary endocrine resistance (34.2%). The majority of patients had 2 (32.3%) or ≥ 3 (51.4%) organs involved at baseline. Only 0.6% had known CNS metastases at baseline. Per eCRF data, the majority of patients had measurable disease (non-measurable/ evaluable disease, including bone-only, was excluded) (96.6%), visceral disease (80%; defined as lung, liver, brain, pleural, and peritoneal involvement) and liver metastases (51.7%). The majority of patients had received prior (neo)-adjuvant chemotherapy (82.8%) and/or prior (neo)-adjuvant ET (99.4%); very few patients had received prior adjuvant CDK4/6 inhibitor therapy (1.2%).

The Applicant's Position: Study WO41554 enriched a patient population with poor prognosis clinicopathological characteristics. The two treatment arms were comparable with respect to baseline disease characteristics and breast cancer history and are representative of a patient population with endocrine-resistant *PIK3CA*-mutated, HR+, HER2– advanced breast cancer receiving treatment in a first-line setting.

The FDA's Assessment:

In general, FDA agrees with the Applicant's assessment. The patient population enrolled on this trial had endocrine resistant/refractory tumors that are considered to have a poor prognosis. The majority of patients had "secondary" endocrine resistance. Primary endocrine resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy and secondary endocrine resistance was defined a relapse while on adjuvant endocrine therapy after at least 2 years or relapse within 12 months of completing adjuvant endocrine therapy. In addition, all patients had a *PIK3CA* mutation, which is also considered a poor prognostic factor.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data and the Applicant's Position:

Treatment Compliance: The median relative dose intensity of inavolisib, palbociclib and fulvestrant was high (Inavo+Palbo+Fulv arm: 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 vs. Pbo+Palbo+Fulv arm: 88.4% [range: 33.3%-112.3%] for palbociclib and 100.0% [range: 60.0%-122.2%] for fulvestrant) and comparable between the treatment arms, indicating that the triplet combination was well-tolerated and the addition of inavolisib did not compromise the patients' ability to receive palbociclib and fulvestrant. Further details on exposure to study treatment are presented in **Table 26** in **Section 8.2.4**.

Concomitant medications: Overall, 73.5% patients received at least one prior concomitant medication ongoing at baseline in the study and this was comparable between arms (Inavo+Palbo+Fulv: 75.2% vs. Pbo+Palbo+Fulv: 72.0%). The majority of patients (90.8%) received at least one concomitant medication initiated during study treatment and this was

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comparable between arms (Inavo+Palbo+Fulv: 93.8% vs. Pbo+Palbo+Fulv: 87.8%). The most frequently reported (>20% of all patients) concomitant medications initiated during study treatment in the Inavo+Palbo+Fulv arm and Pbo+Palbo+Fulv arm, respectively, were: dexamethasone (33.5% and 20.1%), paracetamol (26.7% and 18.9%), and metformin (28.0% and 3.7%).

The FDA's Assessment:

FDA agrees with the Applicant's assessment of treatment compliance and concomitant medications. A higher percentage of patients in the inavolisib treatment arm were initiated on dexamethasone, paracetamol and metformin during the study, these treatments are reflective of the toxicities observed more commonly on the inavolisib treatment arm.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data and the applicant's position: The primary endpoint was met with a statistically significant and clinically meaningful improvement in investigator-assessed PFS (Table 20 and Figure 7). The results of the sensitivity analyses of BICR-assessed PFS (stratified HR = 0.50; 95% CI: 0.36, 0.68), investigator-assessed PFS in patients with centrally determined *PIK3CA* mutation-positive status (stratified HR: 0.44; 95% CI: 0.31, 0.62), and additional sensitivity analyses to assess the impact of stratification on PFS (unstratified HR = 0.50; 95% CI: 0.38, 0.67) and missing data (stratified HR = 0.44; 95% CI: 0.32, 0.60) were consistent with the primary analysis of investigator-assessed PFS, demonstrating the robustness of investigator-assessed PFS results. The PFS benefit by investigator-assessment per RECIST v1.1 favoring the Inavo + Palbo + Fulv arm was generally consistent across pre-defined patient subgroups.

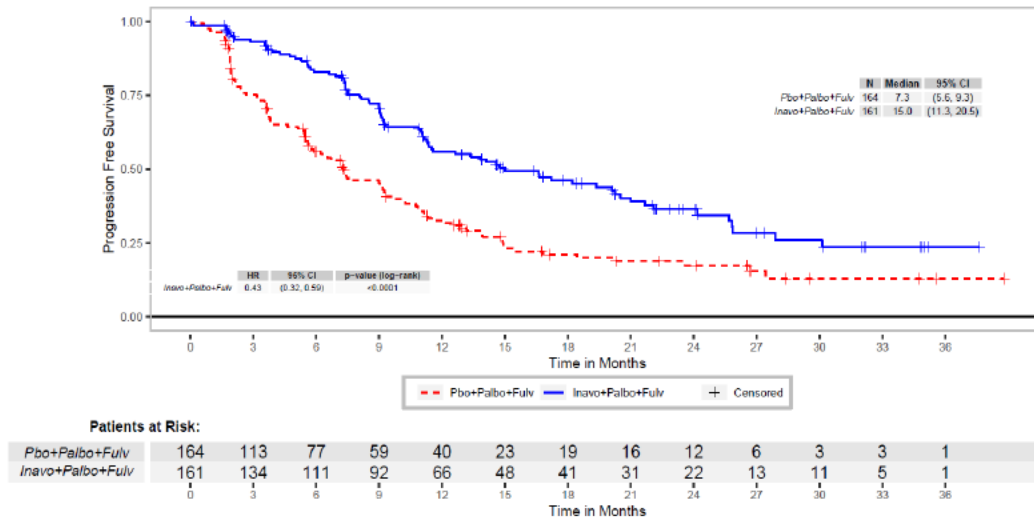
Table 20: Applicant - Overview of Study WO41554 Primary Efficacy Endpoint, Full Analysis Set

	Inavo + Palbo + Fulv N = 161	Pbo + Palbo + Fulv N = 164
Primary Efficacy Endpoints		
Progression-Free Survival (Investigator) per RECIST v1.1		
Patients with event (%)	82 (50.9%)	113 (68.9%)
Median (months) (95% CI)	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified HR (95% CI)	0.43 (0.32, 0.59)	
p-value (log-rank)	< 0.0001	

CI = confidence interval; HR = hazard ratio.

Source: WO41554 CSR, Report 1126696, Table 16; t_ef_tte_PFS_FAS_29SEP2023_41554; Dataset: ADaM: ADTTE

Figure 7: Applicant - Kaplan-Meier Plot for Progression-Free Survival by Investigator, Full Analysis Set



Source: WO41554 CSR, Report 1126696, Figure 4; Dataset: ADaM: ADTTE

The FDA’s Assessment:

FDA agrees that the Inavo + Palbo + Fulv arm demonstrated statistically significant efficacy results over the Pbo + Palbo + Fulv arm for the primary endpoint of PFS per Investigator assessment. FDA also agrees that PFS by BICR results were supportive of the primary endpoint.

FDA evaluated INV-assessed PFS subgroups by age, sex, race, visceral disease, endocrine resistance, and region, which are presented in the table below (Table 21).

Table 21: FDA - PFS by INV Subgroups (ITT)

	Inavo + Palbo + Fulv #events/N	Pbo + Palbo + Fulv #events/N	HR	95% CI
Age				
<65	66/136	91/130	0.37	(0.26, 0.53)
≥65	16/25	22/34	0.80	(0.37, 1.71)
Sex				
Female	80/156	113/163	0.44	(0.33, 0.60)
Male	2/5	0/1	-	-
Race				
White	50/94	65/97	0.45	(0.30, 0.68)
Asian	29/61	45/63	0.38	(0.23, 0.63)
Black	1/1	1/1	-	-
Unknown	2/5	2/3	-	-

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Visceral Disease				
Yes	69/127	95/126	0.42	(0.30, 0.59)
No	13/34	18/38	0.51	(0.24, 1.08)
Endocrine Resistance				
Primary	36/57	46/59	0.31	(0.18, 0.51)
Secondary	46/104	67/105	0.53	(0.36, 0.78)
Region				
Asia	27/58	45/62	0.37	(0.22, 0.61)
N. America/W. Europe	35/62	40/63	0.68	(0.42, 1.09)
Other	20/41	28/39	0.26	(0.13, 0.50)

PFS results were mostly consistent within subgroups but varied somewhat by region, with the North America/Western Europe region performing the worst of the three regions. The difference in survival between arms is diminished in the North America/Western Europe region in OS (HR=1.04 [95% CI: 0.54, 2.00]) and BICR-assessed PFS (HR=0.99 [95% CI: 0.60, 1.66]) as well. However, the sample sizes in these subgroups are small, so these results should be interpreted with caution.

FDA queried the Applicant about subgroup results for the North America/West Europe (NA/WE) patient population. In an Information Request Response dated May 20, 2024, the Applicant stated that they “observed a relatively large extent of imbalances in some baseline characteristics with known prognostic impact between the two arms in the NA/WE subgroup compared to the FAS population, which may negatively impact the performance of the inavolisib arm relative to the placebo arm in this subgroup and potentially explain the numerically larger hazard ratio for PFS.” These included a lower proportion of patients with 1 organ site (lower overall disease burden) in the inavolisib arm compared with the placebo arm (8.1% vs. 25.4%) in the NA/WE subgroup, which would be considered a better prognostic factor compared to >1 organ site involvement. In addition, they noted a higher proportion of patients with liver metastases (56.5% vs 46%) and progesterone receptor (PR)-negative disease (30.6% vs 20.6%) in the inavolisib arm compared with the placebo arm in the NA/WE subgroup, respectively. Both the presence of live metastases and PR negative disease may be poor prognostic factors. The Applicant stated the difference in OS results for NA/WE subgroup when compared to other subgroups could also be attributed to these same imbalances noted for the PFS results and due to the limited number of OS events. FDA agrees that these imbalances may have impacted the subgroup results but again notes these subgroup analyses should be interpreted with caution.

The concordance of PFS assessment between INV and BICR were examined and summarized in the table below (Table 22). The early discordance rate (EDR) and late discordance rate (LDR) were calculated for each arm. EDR is the frequency that the investigator declares recurrence earlier than BICR, and LDR is the frequency that investigator declares recurrence later than

BICR. A negative differential discordance for the EDR and/or a positive differential discordance for the LDR between the experimental arm and the control arm beyond a threshold would suggest bias in the investigator assessment favoring the Inavo+Palbo+Fulv arm. Threshold values ranging from 0.075 to 0.100 were recommended based on simulation studies in Amit et al. 2011.

Table 22: FDA - Concordance of INV and BICR Assessment of PFS in All Patients

INV Assessment	BICR Assessment			
	Inavo+Palbo+Fulv (N = 161)		Pbo+Palbo+Fulv (N = 164)	
	Event	Censor	Event	Censor
Event	74	8	96	17
Censor	3	76	2	49

The concordance was 93.2% (95% CI: 88.1%, 96.5%) for the Inavo+Palbo+Fulv arm and 88.4% (95% CI: 82.5%, 92.9%) for the Pbo+Palbo+Fulv arm. The EDR was 25.6% for the Inavo+Palbo+Fulv arm and 25.7% for the Pbo+Palbo+Fulv arm, a difference of -0.1%. The LDR was 62.5% for the Inavo+Palbo+Fulv arm and 58.0% for the Pbo+Palbo+Fulv arm, a difference of 4.5%. Neither of the differences for EDR or LDR was greater than the threshold recommended in Amit et al. to demonstrate investigator assessment bias in favor of Inavo+Palbo+Fulv.

Data Quality and Integrity

Data and the Applicant’s Position: Information requested by the Office of Scientific Investigations (OSI) is provided in Module 5.3.5.4. No issues were identified with the data quality or integrity which could affect the efficacy results.

A comprehensive assessment of the impact of the COVID-19 pandemic was conducted looking at planned study procedures, data collection, and data analyses. Overall, the impact of the COVID-19 pandemic for these studies was minor and there was no significant impact on the study results and the overall conclusions. Similarly, an assessment on the impact of the Russia-Ukraine conflict on Study WO41554 was also performed and assessed as minor. For Study GO39374, there were no patients enrolled at investigational sites in Russia or Ukraine; therefore, an assessment of the Russia-Ukraine conflict was not applicable for this study.

The FDA’s Assessment:

Refer to Section 4.1 of this Assessment Aid regarding details for OSI inspections conducted by FDA. FDA OSI inspected 3 clinical sites for INAVO120 (site codes 323897, 323629, and 323146). INV-assessed PFS, OS, and BICR-assessed PFS were evaluated excluding these study sites to assess any possible effect on HR. Overall, the results were consistent with those of the ITT population. No action was indicated for the sites.

Efficacy Results – Secondary and other relevant endpoints

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Version date: June 2022 (ALL NDA/ BLA reviews)

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Data: Efficacy data for secondary endpoints of OS, ORR, BOR rate, and DOR and provided in **Table 23**. Secondary and exploratory COA (PRO) endpoints are provided in the following sections.

Table 23: Applicant - Overview of Study WO41554 Secondary Efficacy Endpoints of OS, ORR, BOR Rate, and DOR, Full Analysis Set

	Inavo + Palbo + Fulv N = 161	Pbo + Palbo + Fulv N = 164
Secondary Efficacy Endpoints		
Overall Survival		
Patients with event (%)	42 (26.1%)	55 (33.5%)
Median (months) (95% CI)	NE (27.3, NE)	31.1 (22.3, NE)
Stratified HR (95% CI)	0.64 (0.43, 0.97)	
p-value (log-rank) ^a	0.0338	
Objective Response Rate (Investigator)		
Responders (n) (%)	94 (58.4%)	41 (25.0%)
95% CI (Clopper-Pearson)	50.4, 66.1	18.6, 32.3
Difference in Response rate (%) (95% CI)	33.4 (23.3, 43.5)	
Best Overall Response (Investigator)		
Responders (n) (%)	103 (64.0%)	49 (29.9%)
95% CI (Clopper-Pearson)	56.0, 71.4	23.0, 37.5
Difference in Response rate (%) (95% CI)	34.1 (23.9, 44.3)	
Clinical Benefit Rate (Investigator)		
Responders (n) (%)	121 (75.2%)	77 (47.0%)
95% CI (Clopper-Pearson)	67.7, 81.6	39.1, 54.9
Difference in Response rate (%) (95% CI)	28.2 (18.1, 38.3)	
Duration of Response (Investigator)		
Number of evaluable patients	94	41
Patients with event (%)	46 (48.9%)	27 (65.9%)
Median (months) (95% CI)	18.4 (10.4, 22.2)	9.6 (7.4, 16.6)

CI = confidence interval; HR = hazard ratio; NE = not estimable.

^a The pre-specified interim analysis of two-sided alpha boundary for OS was 0.0098.

Source: WO41554 CSR, Report 1126696, Table 16; t_ef_tte_OS_FAS_29SEP2023_41554; t_ef_rsp_ORR_INV_FAS_29SEP2023_41554; t_ef_rsp_BOR_INV_FAS_29SEP2023_41554; t_ef_rsp_CBR_INV_FAS_29SEP2023_41554; t_ef_tte_DOR_FAS_29SEP2023_41554; Dataset: ADaM: ADRS, ADTTE

Overall Survival: OS is the key secondary endpoint evaluated under Type I error control per the hierarchical testing procedure pre-specified in the SAP. At the planned interim analysis for OS, a total of 97 events had occurred (63% of planned OS events). The stratified HR was 0.64 (95% CI: 0.43, 0.97; p = 0.0338), with 42 deaths in the Inavo + Palbo + Fulv arm and 55 deaths in the Pbo + Palbo + Fulv arm (**Table 23**). Under the interim analysis stopping boundary ($p \leq 0.0098$), statistical significance was not reached. However, the interim OS analysis is highly supportive of the primary endpoint, with the Kaplan-Meier OS curve further indicating treatment benefit. The Kaplan-Meier curve started to separate at the beginning of the study in favor of the Inavo + Palbo + Fulv arm, and remained separated throughout the follow-up period.

Objective Response Rate (Investigator-Assessed): The confirmed ORR based on investigator assessment per RECIST v1.1 was more than doubled in the Inavo + Palbo + Fulv arm (58.4%) as compared with the Pbo + Palbo + Fulv arm (25.0%). An increase of $\Delta 33.4\%$ (95% CI: 23.3, 43.5) in the confirmed ORR favoring the Inavo + Palbo + Fulv arm was considered clinically meaningful.

Best Overall Response Rate (Investigator-Assessed): The proportion of patients with a best

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overall response of CR or PR, based on investigator assessment per RECIST v1.1, was more than doubled in the Inavo + Palbo + Fulv arm (64.0%) as compared with the Pbo + Palbo + Fulv arm (29.9%). An increase of $\Delta 34.1\%$ (95% CI: 23.9, 44.3) in favor of the Inavo + Palbo + Fulv arm was considered clinically meaningful.

Duration of Objective Response: Among patients who achieved a confirmed objective response (CR or PR), the estimated median duration of response was approximately 8.8 months longer in the Inavo + Palbo + Fulv arm (18.4 months) as compared with the Pbo + Palbo + Fulv arm (9.6 months).

Clinical Benefit of Rate (Investigator-Assessed): The proportion of patients with a CR, PR, and/or stable disease (SD) sustained for ≥ 24 weeks, based on investigator assessment per RECIST v1.1, was higher in the Inavo + Palbo + Fulv arm (75.2%) as compared with the Pbo + Palbo + Fulv arm (47.0%), with an increase of $\Delta 28.2\%$ (95% CI: 18.1, 38.3) in favor of the Inavo + Palbo + Fulv arm.

The Applicant's Position: Secondary endpoint analyses of OS, ORR, BOR, CBR rate, and DOR consistently showed a clinically meaningful improvement in Inavo+Palbo+Fulv treated patients over the Pbo+Palbo+Fulv arm.

The FDA's Assessment:

FDA generally agrees with the efficacy results for the secondary endpoints of OS, ORR, BOR, DOR, and CBR as presented by the applicant above. However, FDA notes that CBR is not an endpoint evaluated for regulatory decision-making.

FDA also notes that, since the interim analysis of OS at the time of PFS analysis was not statistically significant, none of the remaining secondary endpoints in the pre-specified testing hierarchy were formally tested at this time and results should be considered descriptive. The final analysis of OS is expected in the second quarter of 2025.

Dose/Dose Response

Data and the Applicant's Position: Please refer to **Section 6.2.2.1** and **Section 19.4.2**.

The FDA's Assessment:

FDA agrees with the Applicant's position. See Sections 6 and 19 of the Assessment Aid for further details on the FDA clinical pharmacology review for this NDA.

Durability of Response

Data and the Applicant's Position: Of the patients who had an objective response, the median duration of response in the Inavo+Palbo+Fulv arm was longer compared to the Pbo+Palbo+Fulv arm (18.4 months vs. 9.6 months) (**Table 23**).

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Among patients achieving an objective response, longer median DOR was observed in the Inavo + Palbo + Fulv arm, 18.4 months, compared with 9.6 months in the Pbo + Palbo + Fulv arm.

Persistence of Effect

Data: The investigator-assessed PFS event-free rate at 6 months, 12 months, and 18 months demonstrated early and durable benefit as shown by consistently and substantially higher PFS rates in the Inavo+Palbo+Fulv arm compared with the Pbo+Palbo+Fulv arm starting from the first tumor assessment and throughout the follow-up. Further evidence of early onset and persistence of efficacy is supported by the interim OS analysis, which although not statistically significant, is highly supportive of the primary endpoint.

The Applicant's Position: Overall, the consistently prolonged PFS, OS and DOR data support that inavolisib, combined with palbociclib and fulvestrant, is durable and persists after treatment.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Efficacy Results – Secondary and exploratory COA (PRO) endpoints

Data: PRO analyses were conducted for the BPI-SF Worst Pain Severity item and the EORTC QLQ-C30 PF, RF, and GHS/QoL scales. High compliance rates (>80%) for the BPI-SF Worst Pain Severity item and EORTC QLQ-C30 were seen in both treatment arms at baseline and through Cycle 15.

TTCD in Worst Pain Severity: Median TTCD in worst pain severity, as assessed by the BPI-SF questionnaire worst pain severity item, was longer for the Inavo + Palbo + Fulv arm (30.9 months) compared to the Pbo + Palbo + Fulv arm (18.1 months), indicating patients receiving inavolisib experienced a longer duration of time without worsening pain severity.

TTCD and Mean Change in Physical Functioning, Role Functioning and HRQoL: Median TTCD was 23.7 months and 22.7 months for physical functioning, 25.7 months and 24.2 months for role functioning, and 29.0 months and 27.4 months for HRQoL, as assessed by the EORTC QLQ-C30 function and GHS/QoL scales, in the Inavo + Palbo + Fulv arm and Pbo + Palbo + Fulv arm, respectively, indicating patients in both arms maintained their day-to-day functioning and HRQoL for a similar duration of time while on treatment. Mean change scores of less than 10 points observed in these scales during treatment demonstrate that patients' baseline levels of functioning and HRQoL were maintained while on treatment in both arms.

The Applicant's Position: These findings demonstrate that adding Inavo to Palbo and Fulv prolongs time without clinically meaningful deterioration in pain severity and does not adversely impact patients' day-to-day functioning and HRQoL, further supporting a positive benefit/risk profile for inavolisib.

The FDA's Assessment:

FDA acknowledges that TTCD in worst pain severity, physical functioning, role functioning, and health-related quality of life were key secondary endpoints included in the testing hierarchy. Completion rates for all PROs were high at baseline, above 90%, and remained above 80% at subsequent assessment timepoints during which the majority of patients remained on treatment in each arm (Cycle 9 and Cycle 5 for the Inavo + Palbo + Fulv versus Pbo + Palbo + Fulv arms, respectively). In general, FDA has concerns about patient-reported time-to-deterioration endpoints, and this was communicated to the Applicant prior to submission. Further, as noted in the secondary endpoints section, these results are considered descriptive at this time because the first key secondary endpoint of OS was not statistically significant. The Applicant did collect PRO-CTCAE and patient-reported overall side effect impact data, which is described in Section 8.2 below.

Additional Analyses Conducted on the Individual Trial

Data and the Applicant's Position: No additional analyses were conducted.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.1.2.2. Supportive Study: G039374, Phase I

The primary endpoint of Study G039374 is safety. The study makes a preliminary assessment of the anti-tumor activity of inavolisib administered as a single agent in patients with locally advanced or metastatic *PIK3CA*-mutated solid tumors or in combination with other therapies in patients with *PIK3CA*-mutated HR+, HER2– LA/mBC. The data provided herein focuses on Arms B (Inavo+Palbo+Letro), E (Inavo+Palbo+Fulv), and F (Inavo+Palbo+ Fulv+ Metf).

Patient Disposition

Data and the Applicant's Position: All patients enrolled in Arm B (N =33), Arm E (N = 20), and Arm F (N =21) were treated except for 1 patient in Arm F. This patient withdrew consent and discontinued from the study prior to receiving any study drug. As of CCOD (27 March 2023), the majority of 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%). A total of 191 patients were enrolled across Arms A-F. At the CCOD, a total of 176 patients (92.1%) discontinued from the study. The majority of study discontinuations were due to progressive disease (141 patients [73.8%]) and symptomatic deterioration (clinical progression of study disease; 15 patients [7.9%]).

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Demographic Characteristics

Data: All patients enrolled in Arm B (N = 33), Arm E (N = 20), and Arm F (N = 21) were female (Table 24). The median age of patients was 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. Half of the patients in Arm E (50%) and the majority of patients in Arm B (78.8%) and Arm F (76.2%) had self-reported race recorded as White. The remaining patients in each arm self-reported as either Asian, Black or African American or were of the race category 'unknown'. All patients in Arm B, Arm E, and Arm F had a baseline Eastern Cooperative Oncology Group (ECOG) status of either 0 or 1. A high proportion of patients in Arm F had a baseline HbA_{1c} ≥ 5.7% (10 patients; 50.0%) and BMI ≥ 30 kg/m² (15 patients; 75.0%) reflecting the inclusion criteria for enrollment in Arm F (patients needed to meet at least one of these 2 eligibility criteria, which are considered risk factors for hyperglycemia).

The overall population of GO39374 comprised of mostly female patients (99.5%) with breast cancer and 1 male patient (0.5%) with colorectal cancer (CRC) (in Stage I Arm A), was predominately self-reported as White (72.8%), and had a median age of 59 years (range: 31-85 years).

Table 24: Applicant - Study GO39374 Demographic Characteristics, Full Analysis Set

	Inavo + Palbo + Letro (N=33) n (%)	Inavo 9 mg + Palbo + Fulv (N=20) n (%)	Inavo 9 mg + Palbo + Fulv + Metf (N=21) n (%)	All Patients (N=191) n (%)
Sex				
Male	0	0	0	1 (0.5%)
Female	33 (100%)	20 (100%)	21 (100%)	190 (99.5%)
Age				
Mean years (SD)	56.5 (10.7)	56.8 (10.8)	60.6 (12.3)	59.1 (10.6)
Median (years)	57.0	55.0	65.0	59.0
Min, max (years)	37 - 80	33 - 73	33 - 77	31 - 85
Age Group				
< 18 years	0	0	0	0
< 65 years	24 (72.7%)	15 (75.0%)	10 (47.6%)	126 (66.0%)
≥ 65 years	9 (27.3%)	5 (25.0%)	11 (52.4%)	65 (34.0%)
≥ 75 years	2 (6.1%)	0	1 (4.8%)	9 (4.7%)
Race				
White	26 (78.8%)	10 (50.0%)	16 (76.2%)	139 (72.8%)
Black or African American	1 (3.0%)	0	0	3 (1.6%)
Asian	1 (3.0%)	0	1 (4.8%)	5 (2.6%)
American Indian or Alaska Native	0	0	0	0

Table 24: Applicant - Study GO39374 Demographic Characteristics, Full Analysis Set

	Inavo + Palbo + Letro (N=33) n (%)	Inavo 9 mg + Palbo + Fulv (N=20) n (%)	Inavo 9 mg + Palbo + Fulv + Metf (N=21) n (%)	All Patients (N=191) n (%)
Native Hawaiian or Other Pacific Islander	0	0	0	0
Multiple	0	0	0	1 (0.5%)
Unknown	5 (15.2%)	10 (50.0%)	4 (19.0%)	43 (22.5%)
Ethnicity				
Hispanic or Latino	1 (3.0%)	1 (5.0%)	0	6 (3.1%)
Not Hispanic or Latino	29 (87.9%)	8 (40.0%)	17 (81.0%)	140 (73.3%)
Region (optional)				
United States	21 (63.6%)	5 (25.0%)	14 (66.7%)	124 (64.9%)
Canada	2 (6.1%)	2 (10.0%)	3 (14.3%)	14 (7.3%)
South America	0	0	0	0
Europe	10 (30.3%)	13 (65.0%)	4 (19.1%)	53 (27.8%)
Asia	0	0	0	0
Australia	0	0	0	0

Source: t_ds_enroll_CSR_FAS_27MAR2023_39374 ; t_dm_CSR_FAS_27MAR2023_39374 ; Dataset:AdaM: ADSL

The Applicant’s Position: The population from Arms B, E, and F of Study GO39374 are representative of *PIK3CA*-mutated, HR+, HER2– LA/mBC patients receiving an endocrine-based combination therapy in a later line setting.

The FDA’s Assessment:

FDA agrees with the demographic characteristics presented for Arms B, E, and F of GO39374 presented in Table 9. Similar to INAVO120, there were very few Black or Hispanic patients enrolled on GO39374.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data: All patients enrolled in Arm B (N = 33), Arm E (N = 20), and Arm F (N = 21) had to have histologically documented, *PIK3CA*-mutated, HR+, HER2– LA/mBC.

At baseline, the majority of patients in Arm B (93.9%), Arm E (95.0%), and all 21 patients (100%) in Arm F had at least one site of metastatic disease. The most common sites of metastatic disease were bone (Arm B: 66.7%; Arm E: 80.0%; Arm F: 76.2%), liver (Arm B: 54.5%; Arm E: 30.0%; Arm F: 61.9%), and lung (Arm B: 39.4%; Arm E: 30.0%, Arm F: 19.0%).

The majority of patients in Arm B (97.0%), Arm E (60.0%), and all 21 patients in Arm F had received prior systemic anti-cancer therapy in the metastatic setting before study enrollment. Among these patients, the median line of prior therapy in the metastatic setting was 2 lines (range: 1-4 lines) for Arm B, 1 line (range: 1-4 lines) for Arm E, and 3 lines (range: 1-9 lines) for Arm F. In Arm B, 21.2% had received prior treatment with a CDK4/6 inhibitor. No patients in Arm E had received prior CDK4/6 inhibitor as per eligibility requirement, while 66.7% of patients in Arm F had received a prior CDK4/6 inhibitor.

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Most patients in Arm B (72.7%), Arm E (80%), and Arm F (95.2%) had received prior AI, with letrozole as the most common aromatase inhibitor therapy reported in all arms. Fourteen out of 33 patients (42.4%) in Arm B, 3/20 patients (15.0%) in Arm E and the majority of patients in Arm F (71.4%) had received a prior selective estrogen-receptor degrader (SERD). In the overall population, 97.4% of patients had at least one site of metastatic disease at baseline. A total of 94.8% of patients had received prior cancer therapy in the metastatic setting. Among the patients who received therapy in the metastatic setting, the median line of prior therapy in the metastatic setting was 2 (range: 1-10).

The Applicant's Position: The population from Arms B, E, and F of Study GO39374 are representative of *PIK3CA*-mutated, HR+, HER2– LA/mBC patients receiving an endocrine-based combination therapy in a later line setting. There were no eligibility restrictions with respect to patients' endocrine sensitivity or resistance; however, the majority of patients enrolled in Arm B, Arm E, and Arm F were endocrine-resistant.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. The majority of patients in Arms B, E and F had received prior systemic therapy in the advanced/metastatic setting. In addition, patients enrolled in GO39374 were not required to have endocrine resistant disease.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data and The Applicant's Position: At the CCOD, the median cumulative inavolisib dose intensity was high at 95.3%, 90.5% and 89.1% in Arms B, E, and F, respectively. The median cumulative palbociclib dose intensity was 80.6% in Arm E and 92.8% in Arm F, and the median cumulative fulvestrant dose intensity was 95.4% in Arm E and 95.7% in Arm F. In the overall population, the median cumulative inavolisib dose intensity across all arms was 96.0% (**Table 28**).

Overall, 93.7% of patients had at least one medication ongoing at baseline. The most commonly used ($\geq 30\%$ of patients overall) medication classes were: analgesics (59.7%); vitamins (44.5%); psycholeptics (44.5%); mineral supplements (40.8%); topical products for joint and muscular pain (36.1%); drugs for acid related disorders (35.1%); ophthalmologicals (31.9%); other dermatological preparations (30.4%).

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Efficacy Results

Data: Supportive efficacy data from Arm B, Arm E, and Arm F of the Phase I Study GO39374 (CCOD of 27 March 2023) are provided in **Table 25**. These results should be interpreted in the context of the single arm study design and relatively small sample size, as well as the specific eligibility requirements in each treatment arm. Efficacy endpoints were tested in the safety analysis set (Arm B: N = 33, Arm E: N = 20 and Arm F: N = 20).

Table 25: Applicant - Overview of Study GO39374 Efficacy: Arm B, Arm E and Arm F

	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: Study GO39374 CSR, Report 1125233, Table 22, Table 23, Table 24, Table 25, Table 26;

t_ef_rsp_CSR_CBOR_SEMD_27MAR2023_39374; t_ef_rsp_CSR_BOR_SEMD_27MAR2023_39374;

t_ef_tte_CSR_CRSD_SEMD_27MAR2023_39374; t_ef_rsp_CSR_CBR_SE_27MAR2023_39374; t_ef_tte_CSR_PFS_SE_27MAR2023_39374;

Dataset: ADaM: ADRS, ADTTE

The Applicant's Position: The triplet combination of inavolisib plus palbociclib and an endocrine agent (fulvestrant or letrozole) across Arm B, Arm E and Arm F from the Phase I GO39374 study resulted in promising clinical activity in terms of investigator-assessed endpoints of ORR, DOR, CBR, and PFS, in patients with *PIK3CA*-mutated HR+, HER2– LA/mBC.

The FDA's Assessment:

The confirmed ORR results in patients with measurable disease in Arm B (N=25), Arm E (N=15), and Arm F (N=18) were 52% (31%, 72%), 40% (16%, 68%), and 17% (0%, 41%), respectively, using the Clopper-Pearson exact method to calculate the 95% confidence intervals. While activity was observed across the three treatment arms based on the confirmed ORR and DOR, given the small sample sizes and wide CI of ORR, the contribution of inavolisib to efficacy was unclear in these single arm cohorts. (b) (4)

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

FDA's conclusions regarding the efficacy of inavolisib plus palbociclib and fulvestrant for the treatment of adults with endocrine resistant, *PIK3CA*-mutated, HR-positive, HER2-negative,

locally advanced, or metastatic breast cancer, following recurrence on or after completing adjuvant endocrine therapy, are based on results from 325 patients enrolled in INAVO120, an ongoing, randomized, double-blind, placebo-controlled, multicenter trial of inavolisib plus palbociclib and fulvestrant versus placebo plus palbociclib and fulvestrant. Patients enrolled on INAVO120 were required to have advanced breast cancer with a PIK3CA mutation, considered to be endocrine resistant, and could not have received prior systemic therapy in the advanced or metastatic setting for breast cancer. PIK3CA mutation was determined through testing of blood plasma-derived ctDNA with a next-generation sequencing (NGS) assay performed at the Sponsor-designated central laboratory, or through local testing of ctDNA or tumor tissue with an appropriately validated NGS or PCR assay. Primary endocrine resistance was defined as relapse while on the first 2 years of adjuvant endocrine therapy (ET) and secondary endocrine resistance was defined as relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET.

The primary efficacy endpoint for INAVO120 was PFS as assessed by investigator. A prospectively planned sensitivity analysis of PFS by BICR assessment was also performed on all patients. Key secondary endpoints included OS, ORR, and TTCD in worst pain severity, physical functioning, role functioning, and health-related quality of life. DOR was a secondary endpoint.

INAVO120 met its primary endpoint with a median PFS of 15 months (95% CI 11.3, 20.5) vs 7.3 months (95% CI: 5.6, 9.3) favoring inavolisib (HR 0.43, 95% CI: 0.32, 0.59; p-value <0.0001). PFS by BICR results were supportive of the primary endpoint. OS is the key secondary endpoint per the hierarchical testing procedure pre-specified in the SAP. The interim OS analysis at the time of PFS analysis with 63% information fraction was not statistically significant. Interim OS results showed a HR of 0.64 (95% CI: 0.43, 0.97) with median OS not estimable (95% CI: 27.3, NE) on the inavolisib with palbociclib plus fulvestrant arm and 31.1 months (95% CI: 22.3, NE) on the placebo + palbociclib + fulvestrant arm. Thus, there appears to be no detriment in OS at this time. The final analysis of OS is expected in the second quarter of 2025. Results for the secondary endpoints of ORR and DOR appear to support the primary endpoint results. However, since the interim analysis of OS at the time of PFS analysis was not statistically significant, none of the remaining secondary endpoints in the pre-specified testing hierarchy were formally tested at this time.

Time to confirmed deterioration (TTCD) in worst pain severity, physical functioning, role functioning, and health-related quality of life were key secondary endpoints included in the testing hierarchy. In general, FDA has concerns about patient-reported time-to-deterioration endpoints, and this was communicated to the Applicant prior to submission. Further, these results are considered descriptive at this time because the first key secondary endpoint of OS was not statistically significant as noted above.

As noted in the Integrated Assessment of Effectiveness (Section 8.1.4), the results of the GO39374 trial were not considered supportive of expanded indication beyond the population enrolled in INAVO120.

The addition of inavolisib to palbociclib and fulvestrant resulted in a statistically significant and clinically meaningful improvement in PFS based on results from INAVO120. Results for secondary endpoints were supportive of the primary endpoint. However, racial and ethnic minorities reflective of the U.S. population of patients with breast cancer were significantly underrepresented in INAVO120. INAVO120 was a multinational trial with just 16 patients (4.9%) enrolled from the US. Almost all patients were female (98%) and the median age of enrolled patients was 54 years. The majority of patients on study were White, with only two Black patients and 20 Hispanic/Latino patients enrolled on study. Due to the lack of diversity in the enrolled population, a Post Marketing Commitment (PMC) is being issued to further characterize the efficacy and safety of inavolisib with palbociclib and fulvestrant for the treatment of breast cancer in study populations whose demographics are more representative of the population of U.S. patients for the proposed indication.

8.1.4. Assessment of Efficacy Across Trials

Data and the Applicant's Position: Because the study designs, patient populations, and the combination regimens differed between Studies WO41554 and GO39374, the efficacy data are presented for each study separately, no pooling of efficacy data between the two studies was conducted.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Additional Efficacy Considerations

The FDA's Assessment:

Not applicable.

8.1.5. Integrated Assessment of Effectiveness

Data: See Section 8.1.1 Pivotal Study: WO41554 (INAVO120), Phase III and Supportive Study: GO39374, Phase I for efficacy data.

The Applicant's Position:

Pivotal Study WO41554: Study WO41554 met its primary endpoint. The addition of inavolisib to the standard of care regimen of palbociclib and fulvestrant reduced the risk of disease progression or death by 57% and more than doubled the median PFS (15.0 months in the Inavo+Palbo+Fulv arm vs. 7.3 months Pbo+Palbo+Fulv arm). The results of the sensitivity analysis of BICR-assessed PFS, the sensitivity analysis of investigator-assessed PFS in patients with centrally determined *PIK3CA* mutation-positive status, and additional sensitivity analyses to assess the impact of stratification and missing data on PFS, were consistent with the primary analysis, and thus overall support the robustness of the observed PFS benefit of Inavo+Palbo+Fulv over Pbo+Palbo+Fulv. The PFS benefit by investigator-assessment favoring the Inavo+Palbo+Fulv arm was generally consistent across pre-defined subgroups.

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The investigator-assessed PFS event-free rate at 6 months, 12 months, and 18 months demonstrated early and durable benefit as shown by consistently and substantially higher PFS rates in the Inavo+Palbo+Fulv arm compared with the Pbo+Palbo+Fulv arm starting from the first tumor assessment and throughout the follow-up. Further evidence of consistent efficacy is supported by the interim OS analysis, which although not statistically significant, is highly supportive of the primary endpoint. In addition, the confirmed objective responses were also durable. Of the patients who had a confirmed objective response, the median duration of response was approximately 8.8 months longer in the Inavo+Palbo+Fulv (18.4 months) arm than in the Pbo+Palbo+Fulv arm (9.6 months).

Patient-reported outcomes showed that adding inavolisib to palbociclib and fulvestrant extends time without clinically meaningful worsening of pain severity without contributing additional burden to patients' day-to-day function and overall quality of life.

Supportive Study GO39374: In Study GO39374, the triplet combination of inavolisib plus palbociclib and fulvestrant or inavolisib plus palbociclib and letrozole resulted in consistent and promising clinical activity in terms of investigator-assessed endpoints of ORR, DOR, CBR, and PFS, regardless of endocrine backbone (letrozole or fulvestrant) and across multiple treatment lines in patients with *PIK3CA*-mutated HR+, HER2– LA/mBC.

The FDA's Assessment:

FDA agrees that INAVO120 (Study WO41554) met its primary endpoint of PFS by investigator. Furthermore, the sensitivity analysis for PFS by BICR was also supportive of the primary endpoint. The interim analysis of OS at the time of PFS analysis was not statistically significant but does appear to be supportive of the primary endpoint results. Results for the additional secondary endpoints of ORR and DOR also support the primary endpoint results; however, since the interim analysis of OS at the time of PFS analysis was not statistically significant, none of the remaining secondary endpoints in the pre-specified testing hierarchy were formally tested.

Data from a phase 1 trial, GO39374, was submitted by the Applicant

(b) (4)

GO39374 is an ongoing, open-label, multicenter, Phase I study designed to evaluate the safety, tolerability, and PK of inavolisib administered orally as a single agent in patients with locally advanced or metastatic *PIK3CA*-mutated solid tumors, including breast cancer, and in combination with standard-of-care endocrine and/or targeted therapies in patients with *PIK3CA*-mutated locally advanced and metastatic breast cancer. Not all patients enrolled on GO39374 had endocrine resistant breast cancer. Arms B (inavolisib in combination with palbociclib and letrozole), E (inavolisib in combination with palbociclib and fulvestrant), and F (inavolisib in combination with palbociclib, fulvestrant, and metformin) were identified by the Applicant to be the most pertinent to the current NDA submission.

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Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

While, activity was observed across the three treatment arms based on the confirmed ORR and DOR, given the small sample sizes and wide CI of ORR, the contribution of inavolisib to efficacy was unclear in these single arm cohorts. (b) (4)

The addition of inavolisib to palbociclib and fulvestrant resulted in a statistically significant and clinically meaningful improvement in PFS for the patient population enrolled on INAVO120. Results for secondary endpoints were supportive of the primary endpoint. The safety profile for inavolisib is reviewed in Section 8.2 of this Assessment Aid. Overall, the benefit-risk assessment is favorable for the triplet combination treatment with inavolisib + palbociclib + fulvestrant in adults with endocrine resistant, PIK3CA mutated, HR-positive, HER2-negative, locally advanced, or metastatic breast cancer, following recurrence on or within 12 months of adjuvant endocrine therapy. There is not adequate data to support a benefit for use of the triplet combination in patients that do not have PIK3CA mutated advanced breast cancer that is not considered endocrine resistant or for use of a different endocrine therapy other than fulvestrant.

Currently, there are no FDA approved treatments specifically for the first line treatment of patients with PIK3CA mutated locally advanced or metastatic HR-positive, HER2-negative breast cancer considered to have endocrine resistant disease. Alpelisib and capivasertib are two drugs approved by the FDA for use in patients with PIK3CA-mutated advanced breast cancer. However, both are for second line and later treatment and are not specifically for patients with endocrine resistant disease. Addition of CDK4/6 inhibitor to ET has improved the outcomes of patients with advanced HR-positive breast cancer. The addition of inavolisib to this standard of care doublet therapy further improves the outcome specifically for patients with endocrine resistant, PIK3CA-mutated advanced breast cancer.

Patients should be selected for treatment based on the presence of PIK3CA mutation using the FoundationOne Liquid CDx (F1LDx). The sPMA P190032-S023 will be contemporaneously approved with this NDA for inavolisib. A PMC has been issued for tissue testing, as the PMA is planned to be submitted at the end of 2024.

8.2. Review of Safety

The Applicant's Position: The clinical safety data is primarily derived from the pivotal Phase III Study WO41554, with supportive data derived from the Phase I Study GO39374 and specifically from Arms B, E and F for the triplet combination (Inavo+Palbo+ET). In Study WO41554, safety data are available from the safety analysis set (SAS) (defined as patients exposed to any study treatment) which included 162 patients in the Inavo+Palbo+Fulv arm and 162 patients in the Pbo+Palbo+Fulv arm. Supportive safety data from Study GO39374, Arms B (N=33) (Inavo+Palbo+Letro), E (N=20) (Inavo+Palbo+Fulv) and F (N=20) (Inavo+Palbo+Fulv+Metf), who received the triplet combination of Inavo+Palbo plus an ET, have been included to allow for a comprehensive assessment of the safety profile of triplet combination in a broader patient population with underlying high risk factors for hyperglycemia and multiple prior lines of

therapies. With the addition of safety data from Arms B, E and F, as well as aggregate data from the overall safety population (Arms A-F) of GO39374 (N = 190), the Sponsor considers the totality of safety data from approximately 350 patients treated with inavolisib as a single agent and in combination therapy across multiple lines of therapy as adequate to characterize the safety and tolerability profile of inavolisib.

Pooling across the studies or presenting data from both studies side-by-side was not considered appropriate due to differences in the patient population, treatment regimens, the range of inavolisib dose levels, and the differences in AE grading criteria for these two studies.

The FDA's Assessment:

The safety analyses were based primarily on FDA's independent review of data from the phase 3 INAVO120 (WO41554) trial. The FDA's safety analysis focused on deaths and treatment emergent adverse events (TEAEs) including serious adverse events (SAEs), TEAEs leading to trial drug discontinuation, dose reduction, or dosage interruption, grade 3-4 TEAEs, and all-grade TEAEs. The FDA also reviewed laboratory data. AEs of special interest included hyperglycemia, stomatitis, and diarrhea.

Topline safety results were reviewed for GO39374 by FDA. In general, no new safety signals were noted from the GO39374 data compared to the safety data from INAVO120. In depth safety analyses were not conducted by FDA for the GO39374 trial, as this trial was not considered to be supportive of expanded indication.

8.2.1. Safety Review Approach

The Applicant's Position: The safety and tolerability assessments consisted of the monitoring and recording of AEs, including SAEs and protocol-specified selected AEs, performing protocol-specified safety laboratory assessments, and assessing protocol-specified vital signs, ECG, ECOG performance status and PRO -CTCAE assessments.

The FDA's Assessment:

FDA agrees that the safety review approach was appropriate to evaluate the safety profile for inavolisib.

8.2.2. Review of the Safety Database

Overall Exposure

Data and the Applicant's Position: See Table 26, Table 27, and Table 28 for an overview of study treatment exposure. The median relative dose intensity of inavolisib in the Inavo+Palbo+Fulv arm (95.8%) of Study WO41554 was high and comparable with the median dose intensity of inavolisib in Study GO39374 Arm B (95.5%), Arm E (93.8%), Arm F (92.0%) and the overall safety population (96.6%), demonstrating good tolerability of a triplet combination with palbociclib,

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plus fulvestrant, or letrozole, across a broad patient population. Furthermore, the median relative dose intensities of combination therapy components were also high and comparable within Study GO39374 and between studies, showing the addition of inavolisib did not compromise the dose intensity of palbociclib, fulvestrant and letrozole.

Table 26: Applicant - Safety Population, Size, and Denominators

Safety Database for the Study Drug ¹		
Individuals exposed to the study drug in this development program for the indication under review N= 351 ^{3,*}		
Clinical Trial Groups	Inavolisib (N = 351)	Placebo (N = 162)
Controlled trials conducted for this indication ² : WO41554	162	162
All other than controlled trials conducted for this indication ³ : GO39374	189	N/A
Controlled trials conducted for other indications ⁴	N/A	N/A

¹ study drug means the drug being considered for approval.

² to be used in product's labeling

³ if placebo arm patients switch to study drug in open label extension, the n should include their number; do not count twice patients who go into extension from randomized study drug arm

⁴ include n in this column only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review. Consider n=0 in this column if no patients treated for other indication(s) were included in this safety database.

*Sum of patients that received at least one dose of study drug (inavolisib).

Table 27: Applicant - Study WO41554 Exposure to Inavolisib, Placebo, Palbociclib, and Fulvestrant (Safety Analysis Set)

	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%)
>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

Table 27: Applicant - Study WO41554 Exposure to Inavolisib, Placebo, Palbociclib, and Fulvestrant (Safety Analysis Set)

	Inavo+Palbo+Fulv (N=162)			Pbo+Palbo+Fulv (N=162)		
	Inavolisib	Palbociclib	Fulvestrant	Placebo	Palbociclib	Fulvestrant
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.

Sources: Primary CSR, Study WO41554, Report 1126696, Table 14; t_ex_IVL_SAS_29SEP2023_41554, t_ex_PAL_SAS_29SEP2023_41554, t_ex_FUL_SAS_29SEP2023_41554; Dataset: ADaM: ADEX

Table 28: Applicant - Study GO39374 Study Treatment Exposure (Safety Analysis Set, Arms B, E, F, and All Patients)

	Inavo + Palbo + Letro (N=33)	Inavo 9 mg + Palbo + Fulv (N=20)	Inavo 9 mg + Palbo + Fulv + Metf (N=20)	All Patients (N=190)
Inavolisib (n=190)				
Median Number of Inavolisib Doses (Range)	433.0 (10-1772)	609.5 (35-1423)	203.0 (24-1051)	195.0 (5-1772)
Median Inavolisib Duration (months) (Range)	15.7 (1.3-66.5)	20.8 (1.8-47.6)	7.2 (1.1-35.4)	7.2 (0.2-66.5)
Median Inavolisib Dose Intensity	95.5%	93.8%	92.0%	96.6%
Median Cumulative Inavolisib Dose Intensity	95.3%	90.5%	89.1%	96.0%
Palbociclib (n=73)				
Median Number of Palbociclib Doses (Range)	321.0 (30-1348)	466.0 (29-1073)	149.0 (38-834)	274.0 (29-1348)
Median Palbociclib Duration (months) (Range)	15.7 (1.4-66.3)	20.7 (1.8-47.6)	6.2 (1.5-35.9)	13.0 (1.4-66.3)
Median Palbociclib Dose Intensity	90.8%	90.9%	94.2%	91.4%
Median Cumulative Palbociclib Dose Intensity	81.3%	80.6%	92.8%	85.1%
Letrozole (n=70)				
Median Number of Letrozole Doses (Range)	502.0 (44-1826)	—	—	191 (5-1826)
Median Letrozole Duration (months) (Range)	17.0 (1.4-66.5)	—	—	6.4 (0.3-66.5)
Median Letrozole Dose Intensity	98.0%	—	—	99.4%
Median Cumulative Letrozole Dose Intensity	98.0%	—	—	99.4%
Fulvestrant (n=100)				
Median Number of Fulvestrant Doses (Range)	—	20.5 (3-53)	7.5 (1-38)	10 (1-53)
Median Fulvestrant Duration (months) (Range)	—	20.0 (0.9-47.4)	5.24 (0.0-35.3)	7.85 (0.0-47.4)
Median Fulvestrant Dose Intensity	—	95.4%	95.7%	97.4%
Median Cumulative Fulvestrant Dose Intensity	—	95.4%	95.7%	97.3%
Metformin (n=20)				
Median Number of Metformin Doses, (Range)	—	—	108 (25-1057)	108 (25-1057)
Median Metformin Duration (months) (Range)	—	—	3.7 (0.8-35.9)	3.7 (0.8-35.9)
Median Metformin Dose Intensity	—	—	96.1%	96.1%

Table 28: Applicant - Study GO39374 Study Treatment Exposure (Safety Analysis Set, Arms B, E, F, and All Patients)

	Inavo + Palbo + Letro (N=33)	Inavo 9 mg + Palbo + Fulv (N=20)	Inavo 9 mg + Palbo + Fulv + Metf (N=20)	All Patients (N=190)
Median Cumulative Metformin Dose Intensity	—	—	90.5%	90.5%

Arm B = inavolisib in combination with palbociclib and letrozole (Stage I: inavolisib at 3 mg [n=3], 6 mg [n=3], and 9 mg [n=7], Stage II: inavolisib at 9 mg [n=20]);

Arm E = inavolisib in combination with palbociclib and fulvestrant (Stage II: inavolisib at 9 mg [n=20]);

Arm F = inavolisib in combination with palbociclib and fulvestrant and metformin (Stage II: inavolisib at 9 mg [n=20]).

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day. Dose intensity is the number of doses actually received divided by the expected number of doses.

If a reason for dose modification is not provided, the record will not be counted in dose modification summaries.

Cumulative dose intensity is calculated as total dose administered during the analysis period divided by total dose scheduled to be administered multiplied by 100.

Dose modification includes dose increase, dose interruption, and dose reduction.

Source: Adapted from Interim CSR, Study GO39374, Report 1125233, Table 10; t_ex_CSR_GDC_SE_27MAR2023_39374,

t_ex_CSR_PALBO_SE_27MAR2023_39374, t_ex_CSR_LETRO_SE_27MAR2023_39374, t_ex_CSR_FULV_SE_27MAR2023_39374,

t_ex_CSR_METF_SE_27MAR2023_39374; Dataset: ADaM: ADEX

The FDA's Assessment:

The FDA's review of safety population for this application is primarily from the INAVO120 Trial (WO41554). FDA agrees that the exposure is adequate to characterize safety of inavolisib. The median relative dose intensity of inavolisib in the Inavo+Palbo+Fulv arm (95.8%) of the INAVO120 (WO41554) trial was high. In addition, the median relative dose intensity of palbociclib and fulvestrant was similar between the two treatment arms of the INAVO120 (WO41554) trial; therefore, the triplet combination therapy including inavolisib did not have a significant impact on the ability to administer full dose of palbociclib+fulvestrant.

In depth exposure analyses were not conducted by FDA for the GO39374 trial.

Relevant characteristics of the safety population:

Data and the Applicant's Position: The safety population in WO41554 was similar to FAS. Refer to **Section 8.1.1** for the summary of demographics and baseline characteristics in the FAS population for WO41554 and SAS population for GO39374, and **Section 8.1** for an overview of the eligibility criteria. Study GO39374 enrolled patients with broader HbA_{1C} and fasting blood glucose (FBG) criteria to allow for the characterization of the risk of hyperglycemia in patients with underlying risk factors.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that the safety population for the INAVO120 trial (WO41554) was similar to the FAS. FDA agrees the safety population for GO39374 is the same as the SAS population summarized in Section 8.1.1.

Adequacy of the safety database:

The Applicant's Position: The evaluation of safety is primarily derived from the pivotal Study WO41554, with supportive data derived from Study GO39374 to support the adequate characterization of efficacy, safety, and tolerability of inavolisib in combination with palbociclib and an ET in patients with *PIK3CA*-mutated HR+, HER2– LA/mBC.

Data from Study GO39374 will supplement the safety database for inavolisib based combinations (aggregate data from Arms A-F), including additional data for patients, who were enrolled with higher baseline FBG (≤ 140 mg/dL) and HbA_{1C} levels (HbA_{1C} <7%) compared to the eligibility criteria for Study WO41554 trial. This will further support the applicability of the inavolisib triplet combination in patients with underlying risk factors for hyperglycemia.

The FDA's Assessment:

The FDA conducted in depth safety analyses based on data from the phase 3 INAVO120 trial. Topline safety results were reviewed by FDA for GO39374.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position: No concerns impacting data integrity, quality, and reporting were identified for the studies included in this submission.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Categorization of Adverse Event

The Applicant's Position: Verbatim descriptions for AEs and diseases entered by the investigators were assigned to Preferred Terms (PTs) by using MedDRA v26.1 (in Study WO41554) and v26.0 (in Study GO39374).

The AE severity grading scale for the NCI CTCAE v5.0 (in Study WO41554) and v4.0 (in Study GO39374) was used for assessing AE severity and routine laboratory parameters. For events of varying severity, the highest grade was used in the summaries, unless specified otherwise. In the summary tables, patients who experienced the same event on more than one occasion were counted once and at the highest grade in the calculation of the event frequency and severity.

Selected AEs for inavolisib were defined based on known and evolving safety profile of inavolisib, known risks for the combination agents and protocol-defined AESI. These selected events are grouped by medical concepts as described in Table 29.

Table 29: Applicant – Selected Adverse Events for Inavolisib

Selected Adverse Event	Search Strategy (MedDRA Preferred Terms, Roche AEGT or SMQ)
Hyperglycemia	Hyperglycemia; Blood glucose increased; Hyperglycemic crisis; Glycated serum protein increased

Table 29: Applicant – Selected Adverse Events for Inavolisib

Selected Adverse Event	Search Strategy (MedDRA Preferred Terms, Roche AEGT or SMQ)
Diarrhea	Non-infectious diarrhea SMQ (narrow)
Nausea	Nausea
Vomiting	Vomiting; Retching
Colitis	Roche colitis AEGT ^a
Stomatitis or mucosal inflammation	Roche PI3K inhibitors stomatitis AEGT ^a
Rash	Roche Standard AEGT for rash ^a
Ocular Toxicities	WO41554 only: PTs mapped to the Eye Disorders SOC as a primary SOC GO39374 only: PTs mapped to the Eye Disorders SOC as either a primary or secondary SOC
Pneumonitis	Interstitial lung disease SMQ (narrow)
Neutropenia	Neutropenia; Neutrophil count decreased
Thrombocytopenia	Thrombocytopenia; Platelet count decreased
AST/ALT elevation	Alanine aminotransferase increased; Alanine aminotransferase abnormal; Aspartate aminotransferase increased; Aspartate aminotransferase abnormal
Lymphopenia	Lymphopenia; Lymphocyte count decreased
Anemia	Anaemia; Haemoglobin decreased, Reticulocyte haemoglobin decreased; Reticulocyte haemoglobin increased

AEGT = adverse event group term; ALT = Alanine aminotransferase; AST = aspartate aminotransferase; SMQ = standardised MedDRA query; SOC = system organ class

^a A list of preferred terms for Sponsor Standard Adverse Events Groups Terms is provided in the respective CSRs (see Primary CSR WO41554, Report 1126696, Section 3.7.4.1; Interim CSR GO39374, Report 1125233, Section 3.7.3.1).

The FDA's Assessment:

In general, FDA agrees with the Applicant's assessment for categorization of adverse events.

FDA's grouped term (GT) for rash differed slightly from the one used by the Applicant. This difference resulted in identifying a few additional patients. The adverse events for the additional patients included eczema, erythema multiforme, palmar-plantar erythrodysesthesia, and skin exfoliation. The incidence of rash was updated by FDA in the USPI reflecting this grouping of PTs.

Routine Clinical Tests

The Applicant's Position: Patients were closely monitored for safety and tolerability throughout the conduct of studies. The assessments performed were considered adequate for the expected toxicities associated with inavolisib and the combination agents. Patients were assessed for toxicity at each clinic visit and prior to each in-clinic dose of study treatment; dosing occurred only if the clinical assessments and local laboratory test values were acceptable. The assessments included, complete physical exam, ECOG performance status, vital signs, tumor and response evaluations, laboratory tests (includes but not limited to hematology, chemistry, fasting insulin, fasting lipid profile, amylase and lipase, HbA_{1c}, serum fibrinogen and coagulation, urinalysis, pregnancy test, PK analysis, and biomarker assays), ophthalmic examinations, electrocardiograms, and clinical outcome assessments.

The FDA’s Assessment:

FDA agrees with the Applicant’s assessment.

8.2.4. Safety Results

Deaths

Data:

Table 30: Applicant - Study WO41554 Summary of Deaths (Safety Analysis Set)

	Inavo+Palbo+Fulv N=162 n (%)	Pbo+Palbo+Fulv N=162 n (%)
Total Deaths	43 (26.5%)	54 (33.3%)
Due to progressive disease	32 (74.4%)	47 (87.0%)
Due to adverse event	6 (14.0%)	2 (3.7%)
Due to other reasons:	5 (11.6%)	5 (9.3%)
Within 30 days after last dose	6	10
Due to progressive disease	1 (16.7%)	8 (80%)
Due to adverse event	5 (83.3%)	2 (20%)
Due to other reasons:	0	0
Beyond 30 days after last dose	36	45
Due to progressive disease	31 (86.1%)	39 (86.7%)
Due to adverse event	1 (2.8%)	0
Due to other reasons:	4 (11.1%)	6 (13.3%)

Source: t_dd_SAS_29SEP2023_41554; l_dd_SAS_29SEP2023_41554; Dataset: ADaM: ADSL

Table 31: Applicant - Study WO41554 Grade 5 Adverse Events (Safety Analysis Set)

Adverse Event	Inavo+Palbo+Fulv N=162 n (%)	Pbo+Palbo+Fulv N=162 n (%)
Deaths due to Adverse Event		
Acute coronary syndrome	1 (0.6%)	0
Cardiac arrest	0	1 (0.6%)
COVID 19	1 (0.6%)	0
COVID-19 pneumonia	0	1 (0.6%)
Cerebral hemorrhage	1 (0.6%)	0
Cerebrovascular accident	1 (0.6%)	0
Gastrointestinal hemorrhage	1 (0.6%)	0
Death	1 (0.6%)	0

Source: t_ae_ctc_SER_SAS_29SEP2023_41554; Dataset: ADaM: ADAE

The Applicant’s Position:

Pivotal Study WO41554: At the time of CCOD (29 Sep 2023), a total of 97 patients (29.9%) had died due to any cause. The proportion of patients who died in the Inavo+Palbo+Fulv arm (26.5%) was lower in comparison with the Pbo+Palbo+Fulv arm (33.3%). The most common cause of death in both treatment arms was progressive disease (Table 30). Grade 5 AEs were reported in 6 patients (3.7%) in the Inavo+Palbo+Fulv arm and 2 patients (1.2%) of patients in the Pbo+Palbo+Fulv arm (Table 31). None of the Grade 5 AEs were reported as related to any study drug by the investigator and no Grade 5 AE by PT was observed in >1 patient in either arm.

Supportive Study GO39374: As of the CCOD (27 March 2023), 7 deaths have been reported in

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the study. All deaths occurred within 30 days following the last study treatment administration. Among these events, 4 deaths (one in Arm A, two in Arm C, and one in Arm F) were due to disease progression. The remaining 3 deaths were due to Grade 5 AEs and were all reported from Arm D (Inavo+Fulv). These Grade 5 AEs (by PT) were: hypertrophic cardiomyopathy, peritonitis, and pleural effusion; none of the events were considered related to inavolisib or fulvestrant by the investigator.

The FDA's Assessment:

In general, FDA agrees with the Applicant's assessment of deaths in the INAVO120 trial (WO41554). FDA agrees that the most common cause for death on either treatment arm was progressive disease.

The death narratives were not reviewed for GO39374.

Following are a summary of the 8 deaths (6 on the inavolisib treatment arm and 2 on the placebo arm) due to an adverse event in the INAVO120 Trial (WO41554). The FDA included these deaths in the USPI as contribution of inavolisib cannot be ruled out for the 6 deaths (3.7%) that occurred on the inavolisib + palbociclib + fulvestrant arm.

Patient ID# [REDACTED] (b) (6) --Applicant Attribution: Cerebral hemorrhage

*60-year-old White female randomized to the **inavolisib** treatment arm was diagnosed with Grade 3 acute coronary syndrome (ACS) on Study Day 493. On Study Day 499, the event of ACS was considered resolved with sequelae (unspecified). There was no change in study treatment due to ACS. On Study Day 500, the patient was diagnosed with Grade 4 cerebral hemorrhage. No treatment was given for the event and the patient died on Study Day 506 due to cerebral hemorrhage. The patient also had six episodes of Grade 2 hyperglycemia during study treatment, all of which resolved. It was unknown if an autopsy was performed.*

The Investigator considered acute coronary syndrome and cerebral hemorrhage to be unrelated to inavolisib, fulvestrant, and palbociclib and related to other cause (unspecified).

Concurrent condition at the time of study entry included blood cholesterol increased. FDA cannot rule whether inavolisib contributed to the ACS event and subsequent cerebral hemorrhage. It is not clear if the patient was on an anticoagulant during or after the diagnosis of ACS. The patient did have reported episodes of Grade 1 platelet count decreased; however, it is unlikely this contributed to the event of cerebral hemorrhage.

Patient ID# [REDACTED] (b) (6) --Applicant Attribution: Acute Coronary Syndrome

*57-year-old Asian female randomized to the **inavolisib** treatment arm was diagnosed with life threatening cardiac arrest on Study Day 4. The patient's condition deteriorated in the ambulance on the way to the hospital and died in the ambulance. An autopsy was not performed.*

The Investigator considered acute coronary syndrome to be unrelated to placebo, fulvestrant, and palbociclib and related to disease under study.

Pertinent concurrent conditions at the time of study entry included myocardial fibrosis, essential hypertension, and pericarditis. It is possible these conditions contributed to the ACS event. It is difficult to assess the cause of cardiac arrest and FDA cannot rule whether inavolisib contributed to the ACS event.

Patient ID# (b) (6) **--Applicant Attribution: Gastrointestinal hemorrhage**

*42-year-old Asian female randomized to the **inavolisib** treatment arm was diagnosed with gastrointestinal hemorrhage on Study Day 491 (symptoms not reported). Cardiopulmonary resuscitation was performed however the patient died. The patient had progression of disease in non-target lesions on Study Day 443 and treatment was permanently discontinued on Study Day 460 with the last dose of palbociclib administered on Study Day 453, fulvestrant on Study Day 454, and inavolisib on Study Day 460. An autopsy was not performed.*

The Investigator considered acute coronary syndrome to be unrelated to placebo, fulvestrant, and palbociclib and related to disease under study.

FDA agrees that the event of gastrointestinal hemorrhage was unlikely related to inavolisib as study treatment had been discontinued more than 30 days prior. The patient had no reported adverse event of thrombocytopenia that may have contributed to bleeding.

Patient ID# (b) (6) **--Applicant Attribution: Death**

*74-year-old White female randomized to the **inavolisib** treatment arm was reported to have poor condition and not get up on Study Day 276. On Study Day 277, the participant died, and the reason of death was unknown as per death certificate. An autopsy was not performed.*

The Investigator considered death to be unrelated to inavolisib, fulvestrant, palbociclib and related to other cause (disease progression).

Given the limited information, FDA considers it difficult to assess the cause of death. Although the death may be due to progression of disease, no clear evidence has been presented, even after FDA review of information requests to the Applicant that were unable to provide additional clinical information for attribution.

Patient ID# (b) (6) **--Applicant Attribution: COVID-19**

*72-year-old Asian female randomized to the **inavolisib** treatment arm was diagnosed with Grade 1 COVID-19 on Study Day 253. On Study Day 256, she had a low oxygen saturation of 88% and was hospitalized for symptomatic treatment, COVID-19 had worsened to Grade 4. On Study Day 260, the patient died due to COVID-19. It was unknown if an autopsy was performed.*

The Investigator considered COVID-19 to be unrelated to inavolisib, fulvestrant, palbociclib and related to other cause (unspecified).

FDA agrees with the diagnosis of COVID-19 and agrees the death was likely due to COVID-19. It is not known if treatment with inavolisib exacerbated the infection.

Patient ID# [REDACTED] (b) (6) --Applicant Attribution: Cerebrovascular accident

75-year-old White female experienced a stroke with right hemiparesis on Study Day 3 and presented to the emergency department in a semi-comatose state. A CT scan showed a thrombus in the left middle cerebral artery, and she then underwent thrombolysis and thrombectomy. The patient died on the same day.

The Investigator considered COVID-19 to be unrelated to inavolisib, fulvestrant, palbociclib and related to other cause (unspecified).

Pertinent medical history includes hyperglycemia and hypertension. FDA agrees with the diagnosis of cerebrovascular accident.

Patient ID# [REDACTED] (b) (6) --Applicant Attribution: COVID-19 pneumonia

*58-year-old White female randomized to the **placebo** treatment arm was diagnosed with Grade 1 COVID-19 pneumonia. On Study Day 57, she was hospitalized. No known treatment was administered for the event as it was reported that medical documents were not available as participant was hospitalized in another hospital. On Study Day 67, the participant died due to COVID-19 pneumonia. An autopsy was not performed.*

The Investigator considered COVID-19 pneumonia to be unrelated to placebo, fulvestrant and palbociclib and unrelated to other cause (unspecified).

FDA agrees with the diagnosis of COVID-19 and agrees the death due to pneumonia was likely due to COVID-19.

Patient ID# [REDACTED] (b) (6) --Applicant Attribution: Cardiac Arrest

*57-year-old Asian female randomized to the **placebo** treatment arm was diagnosed with Grade 4 cardiac arrest on Study Day 4. The patient died later the same day due to cardiac arrest. An autopsy was not performed.*

The Investigator considered cardiac arrest to be unrelated to placebo, fulvestrant and palbociclib and related to disease under study.

Pertinent concurrent conditions at the time of study entry include hypertension and hyperlipidemia. Given the limited information, it is difficult to assess the cause of cardiac arrest.

Serious Adverse Events

Data and the Applicant's Position:

Pivotal Study WO41554: A numerically higher proportion of patients experienced SAEs in the Inavo+Palbo+Fulv arm compared with the Pbo+Palbo+Fulv arm (24.1% vs. 10.5%, respectively). The SAEs were distributed across multiple PTs and no SAE was reported with a $\geq 2\%$ difference between treatment arms. The majority of SAEs were Grade 3 in severity in both the Inavo+Palbo+Fulv arm (16.7%) and the Pbo+Palbo+Fulv arm (7.4%).

The incidence of SAEs of any grade in the Infections and Infestations System Organ Class (SOC) was higher in the Inavo+Palbo+Fulv arm (11 [6.8%]) compared with the Pbo+Palbo+Fulv arm (3 [1.9%]) and was primarily driven by PTs of COVID-19 (4 [2.5%] vs. 1 [0.6%]), pneumonia (3 [1.9%] vs. 0) and urinary tract infection (2 [1.2%] vs. 0), which were all assessed by investigator as not related to any study drug.

The SAEs occurring in ≥ 2 patients in either arm were: COVID-19 (4 [2.5%] Inavo+Palbo+Fulv vs. 1 [0.6%] Pbo+Palbo+Fulv), pneumonia, anemia, febrile neutropenia (3 [1.9%] vs. 0 each), urinary tract infection, diarrhea, pyrexia, and acute coronary syndrome (2 [1.2%] vs. 0 each), vomiting (1 [0.6%] vs. 2 [1.2%]), and pulmonary embolism (0 vs. 2 [1.2%]).

Supportive Study GO39374: In the overall safety population, 85 SAEs were reported in 27.4% of patients. SAEs occurring in ≥ 2 patients (1.1% overall) included: hyperglycemia (4 [2.1%]), cellulitis, hypercalcemia, and urinary tract infection (3 each [1.6%]), and back pain, headache, osteomyelitis, pneumonia, rash, small intestinal obstructions, superior vena cava syndrome, and vomiting (2 each [1.1%]); all other events were reported in one patient each. SAEs assessed by the investigator as related to any study treatment (except metformin) were reported in 14 patients (7.4%).

Amongst Arms B, E, and F,

- In Arm B (Inavo+Palbo+Letro; n=33 patients), 25 SAEs were reported in 42.4% of patients (14 of 33 patients). Cellulitis occurred in 2 patients (7.4%) in Arm B; the remainder of SAEs were single occurrences observed in one patient each (3.7%).
- In Arm E (Inavo+Palbo+Fulv; n=20 patients), 9 SAEs were reported in 30.0% of patients (6 of 20 patients). No SAE occurred in more than one patient.
- In Arm F (Inavo+Palbo+Fulv+Met; n=20 patients), 15 SAEs were reported in 40.0% of patients (8 of 20 patients). No SAE occurred in more than one patient.

The FDA's Assessment:

FDA agrees that the incidence of SAEs were higher on the inavolisib treatment arm in the INAVO120 trial (WO41554). The highest incidence of SAEs on the inavolisib treatment arm occurred in the System Organ Class (SOC) of Infections and Infestations (6.8%), followed by Gastrointestinal disorders (4.3%) and Blood and Lymphatic disorders (4.3%). Most of the

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infections were assessed by the investigator as not related to any study drug. Patients on the inavolisib arm were on treatment for a longer duration (compared to the placebo arm) with potential concomitant neutropenia, which may have led a higher rate of infections. However, it is not known if inavolisib may have exacerbated the risk of infection.

FDA agrees with the Applicant’s assessment of SAEs for GO39374.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 32: Applicant - Study WO41554 Discontinuation from Individual Study Treatment Reasons by Trial Treatment, Full Analysis Set

	Inavo+Palbo+Fulv N=161 n (%)			Pbo+Palbo+Fulv N=164 n (%)		
	Inavo	Palbo	Fulv	Pbo	Palbo	Fulv
Treatment Discontinuation due to AE	11 (6.8%)	8 (5.0%)	5 (3.1%)	1 (0.6%)	0	0
Treatment Discontinuation due to “Other”:						
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

Source: t_ds_tx_FAS_29SEP2023_41554 ; Dataset: ADaM: ADSL

Table 33: Applicant - Study WO41554 Adverse Events Leading to Withdrawal of Any Study Drug, Safety Analysis Set

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

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
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
Gastric ulcer	1 (0.6%)	0
Intestinal perforation	1 (0.6%)	0
Stomatitis	1 (0.6%)	0
Hyperglycaemia	2 (1.2%)	0
Type 2 diabetes mellitus	1 (0.6%)	0
Anal abscess	1 (0.6%)	0
Bone pain	1 (0.6%)	0
Musculoskeletal pain	1 (0.6%)	0
Transitional cell carcinoma	1 (0.6%)	0
Acute kidney injury	1 (0.6%)	0

Investigator text for AEs encoded using MedDRA version 26.1.

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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.

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 19:19 GMT

Output:/ocean/harbour/CDT70123/WO41554/csr-primary/prod/output/t_ae_DSC_SAS_29SEP2023_41554.out

Source: Adapted from t_ae_DSC_SAS_29SEP2023_41554; Dataset: ADaM: ADAE

The Applicant's Position:

Pivotal Study WO41554: The proportion of patients who experienced AEs leading to withdrawal of any study drug was overall low in both arms (Inavo+Palbo+Fulv: 6.8% vs. Pbo+Palbo+Fulv: 0.6%), indicating manageability of AEs and good tolerability of inavolisib in combination with palbociclib and fulvestrant (Table and Table).

Supportive Study GO39374: In the overall safety population, AEs leading to withdrawal of any study treatment were reported in 7 patients (3.7%) and all AEs were single occurrences observed in one patient each. AEs leading to withdrawal of any study drug in Arm B, Arm E, or Arm F were infrequent. Overall, 2 patients each in Arm B, Arm E, and Arm F withdrew from treatment due to an AE; AEs that led to treatment withdrawals were: cerebrovascular disorder and hyperglycemia (one patient each in Arm B), asthenia and diarrhea (one patient each in Arm E), panniculitis (one patient in Arm F), esophageal candidiasis and hypocalcemia (both events in one patient in Arm F).

The FDA's Assessment:

More patients on the inavolisib treatment arm in the INAVO120 trial (WO41554) discontinued treatment due to an AE compared to the placebo arm. The only adverse event that occurred in more than one patient (2 patients) leading to treatment discontinuation on the inavolisib treatment arm was hyperglycemia. All other adverse events occurred in one patient.

The most common reason for treatment discontinuation was progression of disease, which occurred in a high proportion of patients on the placebo arm (62%) compared to the inavolisib treatment arm (42%).

FDA agrees with the Applicant's assessment of discontinuations for GO39374.

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 34: Applicant - Study WO41554 Summary of Adverse Events leading to Dose Modifications (Interruption/ Reduction) of Inavolisib

	Inavo+Palbo+Fulv N= 162 n (%)	Pbo+Palbo+Fulv N= 162 n (%)

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Dose Interruption due to AE (≥5% of patients in either arm), PT:	112 (69.1%)	56 (34.6%)
Hyperglycemia	40 (24.7%)	1 (0.6%)
COVID-19	26 (16.0%)	8 (4.9%)
Neutropenia	20 (12.3%)	16 (9.9%)
Neutrophil count decreased	17 (10.5%)	8 (4.9%)
Diarrhea	11 (6.8%)	1 (0.6%)
Mucosal inflammation	8 (4.9%)	0
Anemia	7 (4.3%)	1 (0.6%)
Upper respiratory tract infection	7 (4.3%)	1 (0.6%)
Stomatitis	6 (3.7%)	3 (1.9%)
White blood cell count decreased	6 (3.7%)	2 (1.2%)
Pyrexia	5 (3.1%)	2 (1.2%)
Dose Reduction due to AE (in ≥ 3 patients in either arm), PT:	23 (14.2%)	5 (3.1%)
Hyperglycemia	4 (2.5%)	0
Stomatitis	3 (1.9%)	1 (0.6%)

Source: t_ae_DSIIVL_SAS_29SEP2023_41554; t_ae_DSRIVL_SAS_29SEP2023_41554; Dataset: ADaM: ADAE

Table 35: Applicant - Study GO39374 Summary of Adverse Events leading to Dose Modifications (Interruption/ Reduction) of Inavolisib

	Inavo + Palbo + Letro (N=33) n (%)	Inavo 9 mg + Palbo + Fulv (N=20) n (%)	Inavo 9 mg + Palbo + Fulv + Metf (N=20) n (%)	All Patients (N=190) n (%)
Dose Interruption/ Reduction due to AE (≥ 10% of patients in any arm), PT:	25 (75.8%)	17 (85.0%)	15 (75.0%)	123 (64.7%)
Hyperglycemia	9 (27.3%)	8 (40.0%)	11 (55.0%)	70 (36.8%)
Vomiting	3 (9.1%)	2 (10.0%)	2 (10.0%)	11 (5.8%)
COVID-19	2 (6.1%)	4 (20.0%)	1 (5.0%)	10 (5.3%)
Neutropenia	6 (18.2%)	2 (10.0%)	1 (5.0%)	9 (4.7%)
Diarrhea	1 (3.0%)	3 (15.0%)	0	9 (4.7%)
Nausea	2 (6.1%)	2 (10.0%)	0	8 (4.2%)
Stomatitis	2 (6.1%)	3 (15.0%)	1 (5.0%)	8 (4.2%)
Fatigue	1 (3.0%)	2 (10.0%)	0	7 (3.7%)
Mucosal inflammation	3 (9.1%)	2 (10.0%)	1 (5.0%)	6 (3.2%)

Source: t_ae_pt_CSR_GDCDMOD_SE_27MAR2023_39374 ; Dataset: ADaM: ADAE

The Applicant’s Position:

Pivotal Study WO41554: A numerically higher proportion of patients in the Inavo+Palbo+Fulv arm (69.1%) compared with the Pbo+Palbo+Fulv arm (34.6%) experienced AEs leading to the dose interruption of inavolisib/placebo. A numerically higher proportion of patients in the Inavo+Palbo+Fulv arm (23 patients [14.2%]) compared with the Pbo+Palbo+Fulv arm (5 patients [3.1%]) experienced AEs leading to the dose reduction of inavolisib/placebo (Table 34). The most common PT leading to dose reductions (2.5%) or interruptions (24.7%) in the Inavo+Palbo+Fulv arm was hyperglycemia.

Supportive Study GO39374: In the overall safety population, AEs leading to dose modification or interruption of inavolisib were reported in 64.7% of patients, with hyperglycemia (36.8%) being the most frequently reported AE (Table 35). Hyperglycemia was the most commonly reported AE leading to dose modification or interruption of inavolisib in Arm B (27.3%), Arm E (40.0%) and Arm F (55.0%).

The FDA’s Assessment:

FDA agrees that a higher proportion of patients on the inavolisib treatment arm in the INAVO120 Trial (WO41554) required a dose interruption or dose reduction compared to the placebo arm. The most common AE leading to an interruption of inavolisib treatment was hyperglycemia, followed by COVID-19, neutropenia, diarrhea, and mucosal inflammation. The most common cause leading to dose reduction in the inavolisib treatment arm was hyperglycemia (in 2.5% of patients). Hyperglycemia, diarrhea, and stomatitis/mucosal inflammation are known side effects of PI3K inhibitors, and these adverse events occurred at a higher incidence in the inavolisib treatment arm compared to the placebo arm. These toxicities could be managed with dose interruption or dose reduction of inavolisib without permanent discontinuation of treatment.

COVID-19 occurred in a higher proportion of patient on the inavolisib treatment arm compared

to the placebo arm and led to a higher rate of dose modifications in the inavolisib treatment arm. The INAVO120 trial was during the COVID-19 pandemic and the higher incidence on the inavolisib treatment arm is likely due to the longer duration of treatment (and potentially with neutropenia) compared to the placebo arm. However, it is not clear if inavolisib may have exacerbated the COVID-19 infection.

Hematologic toxicities, including neutropenia, anemia, and thrombocytopenia, are known side effects of palbociclib. These toxicities occurred in a similar proportion of patients in both treatment arms; however, dose modifications occurred more on the inavolisib treatment arm, likely due to longer duration of treatment compared to the placebo arm.

Significant Adverse Events

Data and the Applicant's Position:

Pivotal Study WO41554: The incidence of Grade 3-4 AEs by highest grade was comparable between the Inavo+Palbo+Fulv (85.8%) and Pbo+Palbo+Fulv (82.1%) arms (Table 36). The incidence rates were driven by Grade 3-4 AEs (by PTs) of neutropenia (47.5% vs. 48.1%) and neutrophil count decreased (34.6% vs. 32.7%). The majority of Grade 3-4 AEs in both treatment arms were associated with myelosuppression. Other common Grade 3-4 AEs (by PTs) were hyperglycemia (Inavo+Palbo+Fulv: 5.6% and Pbo+Palbo+Fulv: 0%), diarrhea (3.7% vs. 0%) and stomatitis/oral mucositis (3.1% vs. 0%). The proportion of patients with Grade 3-4 AEs related to any treatment were comparable between the arms (85.2% vs. 80.2%). See Section 8.2.4 for further information on Grade 5 AEs.

Supportive Study GO39374: In the overall GO39374 safety population the most frequent Grade 3-4 AEs ($\geq 10\%$) were hyperglycemia (24.2%) and neutropenia (23.7%). All Grade 3-4 AEs for neutropenia were reported from palbociclib-containing arms (Arm B, Arm E, and Arm F). The most frequently reported Grade 3-4 AE ($\geq 50\%$ in each arm) among patients in Arm B and Arm E was neutropenia (66.7% and 70.0%, respectively). In Arm F, neutropenia (45.0%) and hyperglycemia (45.0%) were the most frequently reported Grade 3-4 AEs.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. Hyperglycemia, diarrhea, and stomatitis/mucositis are discussed further in Section 8.2.5 (Submission Specific Safety Issues).

Hematologic toxicities were seen in both treatment arms and are known toxicities with palbociclib. Neutropenia and anemia were seen in a similar proportion of patients regarding all grade toxicity. However, grade 3-4 toxicity was slightly higher in the inavolisib treatment arm as noted in Tables 23 and 24. Thrombocytopenia (including platelet count decreased) was higher in the inavolisib treatment arm compared to the placebo treatment arm. There did not appear to be a significantly increased rate of bleeding events associated with the thrombocytopenia. All grade hemorrhage (grouped term) events occurred in 10% of patients on

the inavolisib treatment arm and 6% on the placebo arm.

The most common significant adverse events in GO39374 were neutropenia and hyperglycemia.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 36: Applicant - Study WO41554: Overview of Adverse Events, Safety Analysis Set

	Inavo+Palbo+Fulv N= 162 n (%)	Pbo+Palbo+Fulv N= 162 n (%)
All-Grade AEs	160 (98.8%)	162 (100.0%)
Grade 1	3 (1.9%)	6 (3.7%)
Grade 2	12 (7.4%)	21 (13.0%)
Grade 3	109 (67.3%)	96 (59.3%)
Grade 4	30 (18.5%)	37 (22.8%)
Grade 5 (Deaths due to AEs)	6 (3.7%)	2 (1.2%)
Grade 3-4 AEs	139 (85.8%)	133 (82.1%)
Grade 3-5 AEs	145 (89.5%)	135 (83.3%)
SAEs	39 (24.1%)	17 (10.5%)
Treatment ^a Discontinuation due to AE	10 (6.2%)	1 (0.6%)
Dose Interruption ^b due to AEs	112 (69.1%)	56 (34.6%)
Dose Reduction ^c due to AEs	23 (14.2%)	5 (3.1%)

^aDiscontinuation from inavolisib. ^bDose interruption of inavolisib/placebo. ^cReduction in dose of inavolisib/placebo.

Source: t_ae_ctc_SAS_29SEP2023_41554; t_ae_SER_SAS_29SEP2023_41554; t_ae_DSCM_SAS_29SEP2023_41554; t_ae_DSIVL_SAS_29SEP2023_41554; t_ae_DSRVL_SAS_29SEP2023_41554; Dataset: ADaM: ADAE

Table 37: Applicant - Study GO39374: Overview of Adverse Events, Safety Analysis Set

	Inavo + Palbo + Letro (Arm B) (N=33) n (%)	Inavo 9 mg + Palbo + Fulv (Arm E) (N=20) n (%)	Inavo 9 mg + Palbo + Fulv + Metf (Arm F) (N=20) n (%)	All Patients (Arms A-F) (N=190) n (%)
All-Grade AEs	33 (100%)	20 (100%)	19 (95.0%)	188 (98.9%)
Grade 1	1 (3.0%)	0	0	10 (5.3%)
Grade 2	2 (6.1%)	3 (15.0%)	2 (10.0%)	52 (27.4%)
Grade 3	22 (66.7%)	15 (75.0%)	14 (70.0%)	104 (54.7%)
Grade 4	8 (24.2%)	2 (10.0%)	3 (15.0%)	19 (10.0%)
Grade 5 (Deaths due to AEs)	0	0	0	3 (1.6%)
Grade 3-4 AEs	30 (90.9%)	17 (85.0%)	17 (85.0%)	123 (64.7%)
Grade 3-5 AEs	30 (90.9%)	17 (85.0%)	17 (85.0%)	126 (66.3%)
SAEs	14 (42.4%)	6 (30.0%)	8 (40.0%)	52 (27.4%)
Treatment ^a Discontinuation due to AEs	2 (6.1%)	2 (10.0%)	2 (10.0%)	7 (3.7%)
Dose Reduction/ Interruption ^b due to AEs	25 (75.8%)	17 (85.0%)	15 (75.0%)	123 (64.7%)

^aDiscontinuation from inavolisib; ^bDose reduction/ interruption of inavolisib

Source: t_ae_ctc_CSR_SE_27MAR2023_39374; t_ae_pt_CSR_GDCDMOD_SE_27MAR2023_39374; t_ae_oview_CSR_SE_27MAR2023_39374; Dataset: ADaM: ADAE

Table 38: Applicant - Adverse Drug Reactions (≥ 10% with ≥ 5% [All Grades] or ≥ 2% [Grade 3-4] Higher Incidence in the Inavolisib Arm) in INAVO120

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System Organ Class Adverse Reaction	Inavolisib + Palbociclib + Fulvestrant N=162		Placebo + Palbociclib + Fulvestrant N=162	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Infections and Infestations				
Urinary Tract Infection	13	1.2*	7	0
Blood and Lymphatic System Disorders				
Thrombocytopenia ^a	48	14	45	4.3
Anemia ^b	37	6*	36	1.9*
Metabolism and Nutrition Disorders				
Hyperglycemia ^c	60	6*	10	0
Decreased appetite	24	0	9	0
Hypokalemia	16	2.5	6	0
Nervous System Disorders				
Headache	21	0	14	0
Gastrointestinal Disorders				
Stomatitis ^d	51	6*	27	0
Diarrhea	48	3.7*	16	0
Nausea	28	0.6*	17	0
Vomiting	15	0.6*	4.9	1.2*
Skin and Subcutaneous Tissue Disorders				
Rash ^e	25	0	17	0
Alopecia	19	0	6	0
Dry skin ^f	13	0	4.3	0
General Disorders and Administration Site Conditions				
Fatigue	38	1.9*	25	1.2*
Investigations				
Alanine aminotransferase increased	17	3.7*	13	1.2*
Weight decreased	17	3.7*	0.6	0

Adverse reactions grading according to CTCAE version 5.0.

* No Grade 4 adverse reactions were observed.

^a Includes platelet count decreased and thrombocytopenia.

^b Includes anemia and hemoglobin decreased.

^c Includes hyperglycemia, blood glucose increased, hyperglycemic crisis, glycosylated serum protein increased, glucose tolerance impaired, diabetes mellitus, Type 2 diabetes mellitus, and glycosylated hemoglobin increased.

^d Includes aphthous ulcer, glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal inflammation, and stomatitis.

^e Includes dermatitis, dermatitis acneiform, dermatitis bullous, erythema, folliculitis, rash, rash erythematous, rash maculo-papular, rash papular, rash pruritic, and rash pustular.

^f Includes dry skin, skin fissures, xerosis, and xeroderma.

Source: Inavolisib USPI; Dataset: ADaM: ADAE

The Applicant's Position:

Pivotal Study WO41554: Inavolisib in combination with palbociclib and fulvestrant in patients with *PIK3CA*-mutated, HR+, HER2– LA/mBC demonstrated manageable safety and tolerability profile as shown by the high median relative dose intensity of inavolisib, the comparable median relative dose intensities of palbociclib and fulvestrant in both arms, and low treatment discontinuation rate of the Inavo+Palbo+Fulv combination due to AEs. The safety profile of the Inavo+Palbo+Fulv combination regimen was consistent with the known safety profile of each individual study drug component and the underlying disease. No new safety findings were identified. The addition of inavolisib did not contribute to increased treatment burden in patients, as indicated by the majority of patients in both arms reporting levels of selected symptoms from the PRO-CTCAE and overall bother from treatment side effects at moderate levels or less. A summary of key AE-related safety results are presented in **Table 36**.

Supportive Study GO39374: Inavolisib as monotherapy and in combination therapies with palbociclib, letrozole, fulvestrant, and/or metformin was generally well tolerated, toxicities were manageable, and AEs were in line with the anticipated safety profile of inavolisib, the known safety profiles of the individual components of combination therapies, and the underlying disease. At the time of CCOD, there were no new or unexpected safety signals identified for inavolisib in this study. A summary of key AE-related safety results are presented in **Table 37**.

For the purpose of labeling the Applicant is proposing **Table 38** for the USPI to reflect the safety profile of inavolisib.

The FDA’s Assessment:

All grade adverse events occurred in almost all patients in both arms of INAVO120. A higher proportion of patients experienced SAEs in the inavolisib treatment arm compared to the placebo arm and more patients in the inavolisib treatment arm had treatment discontinuations and dose modifications (both interruptions and dose reductions). Grade 5 adverse events, SAEs and dose modifications are discussed in more detail in the respective sections above. Modifications have been made to the Applicant **Table 38** by FDA for inclusion in the USPI, as noted in **Table 39**, as FDA grouped additional PT terms for certain adverse reactions which the Applicant agreed to. In addition, (b) (4) was removed from the adverse reaction table (b) (4)

See Section 8.2.1.1 for the Integrated Assessment of Safety for the FDA conclusions on the safety review for INAVO120.

Table 39: FDA – Adverse Reactions (≥ 10% with ≥ 5% [All Grades] or ≥ 2% [Grade 3-4] Higher Incidence in the Inavolisib Arm) in INAVO120

Adverse Reaction	ITOVEBI + Palbociclib + Fulvestrant N=162		Placebo + Palbociclib + Fulvestrant N=162	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Gastrointestinal Disorders				
Stomatitis ^a	51	6*	27	0
Diarrhea	48	3.7*	16	0
Nausea	28	0.6*	17	0
Vomiting	15	0.6*	5	1.2*
General Disorders and Administration Site Conditions				
Fatigue	38	1.9*	25	1.2*

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Adverse Reaction	ITOVEBI + Palbociclib + Fulvestrant N=162		Placebo + Palbociclib + Fulvestrant N=162	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Skin and Subcutaneous Tissue Disorders				
Rash ^b	26	0	19	0
Alopecia	19	0	6	0
Dry skin ^c	13	0	4.3	0
Metabolism and Nutrition Disorders				
Decreased appetite	24	0	9	0
Infections and Infestations				
COVID-19 infection	23	1.9	10	0.6
Urinary tract infection ^b	15	1.2*	9	0
Nervous System Disorders				
Headache ^b	22	0	14	0
Investigations				
Decreased weight	17	3.7*	0.6	0
* No Grade 4 adverse reactions were observed.				
^a Includes aphthous ulcer, glossitis, glossodynia, lip ulceration, mouth ulceration, mucosal inflammation, and stomatitis.				
^b Includes other related terms.				
^c Includes dry skin, skin fissures, xerosis, and xeroderma.				

Source: FDA USPI

Laboratory Findings

Data:

Table 40: Applicant - Laboratory Abnormalities (≥ 10% with a Difference between Arms of ≥ 2% [All Grades or Grade 3-4]) in INAVO120

Laboratory Abnormality	Inavolisib + Palbociclib + Fulvestrant ^a		Placebo + Palbociclib + Fulvestrant ^b	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hematology				
Neutrophils (total, absolute) decreased	95	82	97	79
Hemoglobin decreased	88	8*	85	2.5*
Glucose (fasting) increased ^c	85	12	43	0
Platelets decreased	84	16	71	3.7
Lymphocytes (absolute) decreased	72	9	68	14
Chemistry				
Calcium decreased	42	3.1	32	3.7
Potassium decreased	38	6	21	0.6*
Creatinine increased	38	1.9*	30	1.2*
ALT increased	34	3.1*	29	1.2*

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Table 40: Applicant - Laboratory Abnormalities (≥ 10% with a Difference between Arms of ≥ 2% [All Grades or Grade 3-4]) in INAVO120

Laboratory Abnormality	Inavolisib + Palbociclib + Fulvestrant ^a		Placebo + Palbociclib + Fulvestrant ^b	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Sodium decreased	28	2.5 ^c	19	2.5
Magnesium decreased	27	0.6	21	0
Albumin decreased	25	0.6 ^c	18	0
Lipase (fasting) increased	16	1.4 ^c	7	0

ALT = alanine aminotransferase

* No Grade 4 laboratory abnormalities were observed.

^a The denominator used to calculate the rate varied from 122 to 160 based on the number of patients with a baseline value and at least one post-treatment value.

^b The denominator used to calculate the rate varied from 131 to 161 based on the number of patients with a baseline value and at least one post-treatment value.

^c Grading according to NCI CTCAE v4.03

Source: Inavolisib USPI; Dataset: ADaM: ADLB

The Applicant's Position:

Pivotal Study WO41554: Overall, clinically relevant shifts (defined as shifts from Grade 0, 1, or 2 at baseline to Grade 3 or 4 post-baseline) in blood chemistry, coagulation, and hematology during study treatment were infrequent and comparable between the Inavo+Palbo+Fulv and Pbo+Palbo+Fulv arms. The most commonly occurring clinically relevant hematology shift from baseline was low total absolute neutrophils (81.7% Inavo+Palbo+Fulv vs. 78.5% Pbo+Palbo+Fulv). Regardless of baseline fasting blood glucose, the majority of patients (64.8%) in the Inavo+Palbo+Fulv arm maintained fasting blood glucose <160 mg/dL. There was 1 patient in the Inavo+Palbo+Fulv arm and 3 patients in the Pbo+Palbo+Fulv arm who fulfilled the laboratory criteria for potential Hy's law. However, all of these cases were confounded by concurrent worsening of liver metastasis and did not meet the criteria for drug-induced liver injury.

Supportive Study GO39374: For the overall safety population, the most commonly occurring clinically relevant hematology shift from baseline was low total absolute neutrophils (48 patients [25.5%]), while the most commonly occurring clinically relevant biochemistry shifts from baseline were high fasting glucose (34 patients [18.3%]) and high glucose (15 patients [12.8%]).

The FDA's Assessment:

The most common laboratory abnormalities in the INAVO120 trial were observed in the hematologic parameters. The hematologic abnormalities were noted in both treatment arms and are known to occur with palbociclib treatment. Platelets decreased (all grade and grade 3-4) were higher in the inavolisib treatment arm compared to the placebo arm.

Increased fasting glucose occurred in a larger proportion of patients on the inavolisib treatment arm compared to placebo. Increased fasting glucose corresponds with a known toxicity of hyperglycemia for PI3K inhibitors, including inavolisib. Patients were required to have a HbA_{1c} <6% and fasting blood glucose <126 to be eligible for the INAVO 120 trial.

Laboratory abnormalities were not reviewed in the GO39374 Trial.

Vital Signs

Data and the Applicant's Position:

Pivotal Study WO41554: There were no clinically relevant differences between the treatment arms with respect to vital sign parameters during the study.

Supportive Study GO39374: Although there were vital sign parameters outside normal limits noted among patients without an abnormality at baseline, these were not considered to be clinically relevant.

The FDA's Assessment:

FDA agrees with the Applicant's assessment for Study WO41554.

Vital signs were not reviewed for Study GO39374.

Electrocardiograms (ECGs)

Data and the Applicant's Position:

Pivotal Study WO41554: The baseline ECG data were comparable between the arms. No clinically meaningful trends post-baseline vs. baseline in mean ECG parameters were identified in either of the arms.

Supportive Study GO39374: Overall, the ECG data showed no clinically meaningful trends post-baseline vs. baseline in mean ECG parameters.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. No clinically meaningful change (≥ 20 msec mean increase in QTc interval) was noted. Refer to FDA QT-IRT review.

QT

Data:

Pivotal Study WO41554: PTs in the Investigations SOC included ECG QT prolonged (6 patients [3.7%] Inavo+Palbo+Fulv vs. 1 patient [0.6%] Pbo+Palbo+Fulv) and ECG T wave abnormal (1 patient [0.6%] vs. no patient [0%]). In the Inavo+Palbo+Fulv arm, one patient (0.6%) experienced a Grade 3 event of ECG QT prolonged, 2 patients (1.2%) a Grade 2 event and 3 patients (1.9%) a Grade 1 event. The one event of ECG T wave abnormal in the Inavo+Palbo+Fulv arm was reported as Grade 1 in the single patient (0.6%). The Grade 3 event of ECG QT prolonged was considered related to inavolisib, required treatment, led to dose reduction of inavolisib and was considered recovering/resolving at the CCOD (29 Sep 2023). There were no SAEs reported.

Supportive Study GO39374: Six patients experienced AEs within the Investigations SOC related to ECG abnormalities, which included ECG QT prolonged (2.6%) and ECG ST segment depression (0.5%).

The Applicant's Position:

Although in Study GO39374, there is limited ECG data with the triplet combination (inavolisib+ palbociclib+ fulvestrant in Arms E and F) that was selected for the Phase III study, the data from single agent inavolisib arms (Arm A), doublet arms (Arm C: inavolisib+ letrozole and Arm D: inavolisib+ fulvestrant), and the other triplet arm (Arm B: inavolisib+ palbociclib+ letrozole), can be extrapolated to the inavolisib+ palbociclib+ fulvestrant triplet combination due to following reasons:

- Inavolisib exposure is comparable between all the arms, hence no additional potential for QT prolongation is expected with the triplet combination.
- No risk of QT prolongation has been reported for the combination agents, palbociclib and fulvestrant.

Based on the concentration-QTc analysis from study GO39374, it would not be expected that inavolisib would have a clinically relevant QTc prolongation effect.

No clinically significant trends in post-baseline vs. baseline mean ECG parameters were identified in both pivotal and supportive studies.

The FDA's Assessment:

The Interdisciplinary Review Team for Cardiac Safety Studies at the FDA completed a QT review and concluded that inavolisib at the proposed dosage of 9mg daily is unlikely to cause ≥ 20 msec mean increase in QTc interval based on the alternative QT assessment pathway. See Section 6.3.1 for additional details.

See the full review by the IRT for Cardiac Safety Studies (QT-IRT) for further details.

Immunogenicity

Data and the Applicant's Position: Not applicable; immunogenicity assessments were not performed in both studies.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.5. Analysis of Submission-Specific Safety Issues

Data and the Applicant's Position:

Pivotal Study WO41554: A comparable proportion of patients reported selected AEs (based on the known and evolving safety profile of inavolisib and protocol-defined AESI and analyzed using grouped terms) in the Inavo+Palbo+Fulv arm (96.9%) and the Pbo+Palbo+Fulv arm (96.3%). The majority of selected AEs were of Grade 1 or 2 in severity with the exception of

neutropenia in which Grade 3-4 neutropenia was reported in 80.2% of patients in the Inavo+Palbo+Fulv arm and 78.4% of patients in the Pbo+Palbo+Fulv arm. There were no Grade 5 selected AEs in either arm.

The majority of patients who experienced a selected AE of hyperglycemia (known on-target, reversible toxicity associated with PI3K pathway inhibition) in the Inavo+Palbo+Fulv arm had Grade 1 (16.0%) or Grade 2 (37.0%) events; Grade 3 events were reported in 5.6% of patients in the Inavo+Palbo+Fulv arm and no Grade 4-5 events were reported; all events were non-serious, and manageable with oral anti-hyperglycemic agents and dose reductions (2.5%) or interruptions (27.8%) in all patients including pre-diabetic patients enrolled in the Inavo+Palbo+Fulv arm. The majority of events of hyperglycemia in the Inavo+Palbo+Fulv arm were reversible with only 2 patients (1.2%) discontinuing from the study due to AEs of hyperglycemia and Type 2 diabetes mellitus. Among the inavolisib-treated patients who had a key selected event of hyperglycemia, the median time to first onset was 7 days (range: 2.0 to 955.0 days). Frequency of new onset of key selected AE of hyperglycemia was highest during the first 2 months of treatment.

The majority of patients who experienced a selected AE of diarrhea had Grade 1 (27.8%) or Grade 2 (16.7%) events in the Inavo+Palbo+Fulv arm, and more patients experienced all-grade diarrhea events in the Inavo+Palbo+Fulv arm (48.1%) compared with the Pbo+Palbo+Fulv arm (16.0%). Grade 3 events were reported in 3.7% of patients. Two patients (1.2%) in the Inavo+Palbo+Fulv arm experienced diarrhea SAEs, both of which were Grade 3 in severity and recovered/resolved at the CCOD. No patient experienced a Grade 4 or 5 diarrhea event in either arm and no event led to withdrawal of any study drug in either arm. In the Inavo+Palbo+Fulv arm, diarrhea events led to dose reduction of any study drug in 2 patients (1.2%) and dose interruption of any study drug in 12 patients (7.4%). Among the inavolisib-treated patients who had a key selected event of diarrhea, the median time to first onset was 15 days (range: 2.0 to 602.0 days). Frequency of new onset of key selected AE of diarrhea was highest during the first month.

All patients who experienced a selected AE of rash had Grade 1 (Inavo+Palbo+Fulv: 21.0%) or Grade 2 events (4.3%). There were no Grade 3 or 4 events, no rash events that led to withdrawal of any study drug and no patient experienced an SAE of a rash event during the study in either arm. In the Inavo+Palbo+Fulv arm, rash events led to dose reduction of any study drug in 1 patient (0.6%) and dose interruption of any study drug in 3 patients (1.9%). Among the inavolisib-treated patients who had key selected event of rash, the median time to first onset was 29 days (range: 1.0 to 952.0 days). There was no clear trend in terms of the frequency of new onset of key selected AE of rash.

The majority of patients who experienced a selected AE of stomatitis and mucosal inflammation had Grade 1 (32.1%) or Grade 2 (13.6%) events in the Inavo+Palbo+Fulv arm. Grade 3 stomatitis/mucosal inflammation events were only reported in patients in the Inavo+Palbo+Fulv

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arm (5.6% of patients) and no Grade 4, Grade 5 or SAEs were reported in either arm. In the Inavo+Palbo+Fulv arm, stomatitis and mucosal inflammation events led to withdrawal, dose reduction, and dose interruption of any study drug in 1 patient (0.6%), 6 patients (3.7%), and 19 patients (11.7%) respectively. Among the inavolisib-treated patients who had key selected event of stomatitis and mucosal inflammation, the median time to first onset was 13 days (range: 1.0 to 610.0 days). Frequency of new onset of a key selected AE of stomatitis and mucosal inflammation was highest during the first 3 months.

Neutropenia events were well-balanced between the two arms. The majority of patients who experienced a selected AE of neutropenia had Grade 3 (64.2%) or Grade 4 (16.0%) events in the Inavo+Palbo+Fulv arm. No patient experienced a Grade 5 neutropenia event in either arm. Neutropenia events led to withdrawal of any study drug in 1 patient (0.6%) in the Inavo+Palbo+Fulv arm. In the Inavo+Palbo+Fulv arm, neutropenia events led to dose reduction of any study drug in 30.9% of patients and dose interruption of any study drug in 56.8% of patients.

Supportive Study GO39374: For the overall safety population, the most commonly reported ($\geq 50\%$) selected AEs (by grouped terms) were hyperglycemia (66.8%), diarrhea (64.7%), and nausea (56.8%), which were manageable with standard of care measures and dose modifications or interruptions. In Arm B, Arm E, and Arm F, the most commonly reported selected AEs ($\geq 50\%$ in each arm) were, respectively: hyperglycemia (63.6% in Arm B, 70.0% in Arm E and Arm F), diarrhea (75.8%, 85.0% and 60.0%), nausea (51.5%, 70.0% and 60.0%), stomatitis and mucosal inflammation (66.7, 90.0% and 55.0%) and neutropenia (81.8%, 85.0%, 55.0%), which were manageable with standard of care measures and dose modifications or interruptions. Only one patient in Arm E had a selected AE of diarrhea leading to withdrawal of all study drugs including inavolisib.

The FDA's Assessment:

Hyperglycemia is a known toxicity with PI3K inhibitors. Patients were required to have FBG < 126 mg/dL and HbA1C < 6% at study entry for INAVO 120. Increased fasting glucose (based on laboratory abnormality) occurred in 85% of patients treated with inavolisib, including Grade 3 events in 12% of patients. There were no grade 4 or 5 events or cases of diabetic ketoacidosis (DKA) or hyperosmotic hyperglycemic nonketotic (HHNK) states. Sixty-six patients received treatment for hyperglycemia, this included 62 patients receiving metformin and 11 patients receiving insulin. Hyperglycemia was also managed with dose modifications, including dose reduction in 3% of patients and dose interruption in 28% of patients. Permanent treatment discontinuation was required in 1% of patients (2 patient) due to hyperglycemia.

Stomatitis occurred in 51% of patients treated with inavolisib, Grade 3 events in 6% of patients. There was no grade 4 or 5 events or SAE associated with stomatitis. Stomatitis led to interruption inavolisib in 10%, to dose reduction in 3.7%, and to discontinuation of inavolisib in 0.6% of patients. For patients treated with inavolisib in combination with palbociclib and

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fulvestrant, 38% of patients used a mouthwash containing corticosteroid for management or prophylaxis of stomatitis.

Diarrhea occurred in 48% of patients treated with inavolisib, including Grade 3 events in 3.7% of patients. There were no grade 4 or 5 events or cases of colitis on the INAVO120 Trial. There were two SAEs associated with diarrhea, both of which resolved. In addition, there was a case of acute kidney injury associated with diarrhea and cases of dehydration associated with diarrhea. Dose interruptions were required in 7% of patients, and dose reductions occurred in 1.2%. Anti-diarrheal medicines were used in 28% of patients treated with inavolisib to manage symptoms.

Ocular toxicity occurred in 22% of patients treated with inavolisib compared to 13% on the placebo arm. The most common toxicity was dry eye (9%). There were no grade 3-5 events, no SAEs and ocular toxicity did not lead to dose modifications (discontinuation, reduction or interruption).

Neutropenia is a known toxicity with treatment of palbociclib and occurred at similar rates in both treatment arms.

Pneumonitis occurred in 3 patients on inavolisib treatment arm (compared to 0 on the placebo arm). There were no grade 3-4 events or SAEs. One patient had a dose interruption, there were no dose reductions or drug discontinuations.

The Applicant included hyperglycemia in the Warnings and Precautions section of the proposed USPI. In addition, FDA required inclusion of stomatitis and diarrhea in the Warnings and Precautions section based on the incidence of these events and the occurrence of severe cases for both stomatitis and diarrhea in the INAVO120 trial.

Table 41: Applicant - Study WO41554: Summary of Selected Adverse Events (Safety Analysis Set)

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%)

Table 42: Applicant - Study WO41554: Summary of Selected Adverse Events (Safety Analysis Set) (cont.)

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%)

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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
 Source: Primary CSR, Study WO41554, Report 1126696, Table 38; t_ae_sel_AESEL_SAS_29SEP2023_41554, t_ae_ctc_sel_AESEL_SAS_29SEP2023_41554, t_ae_ctc_sel_AESEL_SER_SAS_29SEP2023_41554, t_ae_sel_AESEL_DSC_SAS_29SEP2023_41554, t_ae_sel_AESEL_DSR_SAS_29SEP2023_41554, t_ae_sel_AESEL_DSI_SAS_29SEP2023_41554, t_ae_sel_AESEL_AECON_SAS_29SEP2023_41554; Dataset: ADaM: ADAE

Table 43: Applicant - Study GO39374: Overview of Safety for Selected Adverse Events (Arms B, E, F, and A-F, Safety Analysis Set)

	Inavo + Palbo + Letro (Arm B) (N=33)	Inavo 9 mg + Palbo + Fulv (Arm E) (N=20)	Inavo 9 mg + Palbo + Fulv + Metf (Arm F) (N=20)	All Patients (Arms A-F) (N=190)
Medical concepts*: patients with				
Hyperglycemia	21 (63.6%)	14 (70.0%)	14 (70.0%)	127 (66.8%)
Diarrhea	25 (75.8%)	17 (85.0%)	12 (60.0%)	123 (64.7%)
Nausea	17 (51.5%)	14 (70.0%)	12 (60.0%)	108 (56.8%)
Stomatitis and mucosal inflammation	22 (66.7%)	18 (90.0%)	11 (55.0%)	92 (48.4%)
Vomiting	16 (48.5%)	11 (55.0%)	7 (35.0%)	77 (40.5%)
Neutropenia	27 (81.8%)	17 (85.0%)	11 (55.0%)	64 (33.7%)
Ocular toxicities	15 (45.5%)	11 (55.0%)	6 (30.0%)	60 (31.6%)
Rash	14 (42.4%)	6 (30.0%)	5 (25.0%)	47 (24.7%)
ALT/AST elevation	10 (30.3%)	3 (15.0%)	3 (15.0%)	42 (22.1%)
Thrombocytopenia	17 (51.5%)	10 (50.0%)	4 (20.0%)	38 (20.0%)
Pneumonitis	1 (3.0%)	0	1 (5.0%)	2 (1.1%)
Colitis	0	0	0	1 (0.5%)

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DLT=dose limiting toxicity; Inavo=Inavolisib; Palbo=Palbociclib; Letro=Letrozole; Fulv=Fulvestrant; Metf=Metformin.

Investigator text for AEs encoded using MedDRA version 26.0.

Only treatment emergent AEs are displayed. Percentages are based on N in the column headings. Numbers presented reflect AEs of all grades.

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.

*The methodology of data analyses has evolved between Studies GO39374 and WO41554 for selected AE categories of "Lymphopenia" and "Anemia". For Study GO39374, the analyses of these two categories are presented by individual MedDRA Preferred Terms contained within each category, and therefore not presented in the current table as grouped term analyses.

Source: Adapted from Interim CSR, Study GO39374, Report 1125233, Table 18; t_ae_grp_oview_CSR_SE_27MAR2023_39374; t_ae_pt_CSR_SE_27MAR2023_39374; Dataset: ADaM: ADAE

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data and the Applicant's Position:

Pivotal Study WO41554: Seven AEs deemed most applicable to inavolisib, palbociclib, and fulvestrant based on preliminary safety or published studies (i.e. diarrhea, nausea, vomiting, fatigue, mouth sores, decreased appetite, and rash), were selected from the PRO-CTCAE item library for assessment, along with an additional single item assessing bother due to side-effects of treatment.

In both arms, worst post-baseline levels of “moderate”/ “occasionally” or less were reported by >70% of patients for decreased appetite, nausea, and vomiting, and by >60% of patients for mouth sores, diarrhea and fatigue. Results of bother from treatment side effects showed a similar pattern with >55% patients in both arms reporting no more than moderate levels of bother, suggesting that inavolisib did not contribute increased treatment burden when added to fulvestrant and palbociclib.

Higher, i.e. worse, ratings of post-baseline severity/frequency (“severe”/ “frequently” or “very severe”/ “almost constantly”), were reported by a greater proportion of patients in the Inavo+Palbo+Fulv arm than the Pbo+Palbo+Fulv arm, particularly for diarrhea (Inavo+Palbo+Fulv: 32.9% vs. Pbo+Palbo+Fulv: 10.1%), mouth/throat sores (30.2% vs. 8.9%), and decreased appetite (27.0% vs. 12.7%). The proportion of patients reporting post-baseline rash (rated in terms of presence as “Yes”/ “No”) was 53.9% vs. 40.5% in the Inavo+Palbo+Fulv and the Pbo+Palbo+Fulv arm, respectively. These higher rates reported by patients in the inavolisib arm mirror the safety data showing higher prevalence of stomatitis, diarrhea, and rash associated with inavolisib. Despite greater proportions of patients in the inavolisib arm reporting higher/worse levels of treatment-related symptoms post-baseline, no additional detriment to their baseline levels of day-to-day functioning or HRQoL was observed while on treatment, further demonstrating the tolerability of the inavolisib regimen.

The FDA's Assessment:

The Applicant collected PRO-CTCAE items as described above. In general, these patient-reported symptoms were observed to be worse in the inavolisib arm, with the greatest difference observed for diarrhea, mouth sores, decreased appetite, and rash. These symptoms are supportive of the clinician reported safety information and were considered informative for labeling.

The Applicant also collected overall side effect impact using the MBI which prompted patients “I am bothered by side effects of treatment”. At baseline, the proportion of patients with MBI responses of “not at all” were similar between arms. Throughout the trial, patients in the inavolisib with palbociclib and fulvestrant arm reported more side effect bother compared to the placebo with palbociclib and fulvestrant arm. For example, at Cycle 2 Day 15, the

proportion of patients with MBI responses of “not at all” were 25% in the ITOVEBI with palbociclib and fulvestrant arm and 53% in the placebo with palbociclib and fulvestrant arm. This disparate overall side effect bother was similar across cycles and also supports the safety findings above.

These PRO data were assessed appropriately with acceptable data quality. The patient-reported data provide additional insight into the safety and tolerability of the approved regimen and were included in section 6 of the USPI to further inform patients and providers.

8.2.7. Safety Analyses by Demographic Subgroups

Data and the Applicant’s Position:

Pivotal Study WO41554: Given the relatively small number of patients included in the analyses by age, gender, race, and ethnicity, these subgroup comparisons should be interpreted with caution.

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

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). In the male patients, no AEs leading to death or AEs leading to withdrawal of treatment were reported.

The majority of the 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%). AEs leading to withdrawal from any study treatment or dose modification/interruption of inavolisib were comparable between the White and Asian racial subgroups, and across regions, supporting the manageability and tolerability of inavolisib in combination with palbociclib and fulvestrant in both White and Asian racial subgroups and across geographical regions.

The FDA’s Assessment:

incidences of SAEs and AEs leading to dose modification/interruption of any study treatment was numerically higher in elderly patients; however, there were only 11 patients >75 years and 47 patients between 65-74 years of age enrolled on study. In addition, there is limited information regarding different racial/ethnic groups from the INAVO120 Trial (WO41554) as the majority of patients enrolled were White. Overall, only two Black patients and 20 Hispanic/Latino patients were enrolled on INAVO120 trial (WO41554). Due to the lack of diversity in the enrolled population, a Post Marketing Commitment (PMC) is being issued to further characterize the efficacy and safety of inavolisib for the treatment of breast cancer in study populations whose demographics are more representative of the population of U.S.

patients for the proposed indication.

8.2.8. Specific Safety Studies/Clinical Trials

Data and the Applicant's Position: The clinical safety data supporting evaluation of the intended indication is primarily derived from the pivotal Phase III Study WO41554, with supportive data derived from the Phase I Study GO39374. No studies were conducted to evaluate a specific safety concern.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that the safety data supporting the intended indication is primarily from the INAVO120 trial (WO41554). GO39374 was not reviewed in depth by the FDA, as it was not considered to support the intended indication.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position: No carcinogenicity studies with inavolisib have been conducted. No carcinogenicity studies are currently planned because such studies are not required for drugs intended for advanced cancer patients per ICH-S9 ([DHHS 2010](#)).

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Human Reproduction and Pregnancy

The Applicant's Position: There were no pregnancies reported in patients treated with inavolisib in either of the two studies. No fetus should be exposed to inavolisib. Because inavolisib will likely cross the placental membrane, inavolisib should not be administered to pregnant women.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Pediatrics and Assessment of Effects on Growth
Data and the Applicant's Position: The Applicant received the Agreed Initial Pediatric Study Plan (iPSP) Agreement for Study WO41554 from the Agency on 12 September 2022. Further details are in Module 1 of the dossier.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data: There is limited experience with overdose with inavolisib in clinical trials. In clinical studies, inavolisib was administered at doses up to 12 mg once daily. Accidental overdosage of

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inavolisib have been reported in clinical studies as an AE. The highest dose administered in Study WO41554 was 18 mg in one patient. The patient erroneously took two 9 mg tablets of inavolisib on one occasion. The event of accidental overdose was resolved in one day and did not require treatment or lead to dose modification of any study drugs. There were no additional AEs reported due to the accidental overdose.

In Study GO39374, 3 patients deviated from assigned study drug dose which resulted in an overdose of inavolisib administration which were reported as major protocol deviations. The highest dose administered in Study GO39374 due to deviation was 20 mg in two patients. All overdoses of inavolisib were for one occasion and associated with no AEs.

The Applicant's Position: Patients who experience overdose should be closely supervised and supportive care instituted. There are no known antidotes for inavolisib.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.10. Safety in the Post-market Setting

Safety Concerns Identified Through Post-market Experience

The Applicant's Position: Inavolisib has not been approved for use anywhere in the world; therefore, no post-marketing data regarding its use are currently available.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Expectations on Safety in the Post-market Setting

The Applicant's Position: Toxicities have been adequately represented in 351 patients in both Study WO41554 and Study GO39374 for this application and are expected to be similar in the post-market setting. It is expected that safety issues can be adequately managed through labeling, additional risk minimization measures and routine post-marketing surveillance.

The FDA's Assessment:

The safety assessment for inavolisib for this NDA review is primarily based on the 162 patients treated on the inavolisib+palbociclib+fulvestrant treatment arm of the INAVO120 trial. The FDA will continue to monitor post-marketing reports and safety reports submitted after approval.

8.2.11. Integrated Assessment of Safety

The Applicant's Position: In line with the efficacy benefit described in Section 8.1.4, the safety and tolerability profile of inavolisib in combination with palbociclib and ET as observed in the pivotal Study WO41554 and supportive Study GO39374 appeared to be manageable and acceptable.

The overall safety profile of inavolisib in combination with palbociclib and fulvestrant in Study WO41554 was comparable with the overall safety population (Arms A-F) and Arms B, E and F of Study GO39374, strengthening the characterization of the inavolisib safety profile across inavolisib-containing treatment regimens including triplet regimens with palbociclib and fulvestrant or with palbociclib and letrozole and supporting the tolerability and AE management of inavolisib. Data from both studies were consistent with the anticipated safety profile of inavolisib and the respective safety profiles of palbociclib, fulvestrant, and letrozole. No new or unexpected safety findings were identified in either of the studies.

In both Studies WO41554 and GO39374, the proportion of patients who experienced AEs leading to withdrawal of any study drug was overall low indicating manageability of AEs and good tolerability of inavolisib in combination with palbociclib and an ET.

Hyperglycemia is a reversible on-target toxicity with early onset associated with drugs that target the PI3K-AKT-mTOR pathway. In Study WO41554, the majority of patients who experienced a selected AE of hyperglycemia in the Inavo+Palbo+Fulv arm had Grade 1 or Grade 2 events; all events were non-serious, and manageable with oral anti-hyperglycemic agents and dose reductions (2.5%) or interruptions (27.8%) in all patients including pre-diabetic patients enrolled in the Inavo+Palbo+Fulv arm. Grade 3 hyperglycemia events were reported in a low proportion of patients in the Inavo+Palbo+Fulv arm and no Grade 4 or Grade 5 hyperglycemia events were reported in either arm. Median time to first onset of hyperglycemia was 7 days. The majority of events of hyperglycemia in the Inavo+Palbo+Fulv arm were reversible with only 2 patients (1.2%) discontinuing from the study due to AEs of hyperglycemia and Type 2 diabetes mellitus. The overall incidences of hyperglycemia AEs in the Inavo+Palbo+Fulv arm of Study WO41554 (58.6%) was lower than that seen in the overall safety population (66.8%) or in Arm E or Arm F individually (70.0% each) of Study GO39374 and could be due to differences in NCI-CTCAE grading criteria, more restrictive hyperglycemia inclusion criteria and an improved manageability of hyperglycemia in Study WO41554. No cases of diabetic ketoacidosis or hyperosmotic hyperglycemic nonketotic states were reported across both studies thereby indicating that hyperglycemia was well-managed per the protocol-defined guidance irrespective of underlying risk factors.

The majority of diarrhea AEs across both studies were Grade 1-2 with no Grade 5 events and a total of 3 SAEs (2 in Study WO41554 and 1 in Study GO39374). Dose reduction, interruption and withdrawal of any study drug due to diarrhea were not frequent and supported the manageability of diarrhea AEs.

Across both studies, most rash events were Grade 1-2 with one Grade 3 event, no Grade 4 or 5 events and a total of 2 SAEs (both in Study GO39374). No patient discontinued any study drug due to rash across both studies. A low proportion of patients required dose interruptions or dose reductions due to rash AEs.

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The incidence of neutropenia AEs in the Inavo+Palbo+Fulv arm of Study WO41554 was consistent with the palbociclib-containing Arms B, E, and F of Study GO39374. Across both studies, the majority of neutropenia events were Grade 3-4 with no Grade 5 events reported. Two SAEs, 1 event in the placebo arm of Study WO41554 and 1 event in Arm B of Study GO39374, were reported. Among common selected AEs in Study WO41554, the incidence and severity of neutropenia were well balanced between the two treatment arms and consistent with the incidence of this AE reported with palbociclib ([IBRANCE® USPI](#)); thereby, indicating that inavolisib has minimal impact on the known risk of neutropenia associated with palbociclib.

Across both studies, most of the stomatitis and mucosal inflammation events were Grade 1-2 with no Grade 5 events. One SAE was reported in Study GO39374. The AEs of stomatitis and mucosal inflammation were manageable with standard clinical measures and dose modifications/interruptions.

The median dose intensity of triplet combination of Inavo+Palbo+Fulv was high across both studies thereby showing that the addition of inavolisib did not compromise the dose intensity of palbociclib and fulvestrant (current standard of care). At the time of CCOD for Study WO41554, the majority of patients in the Inavo+Palbo+Fulv arm had been on treatment for longer than 6 months in comparison to the majority of the patients in the Pbo+Palbo+Fulv arm being on treatment for less than 6 months.

The FDA's Assessment:

The safety profile for inavolisib in combination with palbociclib and fulvestrant is primarily based on data from the safety population from the INAVO120 trial (WO41554). This includes 162 patients treated with inavolisib+palbociclib+fulvestrant. Data from Study GO39374 was not considered supportive of the intended indication and was not reviewed in depth. The patient population in Study GO39374 was different than the patient population for the granted indication.

The overall safety profile for the triplet combination was consistent with the anticipated safety profile for inavolisib and the known safety profile for palbociclib and fulvestrant.

Adverse events known to occur with PI3K inhibitors include hyperglycemia, stomatitis, diarrhea, and rash. Hyperglycemia (increased laboratory glucose) occurred at much higher rates on the inavolisib treatment arm (85%) compared to the placebo arm (43%). Hyperglycemia was managed with dose modifications and implementation of anti-hyperglycemic therapy as needed. Only two patients required permanent discontinuation of inavolisib due to hyperglycemia. Grade 3 increased laboratory blood glucose (FPG > 250 to 500 mg/dL) occurred in 12% of patients, and 0.6% with Grade 4 (FPG > 500 mg/dL) events. There was no grade 5 cases of hyperglycemia or cases of DKA and HHNK. However, patients that enrolled on the trial were required to have fasting blood glucose (FBG) <126 and HBA_{1c}<6%. Therefore, the safety

of inavolisib in patients with a history of diabetes or higher baseline risk factors (FBG>126 and HB1_c>6%) is not known. Patients treated with inavolisib will need to be closely monitored for hyperglycemia and start treatment as indicated, including anti-glycemic therapy, dietary modifications, adequate hydration, and evaluation by a specialist. Hyperglycemia is labeled in the warnings and precautions section of the USPI.

Stomatitis occurred at higher rates in the inavolisib treatment arm (51%) compared to the placebo arm (27%), including 6% of patients on the inavolisib arm having grade 3 events. There were no grade 4-5 events or SAEs. Stomatitis was managed with dose modifications and required permanent discontinuation in one patient. For patients treated with inavolisib, 38% used a mouthwash containing corticosteroid for management or prophylaxis of stomatitis. Patients should be monitored for stomatitis and have treatment instituted as indicated. Stomatitis is labeled in the warnings and precautions section of the USPI.

Diarrhea occurred at higher rates in the inavolisib treatment arm (48%) compared to the placebo arm (16%), including 4% of patients on the inavolisib arm having grade 3 events. There were two SAEs and no grade 4-5 events or colitis. Diarrhea was managed with dose modifications and no patients required treatment discontinuation due to diarrhea. Anti-diarrheal medicines were used in 28% of patients treated with inavolisib to manage symptoms.

Rash occurred in 26% of patients treated with inavolisib compared to 19% of patients on the placebo arm. There were no grade 3-5 events or SAEs. Few patients needed dose modifications due to rash (3 patients had dose interruption and one patient had dose reduction) and no patients required treatment discontinuation.

Ocular toxicity occurred in 22% of patients treated with inavolisib compared to 13% on the placebo arm. The most common toxicity was dry eye (9%). There were no grade 3-5 events, no SAEs and ocular toxicity did not lead to dose modifications (discontinuation, reduction, or interruption).

Hematologic toxicities were seen in both treatment arms and are known toxicities with palbociclib. Neutropenia and anemia were seen in a similar proportion of patients regarding all grade toxicity. However, grade 3-4 toxicity was slightly higher in the inavolisib treatment arm. Thrombocytopenia (including platelet count decreased) was also higher in the inavolisib treatment arm compared to the placebo treatment arm.

The addition of inavolisib to palbociclib and fulvestrant resulted in increased toxicity. However, the median relative dose intensity of palbociclib and fulvestrant was similar between the two treatment arms of the INAVO120 (WO41554) Trial; therefore, the triplet combination therapy including inavolisib did not have a significant impact on the ability to administer full dose palbociclib+fulvestrant. The most notable increase in adverse events were observed in hyperglycemia, stomatitis, and diarrhea, including severe cases. Therefore, hyperglycemia,

stomatitis and diarrhea are labeled under Warnings and Precautions in the USPI to better inform providing physicians and to provide guidance for dose modifications. These adverse events could be managed with dose interruptions and dose reductions in most cases. Other adverse events (including laboratory abnormalities) noted in $\geq 20\%$ of patients treated with inavolisib+palbociclib+fulvestrant include decreased neutrophils, decreased hemoglobin, increased fasting glucose, decreased platelets, decreased lymphocytes, stomatitis, diarrhea, decreased calcium, fatigue, decreased potassium, increased creatinine, increased ALT, nausea, decreased sodium, decreased magnesium, rash, decreased appetite, COVID-19 infection, and headache.

In addition, the Applicant further explored safety and tolerability through assessment of patient-generated data. A list of expected symptomatic adverse events from the combination of inavolisib, palbociclib, and fulvestrant (diarrhea, nausea, vomiting, fatigue, mouth sores, decreased appetite, and rash), was selected from the patient reported outcome (PRO)-CTCAE item library, along with an additional single item assessing bother due to side-effects of treatment. These PRO data were assessed appropriately with acceptable data quality. Analysis of patient-reported symptoms that worsened from baseline were generally observed to be worse in the inavolisib arm, with the greatest difference observed for diarrhea, mouth sores, decreased appetite, and rash. The patient-reported data provide additional insight into the safety and tolerability of the approved regimen and were included in section 6 of the USPI to further inform patients and providers.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There were no major statistical issues with this application. The INAVO120 study met its primary endpoint of INV-assessed PFS, showing a statistically significant improvement in PFS with the treatment of inavolisib + palbociclib + fulvestrant. The results were generally consistent across sensitivity analyses and subgroup analyses, except for Region, where the difference in survival between arms is diminished in the North America/Western Europe region. However, subgroup analyses should be interpreted with caution due to small sample sizes in each subgroup. The interim OS analysis at the time of PFS analysis with 63% information fraction was not statistically significant. Interim OS results showed a HR of 0.64 (95% CI: 0.43, 0.97) with median OS not estimable (95% CI: 27.3, NE) on the inavolisib + palbociclib + fulvestrant arm and 31.1 months (95% CI: 22.3, NE) on the placebo + palbociclib + fulvestrant arm. Thus, there appears to be no detriment in OS at this time. The final analysis of OS is expected to occur in the second quarter of 2025.

8.3.1. Conclusions and Recommendations

The FDA's Assessment:

INAVO120, a randomized, placebo-controlled, double-blind, multicenter trial in 325 patients with endocrine resistant, PIK3CA mutated, HR-positive, HER2-negative (defined as IHC 0 or 1+, or IHC 2+/ISH-), advanced or metastatic breast cancer, following recurrence on or after completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease, demonstrated statistically significant and clinically meaningful improvement in PFS by investigator which was supported by an interim OS that showed no detriment. Inavolisib is associated with increased hyperglycemia, stomatitis, and diarrhea compared to placebo and are included as Warnings and Precautions, as these were considered severe, and occurred in a significant proportion of patients as noted in labeling.

The review team recommends granting regular approval to inavolisib + palbociclib + fulvestrant for the following indication:

Inavolisib (ITOVEBI), in combination with palbociclib and fulvestrant, is indicated for the treatment of adults with endocrine-resistant, PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.

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X

X

Primary Statistical Reviewer
Haley Gittleman, PhD

Statistical Team Leader
Joyce Cheng, PhD

X

X

Primary Clinical Reviewer
Suparna Wedam, MD

Clinical Team Leader
Preeti Narayan, MD

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

No Advisory Committee was convened for this application.

10 Pediatrics

The Applicant's Position: Not applicable as the applicant has not proposed any pediatric sections in the proposed labeling (Agreed iPSP; Reference ID 5044201).

The FDA's Assessment:

FDA agrees with the Applicant's assessment. No pediatric patients were included in INAVO120 (WO41554), which was the primary study used to evaluate efficacy in this NDA. FDA issued an Agreed Initial Pediatric Study Plan (iPSP) Agreement for a full waiver for the indication to IND 130909 on September 12, 2022.

FDA waived the pediatric study requirement for this application because necessary studies are impossible or highly impracticable. This is due to the rarity of patients with breast cancer and pediatric cancers with PI3KCA mutations. Across pediatric cancers, PIK3CA mutations are far less common in pediatric tumors and are primarily limited to central nervous system (CNS) tumors. Inavolisib is not expected to be effective in CNS tumors, because inavolisib is a substrate of P-glycoprotein and breast cancer resistance protein which limits accumulation and activity within the CNS.

11 Labeling Recommendations

The Applicant’s Position: This is an original application. Please see draft labeling text in Module 1.14 for proposed labeling.

The FDA’s Assessment:

The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. The table below summarizes key changes.

Section	Applicant’s Proposed Labeling	FDA’s Proposed Labeling
Highlights of Prescribing Information	The Applicant proposed the following indication: (b) (4)	Indication narrowed, to specify “endocrine-resistant”, consistent with the patient population enrolled in INAVO120. Indication specifies in combination with palbociclib + fulvestrant, as this combination demonstrated convincing efficacy. Added recommended “with or without food” to recommended dosage. Indication specifies “ <i>following recurrence on or after completing adjuvant endocrine therapy</i> ” consistent with trial population in INAVO120. Warnings and Precautions updated to include stomatitis and diarrhea. Added laboratory abnormalities to adverse reactions (i.e., decreased calcium, decreased potassium, increased creatinine, increased ALT, decreased sodium, decreased magnesium).

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Section	Applicant’s Proposed Labeling	FDA’s Proposed Labeling
Indications and Usage (Section 1)	The Applicant proposed the following indication: (b) (4)	For consistency with 21 CFR 201.57(c)(2)(i)(B), the indication was narrowed to describe the patients who demonstrated clinical benefit when treated with ITOVEBI: <i>ITOVEBI is a kinase inhibitor indicated in combination with palbociclib and fulvestrant for the treatment of adults with endocrine-resistant, PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer, as detected by an FDA-approved test, following recurrence on or after completing adjuvant endocrine therapy.</i>
Dosage and Administration (Section 2)		Section 2.1 edited to specify selecting patients based on the presence of one or more <i>PIK3CA</i> mutations in plasma specimens. Removed (b) (4) Section 2.2 added statement “Do not chew, crush, or split prior to swallowing”. Section 2.3 edited for clarity. Consolidated all dosage modifications for adverse reactions into Table 2 Dosage Modifications for Adverse Reactions edited to include dose modification for stomatitis, diarrhea, and hematologic toxicities. Hyperglycemia edited to be consistent

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		with recommended modifications. Removed (b) (4)
Dosage Forms and Strengths (Section 3)		Edited for clarity.
Contraindications (Section 4)	None	None
Warnings and Precautions (Section 5)		FDA revised Section 5 for clarity, brevity and consistency with current labeling practices. FDA adjudicated all incidence percentages and based the incidence rates for hyperglycemia (5.1) on increased fasting glucose for accuracy. Removed (b) (4) FDA added stomatitis (5.2) and diarrhea (5.3) as Warnings and Precautions, including severity and incidence. FDA added nonclinical information (5.4) to describe adverse developmental outcomes in animal studies at the recommended dose. Added advice for females of reproductive potential to use effective nonhormonal contraception.
Clinical Trials Experience (Section 6)		FDA revised Section 6 for clarity, brevity and consistency with current labeling practices. The incidence rates for safety information reported in Section 6 were revised to (b) (4) ((b) (4) 24%), adverse reactions that led to permanent discontinuation ((b) (4)

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		6%), dosage interruption ((b) (4) 69%), dose reduction ((b) (4) 14%). Fatal adverse reactions added including incidence and reported causes. FDA adjudicated all incidence percentages and adjusted to reflect ARs regardless of attribution. FDA edited Table 3 to include addition grouped PT terms for select ARs. Added COVID-19 infection. Removed (b) (4) FDA edited Table 4 to include increased fasting glucose (85%; 12%) as this incidence more accurately reflected incidence of hyperglycemia. (b) (4) FDA added Table 5 to include Patient Reported Symptoms assessed by PRO-CTCAE to further inform healthcare providers of overall side effect impact.
Use in Specific Populations (Section 8)		Section 8.1 Pregnancy edited by FDA for clarity. Added additional fetal malformations observed in animal studies.

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		Section 8.3 edited by FDA for clarity and added cross references to palbociclib and fulvestrant prescribing information. Section 8.5 edited to include higher incidence of dosage modifications for patients $\geq$ 65 years of age. Section 8.6 Renal Impairment edited to indicate ITOVEBI has not been evaluated in patients with severe renal impairment.
Description (Section 11)		FDA edited for clarity.
Clinical Pharmacology (Section 12)		Section 12.1 revised to align to data provided and removed phrases that lacked a commonly understood meaning and were vague, misleading, or potentially promotional. Section 12.2 Pharmacodynamics edited by FDA to convey increased anemia, hyperglycemia, and dosage modification with higher systemic exposure. Section 12.3 AUC values and clearance edited and for clarity. Specific population edited for findings for renal impairment.
Nonclinical Toxicology (Section 13)		FDA revised Section 13.1 for clarity, including studies for male and female rats. Section 13.2 edited for clarity to include information on lens degeneration.
Clinical Studies (Section 14)		FDA edits for clarity on INAVO120 trial design. Inclusion of endocrine resistance definition in trial and details on patient population including specifying that

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		disease progressed during or within 12 months of completing adjuvant endocrine therapy and who have not received prior systemic therapy for locally advanced or metastatic disease. FDA edits to include details for determination of PIK3CA mutation status using the FoundationOne Liquid CDx assay on plasma-derived circulating tumor DNA (ctDNA). FDA added baseline disease information for secondary endocrine resistance, prior chemotherapy, and CDK4/6 inhibitor use. FDA removed (b) (4) Table 6 Efficacy Results revised to be consistent with trial results and FDA analysis. FDA removed (b) (4) (b) (4) FDA edited footnotes to specify endpoints based on assessment and ORR is confirmed ORR. FDA removed (b) (4) Edits to KM curves to include investigator assessed. FDA removed (b) (4)

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Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		FDA moved (and revised) (b) (4) [Redacted]
How Supplied/Storage and Handling (Section 16)		FDA edited for clarity and that bottles contain 30 tablets.
Patient Counseling Information (Section 17)		FDA added stomatitis and diarrhea as these were added as W/P. Edited Section for clarity.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

No REMS is recommended for inavolisib.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The following postmarketing requirements (PMR) and postmarketing commitments (PMC) were issued by FDA and agreed to by the Applicant:

PMRs:

1. **PMR 4718-1:** Conduct a multicenter, randomized clinical trial to further characterize known serious risks with inavolisib including severe hyperglycemia, stomatitis/mucosal inflammation, and diarrhea, and compare the safety and activity of inavolisib 9 mg daily versus a lower daily dose in patients with *PIK3CA*-mutant, hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer.

Draft Protocol Submission:	04/2025
Final Protocol Submission:	10/2025
Trial Completion:	10/2028
Final Report Submission:	04/2029

FDA Rationale: Conducting additional inavolisib dosage optimization is needed to identify whether alternative dosing would reduce the rate of the known serious risk of increased severe adverse events including increased blood glucose, stomatitis/mucosal inflammation, and diarrhea in the target patient population. The Applicant has not provided sufficient justification and supportive data that inavolisib 9 mg PO QD is the optimized dosage for the target patient population in combination with palbociclib and fulvestrant. There are extremely limited clinical data at lower inavolisib dosages with only 20 patients treated at dosages lower than the proposed 9 mg QD dosage across the entire development program of inavolisib. For the proposed inavolisib combination therapy with palbociclib and fulvestrant, all patients were treated at the proposed 9 mg QD inavolisib dosage. At the proposed 9 mg QD inavolisib dosage in combination with palbociclib and fulvestrant, multiple serious ARs in the pivotal study (i.e., severe cases of increased blood glucose, stomatitis/mucosal inflammation, and diarrhea) occurred at high rates. Toxicities led to dosage modification in 69% of patients treated with the proposed recommended dose regimen. Finally, while there were no apparent exposure-response (E-R) relationships for efficacy endpoints, there were multiple positive E-R relationships for safety endpoints including Grade ≥ 2 anemia, Grade ≥ 2 hyperglycemia, Grade ≥ 3 adverse reactions, and inavolisib dosage modifications due to adverse reactions. Given the limited dose finding, high rates of serious ARs, poor tolerability, and positive E-R relationships for multiple safety endpoints, the proposed inavolisib dosage of 9 mg PO QD is not adequately supported as the optimized dosage. Therefore, the Applicant should conduct additional dosage optimization to identify whether an alternative inavolisib dosage would reduce the risk of serious toxicities.

2. **PMR 4718-2:** Complete the ongoing renal impairment clinical trial and evaluate the pharmacokinetics and safety of inavolisib in participants with normal renal function and patients with severe renal impairment, to evaluate the serious potential risk of increased drug exposure.

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Design and conduct the trial in accordance with the FDA Guidance for Industry titled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

Final Protocol Submission:	08/2023 (completed)
Trial Completion:	12/2024
Final Report Submission:	06/2025

Submit the datasets with the final report submission.

FDA Rationale: The final report and datasets from the ongoing renal impairment study are needed to evaluate the pharmacokinetics and safety of inavolisib in participants with severe renal impairment and to support dosage recommendations in this population based on the known serious risk of increased inavolisib exposure in patients with renal impairment. Inavolisib is cleared in part via renal excretion. The Applicant provided data to support dosage recommendations for patients with mild and moderate renal impairment but did not provide sufficient data to support dosage recommendations for patients with severe renal impairment. Patients with moderate renal impairment had ~60% higher inavolisib exposure compared to patients with normal renal function. Given the increased exposure and multiple positive exposure-response relationships for safety, a reduced starting dosage is needed in patients with moderate renal impairment to mitigate the risk of increased serious toxicities including increase blood glucose, stomatitis/mucosal inflammation, diarrhea, and Grade ≥ 3 adverse events. Increased exposure of inavolisib and the need for a reduced starting dosage are expected in patients with severe renal impairment given the known renal excretion and findings in patients with moderate renal impairment. A dedicated renal impairment study including subjects with severe renal impairment is currently ongoing, but results are not expected until 2025 per discussion with the Applicant.

- 3. PMR 4718-3:** Conduct a hepatic impairment clinical trial to evaluate the serious potential risk of increased drug exposure and determine a safe and appropriate dose of inavolisib in patients with moderate and severe hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

Draft Protocol Submission:	03/2025
Final Protocol Submission:	07/2025
Trial Completion:	07/2028
Final Report Submission:	01/2029

Submit the datasets with the final report submission.

FDA Rationale: A clinical hepatic impairment study is needed to evaluate the pharmacokinetics and safety of inavolisib in participants with moderate and severe hepatic impairment and to support dosage recommendations in this population. This study is intended to assess the serious potential risk of increased inavolisib exposure as described below. Per the Mass Balance and Absolute Bioavailability Study GP42652, the absolute oral bioavailability of inavolisib is 76%.

Circulating metabolites were minimal with the majority (99.5% of drug-related material in plasma) being parent inavolisib in the human mass balance study. A mean of 48% of the dose (40% as the parent drug and 8% as metabolites) was recovered in urine, and 48% (10% as the parent drug and 38% as metabolites) was recovered in feces. The amount of drug recovered as metabolites in feces and urine accounts for approximately 46% of the administered dose. Therefore, a >20% contribution of hepatic elimination cannot be ruled out and patients with hepatic impairment may have increased exposure to inavolisib. The Applicant provided data to support dosage recommendations for patients with mild hepatic impairment but did not provide sufficient data to support dosage recommendations for patients with moderate or severe renal impairment. If patients with moderate or severe hepatic impairment have increased inavolisib exposure, a reduced starting dosage may be needed to mitigate the serious risk of increased severe toxicity including hyperglycemia, stomatitis/mucosal inflammation, diarrhea, and other severe adverse reactions.

PMCs

1. **PMC 4718-4:** Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of inavolisib on the single dose pharmacokinetics of a sensitive CYP3A substrate to inform appropriate management strategies for clinically relevant drug interactions. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.”

Draft Protocol Submission:	04/2025
Final Protocol Submission:	08/2025
Trial Completion:	02/2027
Final Report Submission:	08/2027

FDA Rationale: In an in vitro study (16-0131), inavolisib increased CYP3A mRNA up to 40-fold. Based on FDA assessment, available data cannot rule out potential induction effect of inavolisib on sensitive CYP3A substrates. Induction of CYP3A by inavolisib may result in reduced exposure of sensitive CYP3A substrates which could reduce effectiveness of concomitantly administered CYP3A substrates.

The Applicant did not evaluate the induction potential of inavolisib on CYP2C isoforms. If the induction potential of inavolisib on CYP3A is confirmed, an additional study to evaluate the induction potential of inavolisib on CYP2Cs in an in vitro setting and/or in a clinical trial may be needed.

In addition, if inavolisib is at least a weak inducer of CYP3A in vivo, there is the potential for drug-drug interaction between inavolisib and combined oral contraceptives (COC), which are known substrates of CYP3A, which could reduce the effectiveness of the COC and increase the risk of unintended pregnancy. If the induction potential of inavolisib on CYP3A is confirmed, an additional study to evaluate the DDI potential between inavolisib and COC in a clinical trial may be needed.

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2. **PMC 4718-5:** Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of inavolisib on the single dose pharmacokinetics of a CYP2B6 substrate to inform appropriate management strategies for clinically relevant drug interactions. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions.”

Draft Protocol Submission:	04/2025
Final Protocol Submission:	08/2025
Trial Completion:	02/2027
Final Report Submission:	08/2027

FDA Rationale: In an in vitro study (16-0131), inavolisib increased CYP2B6 mRNA up to 4-fold. Based on FDA assessment, available data cannot rule out potential induction effect of inavolisib on sensitive CYP2B6 substrates.

3. **PMC 4718-6:** Complete the ongoing clinical trial, INAVO120 (Study WO41554), titled “A Phase III, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Inavolisib plus Palbociclib and Fulvestrant versus Placebo plus Palbociclib and Fulvestrant in Patients with PIK3CA-Mutant, Hormone Receptor-Positive, HER2- Negative Locally Advanced or Metastatic Breast Cancer”, to provide the final overall survival (OS) analysis.”

Trial Completion:	07/2025
Final Report Submission:	01/2026

Submit the datasets with the final report submission.

FDA Rationale: Inavolisib in combination with fulvestrant and palbociclib will be granted regular approval based on results primarily from the INAVO120 clinical trial (Study WO41554). It is important to review the final OS results for this study to confirm there is continued clinical benefit with use of inavolisib for the treatment of patients with PIK3CA-mutant, hormone receptor-positive, HER2- negative locally advanced or metastatic breast cancer.

4. **PMC 4718-7:** Conduct an integrated analysis containing data from clinical trials and post-marketing reports, observational studies (e.g., real-world evidence), and other sources to further characterize the pharmacokinetics (PK), pharmacodynamics (PD), safety and efficacy of inavolisib in racial and ethnic minority patients and older patients age >65 years with PIK3CA-mutant, hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer. The analyses should support comparative safety and efficacy outcome analyses and characterization of potential differences in PK and PD between racial and ethnic minority patients and White patients, and older and younger patients.

Draft Protocol Submission (Analysis Plan):	06/2025
Final Protocol Submission (Analysis Plan):	12/2025
Study Completion:	12/2029
Final Report Submission:	06/2030

FDA Rationale: INAVO120 was conducted globally and only 4.9% of the efficacy population in

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this application was enrolled in the U.S. In addition, racial and ethnic minorities reflective of the U.S. population of patients with breast cancer, particularly Black/African American and Hispanic/Latino patients, were significantly underrepresented in the efficacy and safety population that supported this application, with only 2 Black/African American patients and 20 Latino/Hispanic patient enrolled. Therefore, it is important to evaluate data further characterizing the efficacy and safety of inavolisib for the treatment of breast cancer in study populations whose demographics are more representative of the population of U.S. patients for the proposed indication.

5. **PMC 4718-8:** Conduct an appropriate analytical and clinical validation study using the INAVO120 clinical trial or other data adequate to support the development of an in vitro diagnostic device for tumor tissue that is essential to the safe and effective use of inavolisib for treatment of patients with PIK3CA-mutant, hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer.

Final Report Submission: 12/2024

FDA Rationale: The clinical validity of F1LCDx was demonstrated by assessing clinical efficacy in the F1LCDx PIK3CA mutation-positive population from the INAVO120 clinical trial based on PFS as the primary efficacy endpoint. However, F1LCDx is a plasma-based test and it is known that identifying the PIK3CA mutation status with a plasma based test may potentially result in a high rate of false-negative results given the low shedding of ctDNA into circulation. A false-negative result could result in delayed treatment or deprive a patient from a potentially beneficial treatment with inavolisib. A companion diagnostic device that can detect PIK3CA mutation in tumor tissue from the intent-to-treat population is needed for the safe and effective use of inavolisib for treatment of patients with PIK3CA-mutant, hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer.

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA’s review:		Is a PMC/PMR needed?
X	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	☒ Yes ☐ No
X	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	☒ Yes ☐ No
X	Other considerations (e.g.: PK/PD), if applicable:	☒ Yes ☐ No

APPEARS THIS WAY ON ORIGINAL

14 Division Director (DHOT) (NME ONLY)

X

Tiffany Ricks, PhD

15 Division Director (OCP)

X

Nam Atiqur Rahman, PhD

16 Division Director (OB)

X

Shenghui Tang, PhD

17 Division Director (Clinical)

X

Laleh Amiri-Kordestani, MD

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Paul Kluetz, MD

19 Appendices

19.1. References

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19.2. Financial Disclosure

The Applicant's Position: Information on financial disclosures for WO41554 and GO39374 is provided in Module 1.3.4 of the NDA.

Covered Clinical Study (Name and/or Number):* Pivotal Study WO41554 and supportive Study GO39374

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: WO41554: 1695; GO39374: 298		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): WO41554: 4; GO39374: 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: WO41554: 4; GO39374: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 5		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant and confirmed/edited by the FDA.

The FDA's Assessment:

FDA agrees with the Applicant that there were no apparent financial conflicts that would have impacted the overall integrity of the two studies listed in the table above.

Out of 1695 investigators in INAVO120 (WO41554), the Applicant was unable to provide financial disclosure for

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5 investigators and the following 4 investigators had disclosable financial interests:

1. (b) (6) (Site (b) (6)): (b) (6) received more than \$25000 for speaking honoraria. This site enrolled (b) (6) patients.
2. (b) (6) (Site (b) (6)): (b) (6) received approximately \$30000 for speaking honoraria. This site enrolled (b) (6) patients.
3. (b) (6) (Site (b) (6)): (b) (6) received a research grant of 35000EUR. This site enrolled (b) (6) patients.
4. (b) (6) (Site (b) (6)): (b) (6) received \$84810 for consulting and speaking honoraria. This site enrolled (b) (6) patients.

Out of 298 investigators in GO39374, the following 3 investigators had disclosable financial interests:

1. (b) (6) (Site (b) (6)): (b) (6) received \$84810 for consulting and speaking honoraria. This site enrolled (b) (6) patients.
2. (b) (6) (Site (b) (6)): (b) (6) received in excess of \$25000 for speaking honoraria. This site enrolled (b) (6) patients.
3. (b) (6) (Site (b) (6)): (b) (6) spouse received more than \$25000 as a consultant (b) (6). This site enrolled (b) (6) patients.

19.3. Nonclinical Pharmacology/Toxicology

Data and the Applicant's Position: Not applicable.

The FDA's Assessment:

Not Applicable. See Section 5 of this Assessment Aid for FDA's Nonclinical review of this application.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Bioanalytical Methods

The FDA's Assessment:

FDA finds the Applicant's bioanalytical method validation and performance acceptable to determine the concentration of inavolisib, fulvestrant, palbociclib, and letrozole.

The Applicant submitted the following method validation and cross-validation reports:

- 1) Validation of a Method for the Determination of GDC-0011 in Human Plasma by HPLC with MS/MS Detection; report No. 21-0686
- 2) Validation of a Method for the Determination of Fulvestrant in Human Plasma by HPLC with MS/MS Detection; report No. 11-0261
- 3) Validation of a Method for the Determination of Palbociclib in Human Plasma by HPLC with MS/MS Detection; report No. 15-3983
- 4) Validation of a Method for the Determination of Letrozole in Human Plasma by HPLC with MS/MS Detection; report No. 8264525
- 5) Cross Validation of Two Methods (b) (4) for the analysis of GDC-0077 in Human Plasma by HPLC with MS/MS Detection, report No. 22-0871
- 6) Cross Validation of Two Methods (b) (4) for the analysis of Palbociclib in Human Plasma by HPLC with MS/MS Detection, report No. 22-0870
- 7) Cross Validation of Two Methods (b) (4) for the analysis of fulvestrant in Human Plasma by HPLC with MS/MS Detection, report No. 22-0872

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Inavolisib (GDC-0077) was detected using a validated analytical method GD07HPP ((b) (6) No. 8463977), entitled “Determination of GDC-0077 in human plasma containing K2EDTA by HPLC with MS/MS detection.”.

The method validation results and cross validation for Inavolisib are summarized in **Table 44** and **Table 45**, respectively. The method validation and cross validation summary results for palbociclib and fulvestrant will not be included in this review; however, the review has determined that the method validation and cross validation for palbociclib and fulvestrant are acceptable.

Table 44: Bioanalytical Method Validation Summary for Inavolisib

Bioanalytical method validation report name, amendments	Validation of a Method for the Determination of GDC-0077 in Human Plasma by HPLC with MS/MS Detection		
Method description	Supported-liquid extraction / HPLC-MS/MS		
Materials used for standard calibration curve and concentration	GDC-0077, Lot #3141203, Retest date 28 February 2023		
Validated assay range	0.100 to 100 ng/mL		
Material used for quality controls (QCs) and concentration	GDC-0077, Lot #3141203, Retest date 28 February 2023		
Minimum required dilutions (MRDs)	NA		
Source and lot of reagents	NA		
Regression model and weighting	Linear regression and 1/x ² weighting		
Validation parameters	Method validation summary		Acceptability
Standard calibration curve performance	Number of standard calibrators from LLOQ to ULOQ	8	Yes
during accuracy and precision runs	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.0 to 1.8%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 4.9%	Yes

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Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 6 QCs	-1.4% to 6.0%	Yes
	Inter-batch %CV	≤8.7%	Yes
	Total Error (TE)	NA	NA
Selectivity & matrix effect	6 individual lots tested, Range of bias -3.1% to 12.0%, No observed issue.		Yes
Interference & specificity	One lot tested Co-admin drug: [13C6]-GDC-0077 (50.0 ng/mL) Range of bias: -11.4% to 7.0% No observed issue		Yes
Hemolysis effect	One lot tested at 0.300 ng/mL (LQC) and 80.0 ng/mL (HQC). Range of bias: -9.0% to 9.3% No observed issue		Yes
Lipemic effect	One lot tested at 0.300 ng/mL (LQC) and 80.0 ng/mL (HQC). Range of bias: -3.0% to 6.1% No observed issue		Yes
Dilution linearity & hook effect	500 ng/mL (DQC) was diluted by 10-fold. Range of bias -1.0 to 6.0% NA for Hook effect		Yes
Bench-top/process stability	24 hours at room temperature		Yes
Freeze-Thaw stability	LQC, HQC: 8 cycles at -10°C to -30°C DQC: 5 cycles at -10°C to -30°C LQC, HQC: 8 cycles at -60°C to -80°C DQC: 5 cycles at -60°C to -80°C		Yes
Long-term storage	116 days at -10°C to -30°C 116 days at -60°C to -80°C		Yes

Parallelism	NA	
Carry over	There was no evidence of carryover within the chromatographic regions of the analyte and ISTD.	Yes

Table 45: Cross Validation Summary for Inavolisib

Bioanalytical method validation report name	Validation of a Method for the Determination of GDC-0077 in Human Plasma by HPLC with MS/MS Detection		
Changes in method	NA		
New validated assay range if any	NA		
Validation parameters	Cross-validation performance		Acceptability
Standard calibration curve performance during accuracy and precision runs	Cumulative accuracy (% bias) in standard calibrators from LLOQ to ULOQ	(b) (4) -13.4 to 7.3% (b) (4) -2.1 to 3.8%	Yes
	Cumulative precision (% CV) from LLOQ to ULOQ	NA	NA
Performance of QCs during accuracy and precision runs	Cumulative accuracy (% bias) in 5 QCs	(b) (4) -1.7 to 4.3% (b) (4) -14.9 to 3.8%	Yes
	Inter-batch % CV	NA	NA
	Percent TE	NA	NA
Cross-validation	Spiked Samples Analyzed in n=6 %Difference: -11.6 to -3.9 Incurred Sample Pools Analyzed in n=4 %Difference: -8.4 to 2.3		Yes

Assessment Conclusions:

The precision and accuracy of quality control (QC) and standard (STD) were within the pre-specified acceptance limits. The Applicant also adequately validated the selectivity, matrix effect, hemolytic effect, freeze-thaw stability, dilution, and recovery. The short-term and long-term stability of low concentration quality control (LQC), medium concentration quality control (MQC), dilution concentration quality control (DQC) was validated to 116 days both at -10 °C to

-30 °C and at -60 °C to -80 °C. The Applicant also cross validated the analytical method at two sites (b) (4)

The Applicant has sufficiently validated bioanalytical methods for inavolisib, palbociclib, and fulvestrant.

19.4.2. Population PK Analysis

19.4.2.1. Executive Summary

The FDA's Assessment:

The Applicant submitted a population PK report entitled "Population PK Analysis of Inavolisib in Patients with Locally Advanced or Metastatic PIK3CA-Mutant Hormone-Receptor Positive Breast Cancer" to characterize the pharmacokinetics of inavolisib after oral administration in patients from studies GO39374 and WO41554. The final population PK model was used to estimate the PK parameters and exposure of inavolisib as a single agent or in combination with other agents in patients with locally advanced or metastatic PIK3CA-mutated solid tumors and in patients with locally advanced or metastatic, PIK3CA-mutated breast cancer. The potential effect of the intrinsic and extrinsic factors on inavolisib were also assessed.

The population PK model for inavolisib was developed based on PK observations from a total of 336 subjects, with 187 patients from Study GO39374 and 149 patients from Study WO41554. The final population PK model of inavolisib was a three-compartment model with first-order absorption, linear elimination, and a mixed proportional and additive error model. Effects of eGFR on CL, body weight and race on Vc and formulation on Ka were included in the final model. The typical values of CL and V of inavolisib were 8.83 L/h and 155 L, respectively.

eGFR effect on CL, weight and race (Asian) effects on Vc were identified as significant covariates, with lower CL for subjects with lower eGFR. The rate of absorption was found to be slower with the phase 1 formulation and the Phase 1 resupply formulation compared to the phase 3 formulation. No impact from combination therapy (fulvestrant, palbociclib, letrozole) was identified.

Patients with moderate renal impairment (N=27) showed higher exposure than patients with normal renal function (N=185) (GMR of steady-state $AUC_{0-\tau}$: 1.42). Patients with mild renal impairment (N=124) and normal renal function had comparable exposure. No impact on inavolisib exposure was observed for patients with mild hepatic impairment (N=111) vs normal hepatic function (N=224).

In general, the Applicant's population PK analysis is considered acceptable for the purpose of estimating the PK and exposure parameters of inavolisib in adult patients with locally advanced

or metastatic, PIK3CA-mutated breast cancer. However, no information is available in the population PK analysis to assess the effect of moderate to severe hepatic impairment and severe renal impairment on inavolisib PK, and information to assess the effect of moderate renal impairment on inavolisib PK is too limited to draw a definitive conclusion. Therefore, dedicated studies to evaluate these effects are warranted. Refer to Section 6.1.2.2 for results of the moderate renal impairment group in the ongoing renal impairment study.

The Applicant's analyses were verified by the reviewer, with no significant discordance identified. The results of the population PK analyses were used to support the proposed labeling statements regarding PK parameters of inavolisib and the effects of intrinsic and extrinsic factors.

19.4.2.2. PPK Assessment Summary

The Applicant's Position: PopPK analysis was performed using 3863 samples from 336 patients (187 from Study GO39374 and 149 from Study WO41554). The final model was a three-compartment model with first-order rate of absorption and linear elimination, a combined additive and proportional error model, a block omega on CL and Vc and between-subject variability (BSV) on Ka, and Vp.

The typical values of CL and Vc of inavolisib were 8.83 L/h and 155 L, respectively. For the peripheral compartments, the typical values of Q, Q2, Vp and Vp2 were 7.50 L/h, 0.14 L/h, 68 L, and 31 L, respectively. The rate of absorption was estimated at 0.92 h⁻¹ for Phase 3 formulation. The population PK model included a significant effect of eGFR on CL, with an exponent of 0.441 [i.e., (eGFR/86)^{0.441}]. This suggests a higher clearance for subjects with higher eGFR. Body weight was significant on Vc, with an exponent of 0.635 [i.e., (WT/65)^{0.635}]. Subjects with a higher body weight had therefore a higher volume of distribution. The volume of distribution was also found to be approximately 25% lower in Asian subjects compared to non-Asian subjects. The rate of absorption was found to be approx. 51% slower with the Phase 1 formulation and phase 1 resupply formulation compared to the phase 3 formulation. No apparent trend remaining between random effects of parameters and the covariates were seen in the final model.

Based on the goodness-of-fit plots and prediction-corrected visual predictive checks, the popPK model was considered adequate to derive the patient-level exposure metrics (AUC, C_{max}, C_{min}) for subsequent exposure-response analyses. The exposure metrics were also used to compare exposures between the sub-groups of interests by simulations.

The sub-groups of interests included race (Asian vs. non-Asian), patients enrolled from China sites (Chinese vs. Non-Chinese), hepatic impairment status (mild vs. normal), renal impairment status (mild or moderate vs. normal), age group (≥65 years vs. <65 years; 65 - <75 years, or ≥75

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years vs. <65 years), body weight group (tertile of body weight) and formulation status (Phase 1/ Phase 1 resupply vs. Phase 3). At steady-state, most of the GMR of exposure metrics between sub-groups of interest were within 0.8 and 1.25, with the exception of the following sub-groups: moderate renal impairment vs. normal renal function (GMR of 1.42, 1.35 and 1.56 for AUC, C_{max}, and C_{min}, respectively); Phase 1 / Phase 1 resupply formulations vs. Phase 3 formulation (GMR of 0.79 and 0.75 for C_{max}, GMR of 1.33 and 1.16 for C_{min}); age ≥75 years vs. age <65 years (GMR of 1.38 for C_{min}), based on only 13 patients with age ≥ 75 years, with GMR for AUC and C_{max} remaining within 0.8 to 1.25. The impact of most of those variables are less pronounced on AUC which reflects the entire inavolisib exposure.

General Information			
Objectives of PPK Analysis		To identify potential covariates effects that may explain the variability in PK parameters. To provide a quantitative assessment of the potential effect of the intrinsic and extrinsic factors on inavolisib PK. To provide post hoc predictions from the PK model that would be used to perform E-R analysis.	
Study Included		Phase I Study GO39374; Phase III Study WO41554 (INAVO120)	
Dose(s) Included		Study GO39374 was a first-in-human, Phase I, open-label, dose-escalation study conducted from 3 to 12 mg (3, 6, 9, 12mg); Study WO41554 (INAVO120) was a Phase III, randomized, double-blind, placebo controlled, multicenter study conducted at 9mg.	
Population Included		Patients with <i>PIK3CA</i> -mutant HR+ LA/mBC	
Population Characteristics (Table 3, Table 4)	General	The median (range) age in the PK population dataset was 56.6 years (27.0 to 85.0 years), with 25.6% ≥ 65 years and 3.9% ≥ 75 years. The median (range) body weight was 65.0 kg (39.0 – 159 kg). Most subjects were White (i.e., 67% White and 18.5% Asian) and female (98%).	
	Organ Impairment	Hepatic impairment (NCI): normal 224 (66.7%); Mild group-1 107 (31.8%); Mild group-2 4 (1.2%) Renal impairment (CrCL): normal 185 (55.1%); Mild 124 (36.9%); Moderate 27 (8.0%)	
	Pediatrics (if any)	No pediatric patients were included.	
No. of Patients, PK Samples, and BLQ		The PK analysis dataset included 4364 PK observations from 346 subjects. After exclusion of Arm G from study GO39374 (48 PK records) and the flagged PK record (107 records), a total of 4209 PK observations from 338 subjects were available. Of these, 3863 (91.8%) from 336 subjects were quantifiable concentrations, and 346 (8.2%) records were BLQ observations. Only 63 BLQ records were observed after administration of the first dose ("post-dose BLQ"), accounting for less than 1.5% of all observations. All the rest of BLQ records (283 records) were "pre-dose BLQ". Hence, exclusion of BLQ samples from the analysis was deemed acceptable.	
Sampling Schedule	Rich Sampling	For WO41554, in a subset of patients from China (n=14), intensive PK sampling was collected (0.5, 1, 2, 3, 8, 24hr at cycle 1 day1 and cycle 1 day 15). For GO39374, in all arms except arm E and F, the intensive sampling was collected at slightly different timepoints	
	In ITT Population	For WO41554, sparse samplings were collected at cycle 1 day1 (Predose, 3 hr post-dose), cycle 1 day8 (Predose), cycle 1 day15 (Predose, 3 hr post-dose) and cycle 2day15 (Predose). For GO39374, sparse samplings were collected at cycle 1 day1 (Predose, 4 and 24hr post-dose) for arm E and cycle 1 day15 (Predose, 24 hr post-dose) for arm E and F.	
Covariates Evaluated	Static	Age, body weight, body mass index, body surface area, sex, race, albumin, alanine transaminase, aspartate transaminase, bilirubin, eGFR, CrCL, renal impairments status, hepatic impairment status, ECOG, tumor burden, presence of liver metastasis, platelets count, neutrophils, lymphocytes, total protein	
	Time-varying	Food, formulation	
Final Model		Summary	Acceptability [FDA's comments]
Software and Version		The population PK analysis was performed using non-linear mixed effect model (NLME) in NONMEM (Version 7.5). Perl Speaks NONMEM (PsN, Version 5.3) was also used for facilitation of NONMEM tasks, such as VPC. Dataset preparation, data exploration, figures and tables, and derivation of posterior Bayes individual exposure levels were performed using R® V4.2 (or higher) with comprehensive R archive network (CRAN) and Certara packages.	Acceptable

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Model Structure	Three-compartment model with first-order absorption and linear elimination, a mixed error model (combined additive and proportional error model), a block omega on CL and Vc.	Acceptable
Model Parameter Estimates	See Table 6 of the inavolisib popPK Report 1129436.	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	See Table 6 of the inavolisib popPK Report 1129436. Bootstrap was not conducted due to the long run time of the final model.	Acceptable
BLQ for Parameter Accuracy	The post-dose BLQ samples represented only 1.5% of the total data and were therefore excluded without further analysis.	
GOF, VPC	See Figures 8 of the popPK Report 1129436 for GOF (and additional diagnostic plots in Appendix 1 Section 13.1 to 13.34); See Figure 9 for VPC (and additional VPC in Appendix 1, Sections 13.35 to 13.52).	Acceptable
Significant Covariates and Clinical Relevance	eGFR on CL, body weight and race on Vc, and formulation on Ka were included as significant covariate in the final model. However, simulation indicated that for steady-state AUC which reflects the overall inavolisib exposure, only the GMR for moderate renal impairment vs. normal renal function is beyond the range of 0.8 to 1.25 (GMR of 1.42 for AUC). See Appendix 2, Section 14.7 and Section 14.8 in Report 1129436.	Acceptable
Analysis Based on Simulation (optional)	The forest plots for the sub-groups listed below were generated by simulations. The purpose was to compare exposure metrics (AUC, C _{max} , C _{min}) between the sub-groups. Asian vs non-Asian, Chinese vs. Non-Chinese, mild hepatic impairment vs normal, mild or moderate renal impairment vs normal, age group (≥65 years vs <65 years; 65 - <75 years, or ≥75 years vs <65 years), body weight group (T1 [36, 59kg], T2 (59, 72 kg), T3 (72, 159 kg)), and formulation status (Phase 1 vs Phase 3; Phase 1 resupply vs Phase 3). For all the sub-groups except formulations, phase 3 formulation was used for simulations. For the comparison of different formulation status, the reference patient with median body weight (65 kg), eGFR (86 mL/min) and being non-Asian race was used for simulations.	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	The following are contents in the labeling that related to popPK model: <u>Distribution:</u> (b) (4) <u>Elimination:</u> (b) (4) <u>Specific Populations:</u> No clinically significant differences in the pharmacokinetics of inavolisib were (b) (4) based on age (27 to 85 years), sex, race (Asian or non-Asian), body weight (39 to 159 kg), (b) (4) mild hepatic impairment (total bilirubin > ULN to ≤ 1.5 * ULN or AST > ULN and total bilirubin ≤ ULN). The effect of (b) (4) (b) (4) moderate to severe hepatic impairment on (b) (4) is unknown. (b) (4)	Acceptable

See Table 3 and 4 of Report 1129436 for Summary of Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Study.

See Table 6 of Report 1129436 for Parameter Estimates and SE from Final Population PK Model.

See Figure 8 and Appendix 1 Section 13.1 to 13.34 in Report 1129436 for Goodness-of-fit Plots for the Final Population PK Model (OBS-PRED/IPRED, CWRES-TIME/PRED).

See Figure 9 and Appendix 1, Sections 13.35 to 13.52 in Report 1129436 for VPC of Final Population PK Model, Stratified by Dose.

See Appendix 2, Section 14.7 and Section 14.8 in Report 1129436 for Impact of Significant Covariates on Exposure.

See Appendix 2, Section 14.7 and Section 14.8 in Report 1129436 for simulation comparisons for the exposure metrics between the sub-groups of interest.

The FDA's Assessment:

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Data: The final datasets for population PK analysis included 3,863 PK observations from 336 subjects. The median (range) age and body weight in the PK population was 57 years (27 to 85 years) and 65 kg (39 to 159 kg), respectively. Most subjects were White (i.e., 67% White and 18.5% Asian), female (98%), and had normal (55%) or mild renal impairment (37%) and normal (67%) or mild (33%) hepatic impairment. A large majority (93%) of patients was assigned to a starting inavolisib dose of 9 mg. Baseline categorical and continuous covariates are summarized in Table 46 and Table 47.

Table 46: Summary of Selected Baseline Categorical Covariates

Covariate	G039374 (N=187)	WO41554 (N=149)	Overall (N=336)
Sex			
Male	1 (0.5%)	5 (3.4%)	6 (1.8%)
Female	186 (99.5%)	144 (96.6%)	330 (98.2%)
Race			
White	137 (73.3%)	87 (58.4%)	224 (66.7%)
Black or African American	3 (1.6%)	1 (0.7%)	4 (1.2%)
Asian	5 (2.7%)	57 (38.3%)	62 (18.5%)
Multiple	1 (0.5%)	0 (0%)	1 (0.3%)
Unknown	41 (21.9%)	4 (2.7%)	45 (13.4%)
Asian Patients			
Yes	5 (2.7%)	57 (38.3%)	62 (18.5%)
No	182 (97.3%)	92 (61.7%)	274 (81.5%)
Ethnicity			
Hispanic or Latino	6 (3.2%)	8 (5.4%)	14 (4.2%)
Not Hispanic or Latino	137 (73.3%)	135 (90.6%)	272 (81.0%)
Not Reported	15 (8.0%)	2 (1.3%)	17 (5.1%)
Unknown	29 (15.5%)	4 (2.7%)	33 (9.8%)
Region			
Asia	0 (0%)	54 (36.2%)	54 (16.1%)
North America/Western Europe	187 (100%)	59 (39.6%)	246 (73.2%)
Other	0 (0%)	36 (24.2%)	36 (10.7%)

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Covariate	G-O39374 (N=187)	WO41554 (N=149)	Overall (N=336)
ChinaSite			
China	0 (0%)	28 (18.8%)	28 (8.3%)
Non-China	187 (100%)	121 (81.2%)	308 (91.7%)
Baseline ECOG Status			
0	107 (57.2%)	96 (64.4%)	203 (60.4%)
1	80 (42.8%)	53 (35.6%)	133 (39.6%)
Hepatic impairments categories according to NCI criterions			
Normal	116 (62.0%)	108 (72.5%)	224 (66.7%)
Mild-1	66 (35.3%)	41 (27.5%)	107 (31.8%)
Mild-2	4 (2.1%)	0 (0%)	4 (1.2%)
Moderate	0 (0%)	0 (0%)	0 (0%)
Severe	0 (0%)	0 (0%)	0 (0%)
Missing	1 (0.5%)	0 (0%)	1 (0.3%)
Renal impairments categories according to CrCL			
Normal	93 (49.7%)	92 (61.7%)	185 (55.1%)
Mild	76 (40.6%)	48 (32.2%)	124 (36.9%)
Moderate	18 (9.6%)	9 (6.0%)	27 (8.0%)
Severe	0 (0%)	0 (0%)	0 (0%)
Nominal Dose			
Inavolisib 3 mg	3 (1.6%)	0 (0%)	3 (0.9%)
Inavolisib 6 mg	17 (9.1%)	0 (0%)	17 (5.1%)
Inavolisib 9 mg	163 (87.2%)	149 (100%)	312 (92.9%)
Inavolisib 12 mg	4 (2.1%)	0 (0%)	4 (1.2%)
Formulation			
Phase 1 Formulation	152 (81.3%)	0 (0%)	152 (45.2%)
Phase 1 Resupply Formulation	35 (18.7%)	0 (0%)	35 (10.4%)
Phase 3 Formulation	0 (0%)	149 (100%)	149 (44.3%)
Actual Treatment Group 2			
Inavolisib 12 mg	4 (2.1%)	0 (0%)	4 (1.2%)
Inavolisib 3 mg + palbociclib + letrozole	3 (1.6%)	0 (0%)	3 (0.9%)
Inavolisib 6 mg	7 (3.7%)	0 (0%)	7 (2.1%)
Inavolisib 6 mg + letrozole	7 (3.7%)	0 (0%)	7 (2.1%)
Inavolisib 6 mg + palbociclib + letrozole	3 (1.6%)	0 (0%)	3 (0.9%)
Inavolisib 9 mg	9 (4.8%)	0 (0%)	9 (2.7%)
Inavolisib 9 mg + fulvestrant	59 (31.6%)	0 (0%)	59 (17.6%)

Source: Adapted from Table 3 on page 28-29 of Applicant's population PK report

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Table 47: Summary of Selected Baseline Continuous Covariates

Covariate	GO39374 (N=187)	WO41554 (N=149)	Overall (N=336)
Age (yrs)			
Mean (SD)	58.9 (10.6)	53.6 (11.0)	56.6 (11.1)
Median [Min, Max]	59.0 [31.0, 85.0]	53.0 [27.0, 77.0]	57.0 [27.0, 85.0]
Body Weight (kg)			
Mean (SD)	70.3 (16.6)	65.7 (15.7)	68.3 (16.3)
Median [Min, Max]	67.0 [43.0, 159]	62.0 [39.0, 124]	65.0 [39.0, 159]
Missing	1 (0.5%)	0 (0%)	1 (0.3%)
Body Height (cm)			
Mean (SD)	162 (7.46)	161 (6.99)	162 (7.26)
Covariate	GO39374 (N=187)	WO41554 (N=149)	Overall (N=336)
Median [Min, Max]	161 [134, 192]	161 [139, 183]	161 [134, 192]
Missing	0 (0%)	1 (0.7%)	1 (0.3%)
Body Mass Index (kg/m²)			
Mean (SD)	26.8 (6.04)	25.3 (5.42)	26.1 (5.82)
Median [Min, Max]	25.8 [17.0, 50.8]	23.9 [16.8, 46.1]	25.3 [16.8, 50.8]
Missing	1 (0.5%)	1 (0.7%)	2 (0.6%)
Body Surface Area (m²)			
Mean (SD)	1.74 (0.192)	1.70 (0.197)	1.72 (0.195)
Median [Min, Max]	1.72 [1.24, 2.64]	1.65 [1.31, 2.29]	1.70 [1.24, 2.64]
Missing	1 (0.5%)	1 (0.7%)	2 (0.6%)
eGFR by MDRD Equation (mL/min)			
Mean (SD)	85.1 (20.5)	92.2 (23.2)	88.2 (22.0)
Median [Min, Max]	83.3 [41.8, 198]	90.2 [46.6, 218]	86.0 [41.8, 218]
Missing	1 (0.5%)	1 (0.7%)	2 (0.6%)
Creatinine (mg/dL)			
Mean (SD)	0.739 (0.137)	0.695 (0.151)	0.720 (0.145)
Median [Min, Max]	0.713 [0.390, 1.23]	0.680 [0.290, 1.21]	0.700 [0.290, 1.23]
Bilirubin (µmol/L)			
Mean (SD)	7.97 (3.70)	9.46 (4.45)	8.63 (4.11)
Median [Min, Max]	6.84 [1.71, 25.7]	8.55 [1.17, 26.9]	7.87 [1.17, 26.9]
Missing	1 (0.5%)	0 (0%)	1 (0.3%)
Albumin (g/L)			
Mean (SD)	41.2 (3.24)	41.9 (3.99)	41.5 (3.60)
Median [Min, Max]	41.0 [30.0, 49.0]	42.0 [27.0, 55.9]	42.0 [27.0, 55.9]
Alkaline Phosphatase (U/L)			
Mean (SD)	110 (77.3)	126 (101)	117 (89.0)
Median [Min, Max]	85.0 [34.0, 498]	93.0 [24.0, 594]	87.0 [24.0, 594]
Alanine Aminotransferase (U/L)			
Mean (SD)	28.1 (19.2)	29.8 (31.1)	28.9 (25.1)
Median [Min, Max]	23.0 [7.00, 149]	19.7 [5.00, 248]	22.0 [5.00, 248]
Aspartate Aminotransferase (U/L)			
Mean (SD)	35.4 (20.7)	36.1 (32.0)	35.7 (26.3)
Median [Min, Max]	29.0 [11.0, 157]	27.0 [13.0, 239]	29.0 [11.0, 239]
Creatinine Clearance (mL/min)			
Mean (SD)	93.6 (27.9)	100 (30.6)	96.4 (29.2)
Median [Min, Max]	89.9 [41.4, 202]	95.8 [49.7, 211]	92.2 [41.4, 211]

Source: Adapted from Table 3 on page 28-29 of Applicant's population PK report

Population PK Model: The final population PK model of inavolisib was a three-compartment model with first-order absorption, linear elimination, and a mixed proportional and additive error model. Effects of eGFR on CL, body weight and race on Vc and formulation on Ka were included. The parameter estimates for the final population PK model are presented in Table 48.

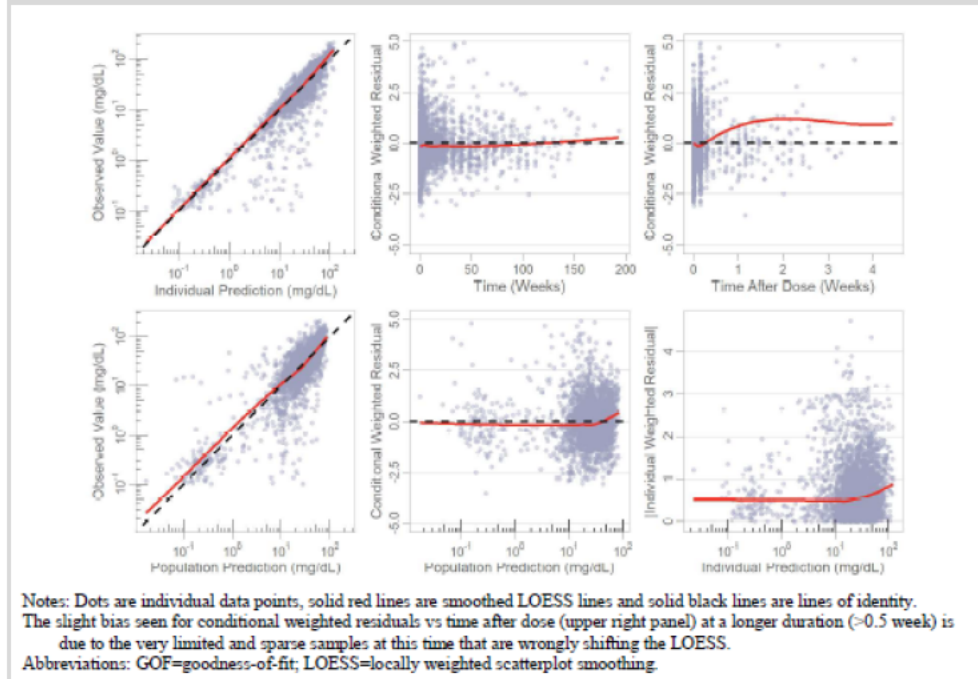
Table 48: Final PK model Parameter Estimates for Inavolisib

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.				

Source: Table 6 on page 40 of Applicant’s population PK report

Model Evaluation: The goodness-of-fit (GOF) plots for the final population PK model are presented in Figure 8. The prediction-corrected VPC plots by study that demonstrate the observed and model-predicted concentrations of inavolisib are shown in Figure 9. Overall, individual observed concentrations of inavolisib were adequately fitted.

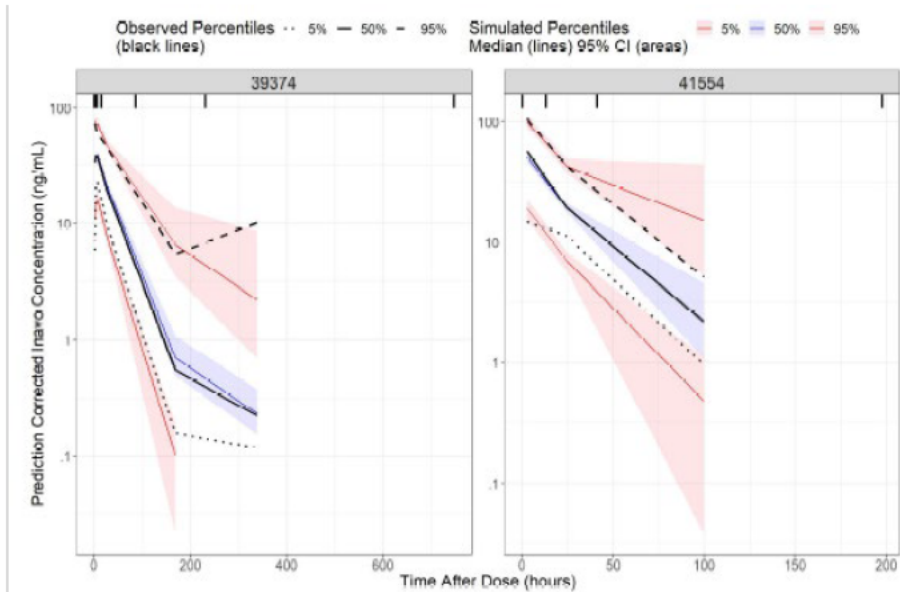
Figure 8: GOF Plots for the Final Model (Semi-Log Scale)



Source: Figure 8 on page 42 of Applicant's population PK report

Figure 9: Prediction-Corrected VPC by Study for Inavolisib (Semi-Log Scale)

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Notes: black dash (small and large dashes) and solid lines represent observed 5th, 95th and 50th percentiles, respectively. Solid colored 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.

Abbreviations: CI=confidence interval; VPC=visual predictive check.

Source: Figure 9 on page 43 of Applicant's population PK report

Exposure Estimates from the Final Population PK Model: The individual PK parameters from the final model were used to simulate the exposure parameters after single and multiple doses of 9 mg PO QD. Summary statistics of exposure estimates of inavolisib by formulation status (Phase 1 vs Phase 3; Phase 1 resupply vs Phase 3) are presented in Table 49 .

Table 49: Summary of PK Exposure Parameters for Inavolisib after Single and Multiple Doses of 9 mg PO QD by Formulation (Phase 1, Phase 1 resupply, and Phase 3)

	Mean (CV%, SD) Median [Minimum, Maximum] Geometric Mean (geomCV%)		
	Ph3 Formulation (N=149)	Ph1 Formulation (N=152)	Ph1 Resupply (N=35)
C_{max} at Single Dose (ng/mL)	49.6 (32.7%,16.2)	30.0 (30.5%,9.15)	31.3 (19.6%,6.12)
	46.2 [18.3,100] 47.2 (32.3%)	29.1 [11.4,56.4] 28.6 (32.2%)	29.4 [21.2,50.1] 30.7 (19.1%)
AUC_{0-τ} at Single Dose (ng.h/mL)	660 (23.4%,155)	527 (26.2%,138)	561 (18.9%,106)
	631 [364,1360] 644 (22.1%)	515 [193,1090] 509 (27.5%)	551 [370,834] 552 (18.7%)
C_{min} (24 hours) at Single Dose (ng/mL)	13.8 (27.5%,3.81)	15.9 (32.9%,5.21)	16.1 (26.9%,4.32)
	12.9 [7.42,31.0] 13.4 (25.2%)	15.0 [5.02,39.4] 15.1 (31.8%)	15.4 [9.42,30.3] 15.6 (25.7%)
C_{max} at Steady-State (ng/mL)	71.0 (28.1%,19.9)	56.3 (31.3%,17.7)	52.8 (22.9%,12.1)
	65.4 [34.5,146] 68.5 (26.9%)	53.8 [20.4,123] 53.8 (31.0%)	50.5 [30.5,79.6] 51.5 (23.6%)
AUC_{0-τ} at Steady-State (ng.h/mL)	1040 (27.1%,283)	1090 (33.9%,370)	1000 (25.9%,259)
	979 [598,2180] 1010 (24.9%)	1020 [405,2850] 1040 (32.2%)	957 [546,1590] 968 (26.8%)
C_{min} at Steady-State (ng/mL)	24.0 (37.9%,9.11)	32.7 (43.7%,14.3)	27.7 (34.1%,9.43)
	22.1 [10.6,65.6] 22.6 (35.2%)	29.6 [11.5,110] 30.2 (41.1%)	27.2 [13.0,54.7] 26.2 (35.4%)
Elimination Half-Life (h) at Day 1	15.5 (21.2%,3.28)	19.1 (50.3%,9.60)	15.8 (23.1%,3.65)
	15.2 [7.92,24.4] 15.2 (21.6%)	16.1 [6.94,75.4] 17.6 (NA%)	15.6 [12.2,31.8] 15.5 (20.0%)
Accumulation Index based on AUC_{0-τ}	0 (0%)	2 (1.3%)	0 (0%)
	1.59 (14.5%,0.229) 1.55 [1.21,2.15]	2.11 (29.5%,0.623) 1.95 [1.37,5.11]	1.77 (13.8%,0.244) 1.72 [1.44,2.35]

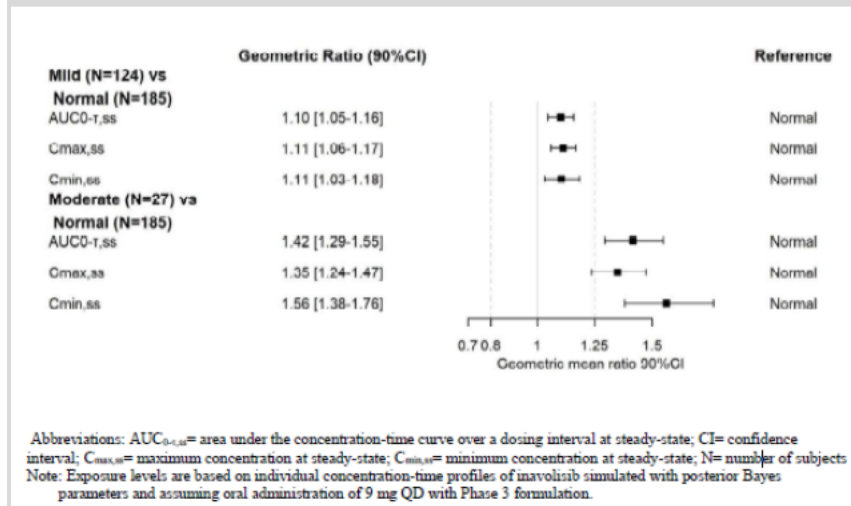
Abbreviations: AUC_{0-τ} = area under the concentration-time curve over a dosing interval; C_{max}=maximum concentration; C_{min}=minimum concentration; CV= coefficient of variation; N=number of subjects; ; PO= oral; QD= once daily; SD=standard deviation.

Note: Exposure levels are based on individual concentration-time profiles of inavolisib simulated with individual PK parameters assuming oral administration of 9 mg QD, using the reference patient (patient with median body weight (65 kg), eGFR (86 mL/min) and being non-Asian race)

Source: Table 8 on page 45-46 of Applicant's population PK report

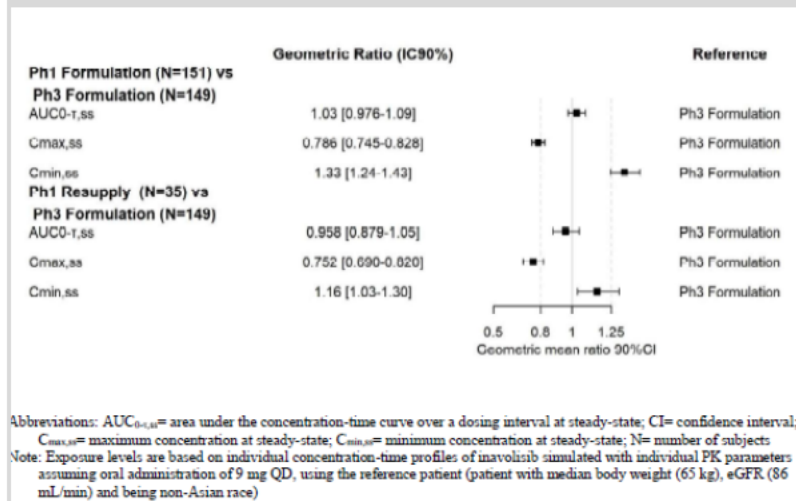
Effect of Covariates: Effects of significant covariates on inavolisib exposure are presented as forest plots. The effects of renal impairment and formulation are demonstrated in Figure 10 and Figure 11, respectively.

Figure 10: Forest Plots- PK Exposure Parameters for Inavolisib after Multiple Doses of 9 mg PO QD Stratified by Renal Impairment



Source: Figure 12 on page 49 of Applicant’s population PK report

Figure 11: Forest Plots-PK Exposure Parameters for Inavolisib after Multiple Doses of 9 mg PO QD Stratified by Formulation Status



Source: Figure 15 on page 51 of Applicant’s population PK report

Reviewer’s comments: The population PK modeling analyses for inavolisib are deemed acceptable. The reviewer was able to repeat and verify the Applicant’s analyses with no significant discrepancies identified. Overall, the final population PK models appeared adequate for characterizing the PK profile of inavolisib both as a single agent and in combination with

palbociclib and fulvestrant in patients with PIK3CA-mutated, HR-positive, HER2- negative locally advanced or metastatic breast cancer, as indicated in the applicant's goodness-of-fit plots and visual predictive check (VPC) plots. The results of the population PK analyses were used to support the proposed labeling statements regarding PK parameters of inavolisib and the effects of intrinsic and extrinsic factors.

However, there is insufficient information to assess the effect of moderate to severe hepatic impairment on inavolisib PK as no patients with moderate or severe hepatic impairment were included in the population PK analyses. Similarly, the information to assess the effect of severe renal impairment (n=0) on inavolisib PK is absent. The covariate analyses suggested a significant increase (43%) in AUC is observed in 27 patients with moderate renal impairment. Refer to Section 6.1.2.2 for results of the moderate renal impairment group in the ongoing renal impairment study. Given the positive ER for safety, intolerable toxicity of 12 mg PO QD as monotherapy, and high rates of AEs observed in clinical studies at the proposed dosage, dedicated studies to accurately assess the impact of severe renal impairment and moderate to severe hepatic impairment on inavolisib PK are warranted.

19.4.3. Exposure-Response Analysis

19.4.3.1. Executive Summary

The FDA's Assessment: The Applicant submitted one exposure-response (E-R) analysis report entitled "Exposure-Response Analyses of Inavolisib in Patients with PIK3CA-Mutant Solid Tumors and in Patients with PIK3CA-Mutant, HR positive, HER2-Negative Locally Advanced or Metastatic Breast Cancer".

The E-R analyses were conducted separately for the Phase 1 study GO39374 and the Phase 3 study WO41554. The E-R analyses were conducted to characterize the relationships between exposures of inavolisib and key efficacy and safety endpoints to support the proposed dosage used in the pivotal studies and in the label.

According to the E-R efficacy analysis for study GO39374, no exposure-response relationship was observed for ORR and BOR based on logistic regression models, and for PFS and DOR based on Cox models; lower and higher exposures of inavolisib achieved in Study GO39374 (dose range 3 to 12 mg with a large majority of patients receiving 9 mg) were associated with similar probabilities of response. In addition, multiple regimens (inavolisib monotherapy, doublet combinations, and triplet combinations) were included in this analysis.

According to the E-R efficacy analysis for study WO41554, no exposure-response relationship was observed for ORR, BOR, and CBR based on logistic regression models, and for PFS, DOR, and TFST based on Cox models; lower and higher exposures of inavolisib achieved at the clinical

dose (9 mg PO QD) were associated with similar effects. These data should be interpreted with caution given that only one inavolisib dose level was evaluated.

Based on exposure-safety analysis for study GO39374 using logistic regression analysis, positive exposure-response relationships were observed for the probability of grade ≥ 3 AE, grade ≥ 2 hyperglycemia, and inavolisib dose modification due to AE increased when AUC or C_{max} were used as exposure metrics.

Based on exposure-safety analysis for study WO41554 using logistic regression analysis, no exposure-response relationship was observed for most adverse events of interest (grade ≥ 3 AE, grade ≥ 2 neutropenia, grade ≥ 2 hyperglycemia, grade ≥ 2 thrombocytopenia, inavolisib dose modification due to AE, grade ≥ 2 diarrhea, and grade ≥ 2 stomatitis). However, the probability of grade ≥ 2 anemia was higher with increasing inavolisib C_{max} values. Similar to the E-R efficacy analysis, these results should be interpreted with caution given that only one inavolisib dose level was evaluated.

The Applicant's analyses were repeated and deemed acceptable.
The Applicant's E-R analyses are summarized in detail below.

19.4.3.2. E-R (efficacy) Assessment Summary

The Applicant's Position:

- Based on the exposure-efficacy analysis on a total of 149 patients with model-predicted exposure parameters in the inavolisib arm from Study WO41554, PFS, ORR, BOR, DOR, CBR, and time to TFST did not show an association with inavolisib exposure, after adjustment to baseline covariates (including baseline neutrophil count, AST, liver metastasis, and body surface area). Although similar OS was seen across C_{min} quartiles 1 - 3, numerically shorter OS was observed for quartile 4. Given that OS data could be confounded by the treatments received after study treatment discontinuation, and that OS data was not yet mature, TFST was investigated as another measure of long-term outcome. As outlined above, exposure-efficacy relationship was not significant for TFST.
- Based on the exposure-efficacy analysis on a total of 183 patients (Arm A to F) with model-predicted exposure parameters from the supportive study GO39374 (Dose range: 3, 6, 9, and 12 mg, with limited data from 3, 6, and 12 mg), ORR, BOR, DOR and PFS were not associated with inavolisib exposure, after adjustment to baseline covariates. However, these results should be interpreted with caution given that the data was pooled across multiple arms of Study GO39374 which include different combination partners across these arms.

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General Information		
Goal of ER analysis	In patients with <i>PIK3CA</i> -mutant, HR+, HER2- LA/mBC: Assess exposure-response relationship for ORR, BOR, PFS and DOR in Study GO39374, and for PFS, OS, DOR, TFST, CBR, ORR, and BOR for Study WO41554	
Study Included	Phase I Study GO39374; Phase III Study WO41554 (INAVO120) The ER analysis was conducted for the two studies separately. To enable pooling across arms for the ER analysis of GO39374, the combination status, i.e., Single, Doublet, and Triplet, were tested as covariate in the analyses.	
Population Included	Patients with <i>PIK3CA</i> -mutant, HR+, HER2- LA/mBC	
Endpoint	<u>Phase III Study WO41554:</u> Primary: PFS Secondary: OS, TFST, ORR, BOR, DOR, CBR <u>Phase I Study GO39374:</u> ORR, BOR, PFS and DOR	
No. of Patients (total, and with individual PK)	183 patients for Study GO39374 and 149 for Study WO41554 (with post-hoc PK parameters)	
Population Characteristics (Table 2, 3, 17, 18)	General	<u>Phase III Study WO41554 (n=149):</u> Age median (range): 53.0 [27.0, 77.0]; 13.4% ≥65 years and 2.68% ≥75 years Weight median (range): 62.0 [39.0, 124] 144 (96.6%) female 57 (38.3%) Asian <u>Phase I Study GO39374 (n=183)</u> Age median (range): 59.0 [31.0, 85.0]; 28.4% ≥ 65 years and 4.92% ≥75 years Weight median (range): 67.0 [43.0, 159] 182 (99.5%) female 5 (2.7%) Asian; 3 (1.6%) Black or African American; 1 (0.5%) Multiple; 134 (73.2%) White, 40 (21.9%) Unknown
	Organ impairment	<u>Phase III Study WO41554 (n=149):</u> Hepatic impairment (NCI): normal 108 (72.5%); Mild 41 (27.5%) Renal impairment (CrCL): normal 92 (61.7%); Mild 48 (32.2%); Moderate 9 (6.0%) <u>Phase I Study GO39374 (n=183):</u> Hepatic impairment (NCI): normal 113 (61.7%); Mild group1 65 (35.5%); Mild group2 4 (2.2%) Renal impairment (CrCL): normal 92 (50.3%); Mild 73 (39.9%); Moderate 17 (9.3%)
	Pediatrics (if any)	No pediatric patients were included
Dose(s) Included	Phase III Study WO41554: 9 mg Phase I Study GO39374: 3, 6, 9, 12mg	
Exposure Metrics Explored (range)	The exposure metrics were derived based on the posthoc PK parameters and the nominal dose. <u>Phase III Study WO41554 (n=149):</u> AUC median (range): 979 [598, 2180] ng·h/mL C _{max} median (range): 65.4 [34.5, 146] ng/mL C _{min} median (range): 22.1 [10.6, 65.5] ng/mL <u>Phase I Study GO39374 (n=183):</u> AUC median (range): 984 [157, 2850] ng·h/mL C _{max} median (range): 57.7 [8.97, 128] ng/mL C _{min} median (range): 25.6 [3.70, 103] ng/mL	
Covariates Evaluated	Age, height, body weight, body mass index, body surface area, ethnicity, race, sex, geographic region, albumin, bilirubin, alkaline phosphatase, alanine transaminase, total protein, lymphocytes, neutrophils, platelets, lactate dehydrogenase, neutrophil lymphocyte ratio, hemoglobin (only for WO41554), serum creatinine, creatinine clearance, estimated glomerular filtration rate, hepatic impairment category, renal impairment category, ECOG, liver metastasis, tumor type, post-menopausal status, Actual treatment for concomitant medication; Combination status (Single, Doublet, Triplet; only for Study GO39374), tumor burden, line of therapy, locally advanced metastatic (all Yes for WO41554), visceral	

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	metastatic, years since locally advanced metastatic (Missing for WO41554), number metastatic sites, endocrine resistance [primary/secondary], PIK3CA mutation (all Yes for WO41554), prior systemic therapy in the metastatic setting (all No for WO41554), prior FULV/SERD/PI3K/AKT/mTOR inhibitors (all No for WO41554), measurable disease per RECIST (all Yes for WO41554)	
Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	The relationships between efficacy and inavolisib exposure were explored using Kaplan-Meier curves and Cox proportional hazard models for the survival endpoints (PFS, OS, DOR, TFST), and logistic regressions for the binary endpoints (ORR, BOR, CBR). The Firth correction was implemented in the logistic regression when required to reduce the bias of maximum /likelihood estimates where small samples with unbalanced risk factors lead to separation problem	Acceptable
Model Parameter Estimates	<u>Phase III Study WO41554:</u> No exposure-response relationship was observed for ORR, BOR, and CBR based on logistic regression models and for PFS, DOR, and TFST based on Cox models after adjustment to baseline covariates. For OS, the upper quartile of C _{min} (Q4) showed numerically shorter survival than other quartiles despite adjustment to baseline covariates while similar OS was seen across the three other quartiles. See Tables 21, 23, 25, 26~29 in Report 1129439. <u>Phase I Study GO39374:</u> No exposure-response relationship was observed for ORR, BOR based on logistic regression models and for PFS and DOR based on Cox models. (see Tables 6, 8, 9, 10 in Report 1129439).	Acceptable
Model Evaluation	Graphical exploration and model evaluation by change of objective function and statistical significance of model parameters (stepwise forward inclusion and backward elimination). First, a stepwise forward addition test was performed on relevant covariates, keeping in the model for the statistically significant covariate that reduce AIC the most, one-by-one, until no further covariate could be included. The statistical significance of model parameters was tested in the logistic regression models with a p-value of 0.05. Each exposure metric (AUC, C _{min} , C _{max}) was tested one by one as the last step of forward addition, and the exposure parameter that reduced the AIC the most (if any), while being statistically significant, was added to the model. The model at this stage was referred to as full model. Next, the full model was inspected where the categorized continuous covariates or the categorical covariates with p-value above 0.1 were lumped with the default category, and the resulting model was re-estimated. Categories with skip ordinal won't be combined (i.e., not combining quartile 1 with quartile 3, or normal renal function with moderate impairment). The model at this stage was referred to as simplified full model. Finally, a stepwise backward elimination was performed by removing covariates/exposure parameter from the simplified full model one at a time, if their deletion leads to insignificant model deterioration. The most insignificant covariate was removed first, and the procedure was repeated until no further insignificant covariate relationship was detected. Significance level of 0.01 was used in the backward elimination. The change of OFV has accounted for the change of degree of freedom, i.e., 6.635, 9.21, and 11.34 points for one, two, three degrees of freedoms, respectively. The model obtained was called the final model.	Acceptable
Covariates and Clinical Relevance	<u>Phase III Study WO41554:</u> Neutrophil count at baseline as quartile was identified as covariates consistently in the final model of CBR, PFS, OS, and TFST, with Q4 being statistically significant (worse response); Other covariates, such as Aspartate Aminotransferase, liver metastasis and BSA were identified in certain efficacy endpoints. Exposure metrics (C _{min}) was only identified as covariate for OS, with Q4 showing worse OS. Given that OS data could be impacted by treatments received after study treatment discontinuation, and that OS data was not yet mature, TFST was investigated as another measure of longer-term outcome, there was no exposure-response relationship for this endpoint. The analyses outcomes indicated that patients benefited similarly across the range of exposures following 9 mg QD. <u>Phase I Study GO39374:</u>	Acceptable

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	For the dose range tested (3, 6, 9, and 12 mg, with limited data from 3, 6, and 12 mg), ORR, BOR, DOR and PFS were not associated with inavolisib exposure, after adjustment to baseline covariates. Measurable disease was identified as covariate in the final model of ORR and BOR (the presence of measurable disease was associated with a higher probability of response); Combination status (Triplet), Liver Metastasis and Baseline Tumor Burden were identified as covariates in the final model of PFS (liver metastasis and higher baseline tumor burden led to shorter PFS, and triplet combination was associated with longer PFS). The analyses outcome indicated better efficacy in Triplet combination (with a CDK4/6 inhibitor and endocrine agent), and worse efficacy for higher tumor burden and Liver Metastasis.	
Simulation for Specific Population	Not applicable	N/A
Visualization of E-R relationships	The relationship between inavolisib exposure metric and the survival endpoints and binary endpoints were graphically explored using Kaplan-Meier plots and logistic plots.	Acceptable
Overall Clinical Relevance for ER	Study G039374 indicated that triplet combination was associated with longer PFS, compared to single agent or doublet combination (with an endocrine agent); Study W041554 indicated that patients benefited similarly across the range of exposures following 9 mg QD.	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	(b) (4)	Labeling languages were modified based on FDA guidance

General Information		
Goal of ER analysis APPEARS THIS WAY ON ORIGINAL	In patients with <i>PIK3CA</i> -mutant, HR+, HER2- LA/mBC: - Assess exposure-response for hyperglycemia, any AE of Grade 3 and above, inavolisib dose modification due to AE for GO39374 and WO41554 studies, and stomatitis, diarrhea, neutropenia, thrombocytopenia, and anemia for Study WO41554. - Assess potential impact of exposure metrics on inavolisib dose intensity on for Study WO41554	
Study Included	Phase I Study GO39374; Phase III Study WO41554 (INAVO120) The exposure-response analysis was conducted for the two studies separately. To enable pooling across arms for the ER analysis of GO39374, the combination status, i.e., Single, Doublet, and Triplet, were tested as covariate in the analyses.	
Population Included	Patients with <i>PIK3CA</i> -mutant, HR+, HER2- LA/mBC	
Endpoint	<u>Phase III Study WO41554:</u> Grade ≥ 2 hyperglycemia, any AE of Grade 3 and above, inavolisib dose modification due to AE, Grade ≥ 2 stomatitis, diarrhea, neutropenia, thrombocytopenia, and anemia <u>Phase I Study GO39374:</u> Grade ≥ 2 hyperglycemia, any AE of Grade 3 and above, inavolisib dose modification due to AE	
No. of Patients (total, and with individual PK)	165 patients for Study GO39374 and 149 for Study WO41554 (with post-hoc PK parameters). Arm F in Study GO39374 was excluded from the safety analysis because anti-hyperglycemic medication was given to all patients in Arm F from Day 1.	
Population Characteristics (Table 17, 18; Appendix 1 Section 9.1)	General	<u>Phase III Study WO41554 (n=149):</u> Age median (range): 53.0 [27.0, 77.0] Weight median (range): 62.0 [39.0, 124] 144 (96.6%) female 57 (38.3%) Asian <u>Phase I Study GO39374 (n=165):</u> Age median (range): 59.0 [31.0, 85.0] Weight median (range): 65.0 [43.0, 159] 164 (99.4%) female 4 (2.4%) Asian; 3 (1.8%) Black or African American; 1 (0.6%) Multiple; 119 (72.1%) White, 38 (23%) Unknown
	Organ impairment	<u>Phase III Study WO41554 (n=149):</u> Hepatic impairment (NCI): normal 108 (72.5%); Mild 41 (27.5%) Renal impairment (CrCL): normal 92 (61.7%); Mild 48 (32.2%); Moderate 9 (6.0%) <u>Phase I Study GO39374 (n=165):</u> Hepatic impairment (NCI): normal 102 (61.8%); Mild group1 58 (35.2%); Mild group2 4 (2.4%); Renal impairment (CrCL): normal 77 (46.7%); Mild 70 (42.4%); Moderate 17 (10.3%)
	Pediatrics (if any)	No pediatric patients were included
	Geriatrics (if any)	<u>Phase III Study WO41554 (n=149):</u> The median (range) age was 53 years (27.0 to 77.0 years), with 13.4% ≥65 years and 2.68% ≥75 years. 144 (96.6%) female <u>Phase I Study GO39374 (n=165):</u> The median (range) age was 59 years (31.0 to 85.0 years), with 26.67% ≥ 65 years and 4.85% ≥75 years. 164 (99.4%) female
Dose(s) Included	Phase III Study WO41554: 9 mg Phase I Study GO39374: 3, 6, 9, 12mg	
Exposure Metrics Explored (range)	The exposure metrics were derived based on the posthoc PK parameters and the nominal dose <u>Phase III Study WO41554(n=149):</u> AUC median (range): 979 [598, 2180] ng-h/mL C _{max} median (range): 65.4 [34.5, 146] ng/mL C _{min} median (range): 22.1 [10.6, 65.5] ng/mL <u>Phase I Study GO39374 (n=165):</u> AUC median (range): 977 [157, 2850] ng-h/mL C _{max} median (range): 57.0 [8.97, 128] ng/mL C _{min} median (range): 25.2 [3.70, 103] ng/mL	
Covariates Evaluated	Include all covariates for the efficacy analysis, plus "Risk factors for Hyperglycemia at Study Entry" and "Steroid PO 10 mg prednisone QD or the equivalent"	
Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	The relationships between safety and inavolisib exposure were explored using Kaplan-Meier curves and Cox proportional hazard models for the time to event endpoints (time to onset for the AE endpoints), and logistic regressions for the binary endpoints (the AE endpoints). The Firth correction was implemented in the logistic regression when required to reduce the bias of maximum /likelihood estimates where small samples with unbalanced risk factors lead to separation problem	

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Model Parameter Estimates	<u>Phase III Study WO41554:</u> No exposure-response relationships (both probability and time to onset) were observed for Grade ≥ 3 AE, Neutropenia Grade ≥ 2, Hyperglycemia Grade ≥ 2, Thrombocytopenia ≥ 2, inavolisib dose Modification due to AE, Diarrhea Grade ≥ 2, Stomatitis Grade ≥ 2; positive exposure-response relationship was observed for probability of Anemia Grade ≥ 2 (see Tables 31-48 in Report 1129439). <u>Phase I Study GO39374:</u> Positive exposure-response relationships (both probability and time to onset) were observed for Grade ≥ 3 AE, hyperglycemia Grade ≥ 2, and inavolisib dose modification due to AE (see Tables 12-16 in Report 1129439).	
Model Evaluation	Same as exposure-efficacy analysis	
Covariates and Clinical Relevance	<u>Phase III Study WO41554:</u> Various baseline covariates were identified for the safety endpoints, such as Hemoglobin for Grade ≥ 2 anemia (probability and time to onset), Neutrophil count for Grade ≥ 2 Neutropenia (probability and time to onset), and Platelet count for Grade ≥ 2 Thrombocytopenia (probability and time to onset). The identification of those covariates in the model were expected because as lab values they are highly relevant to the respective AE endpoints. Race was also identified as covariate for Grade ≥ 2 Hyperglycemia and Thrombocytopenia (probability and time to onset), and for Grade ≥ 2 anemia and Grade ≥ 3 AE (time to onset), with higher probability or early on-set of those AEs in Asian patients, however, the rate of inavo dose modification or dose reduction in Asian or Chinese patients are comparable to those in the global patients. <u>Phase I Study GO39374:</u> Patients with high risk factors for Hyperglycemia at Study Entry (i.e., BMI ≥ 30 or HbA1C $\geq 5.7\%$) are at a higher probability of experiencing an AE Grade ≥ 3 or hyperglycemia Grade ≥ 2; this was expected given hyperglycemia is an on-target AE for inavolisib. Patients receiving inavolisib in combination with palbociclib and fulvestrant are also at a higher probability of experiencing an AE Grade ≥ 3; this was expected given neutropenia is the most common AE for palbociclib.	
Simulation for Specific Population	Not applicable	
Visualization of E-R relationships	The relationship between inavolisib exposure metric and the AE endpoints (time to onset and probability) were graphically explored using Kaplan-Meier plots and logistic plots.	
Overall Clinical Relevance for ER	Although positive relationship between inavolisib exposure and safety endpoints (Grade ≥ 3 AE, hyperglycemia Grade ≥ 2 , and inavolisib dose modification) were revealed in Study GO39374, no positive relationship was found for WO41554 (except Anemia Grade ≥ 2). This can be explained by a wider exposure range in study GO39374 compared to Study WO41554, broader HbA1c and fasting blood glucose eligibility criteria in Study GO39374 compared to Study WO41554, and better AE management in WO41554.	
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	(b) (4)	

See Table 2 and 3 for Study GO39374 and Table 17 and 18 for Study WO41554 in Report 1129439 for Summary of Baseline Characteristics and Laboratory Values in the exposure-efficacy Datasets.

See Appendix 2, Section 10.1 in Report 1129439 for Covariate Distribution over Quartiles of AUC_{SS}, C_{maxSS} and C_{minSS} for All Subjects Included in the exposure-efficacy analysis of inavolisib for Study WO41554.

See Table 6, 8, 9, 10 for Study GO39374 and Table 21, 23, 25, 26-29 for Study WO41554 in Report 1129439 for Parameter Estimates from Final exposure-efficacy Models of Inavolisib.

See Figure 4, 5, 6, 10 and Appendix 1, Section 9.6, 9.10, 9.11, 9.13 in Report 1129439 for exposure-efficacy Curves of Inavolisib vs AUC_{SS}, C_{maxSS} or C_{minSS} for Study GO39374.

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See Figure 17-23 and Appendix 2, Section 10.6, 10.10, 10.14, 10.15, 10.17, 10.19, 10.21 in Report 1129439 for exposure-efficacy Curves of Inavolisib vs AUC_{ss}, C_{maxss} or C_{minss} for Study WO41554.

19.4.3.3. E-R (safety) Assessment Summary

The Applicant's Position: Exposure-safety analyses were performed based on a total of 165 patients with model-predicted exposure parameters from Study GO39374 (Arm F was not part of the safety analysis because anti-hyperglycemic medication was given to all patients in Arm F from Day 1).

Based on exposure-safety analysis of adverse events of interest using logistic regression models, the probability of AE Grade ≥ 3 , hyperglycemia Grade ≥ 2 , and inavolisib dose modification due to AE increased as a function of exposure parameter AUC or C_{max}. In addition, time to first instance of AE Grade ≥ 3 , hyperglycemia Grade ≥ 2 , and inavolisib dose modification due to AE was shorter in patients with higher inavolisib AUC.

Exposure-safety analyses were performed based on a total of 149 patients with model-predicted exposure parameters in the inavolisib arm from Study WO41554. No exposure-response relationship was observed for most adverse events of interest (grade ≥ 3 AE, neutropenia Grade ≥ 2 , hyperglycemia Grade ≥ 2 , thrombocytopenia Grade ≥ 2 , inavolisib dose modification due to AE, diarrhea Grade ≥ 2 , stomatitis Grade ≥ 2) based on logistic regression models; lower and higher exposures of inavolisib achieved at the clinical dose (9 mg PO QD) were associated with similar safety outcomes. The probability of anemia Grade ≥ 2 was higher with increasing inavolisib C_{max} values while there was no relationship between time to onset of anemia and inavolisib exposure.

General Information	
Goal of ER analysis	In patients with <i>PIK3CA</i> -mutant, HR+, HER2- LA/mBC: - Assess exposure-response for hyperglycemia, any AE of Grade 3 and above, inavolisib dose modification due to AE for GO39374 and WO41554 studies, and stomatitis, diarrhea, neutropenia, thrombocytopenia, and anemia for Study WO41554. - Assess potential impact of exposure metrics on inavolisib dose intensity on for Study WO41554
Study Included	Phase I Study GO39374; Phase III Study WO41554 (INAVO120) The exposure-response analysis was conducted for the two studies separately. To enable pooling across arms for the ER analysis of GO39374, the combination status, i.e., Single, Doublet, and Triplet, were tested as covariate in the analyses.
Population Included	Patients with <i>PIK3CA</i> -mutant, HR+, HER2- LA/mBC
Endpoint	<u>Phase III Study WO41554:</u> Grade ≥ 2 hyperglycemia, any AE of Grade 3 and above, inavolisib dose modification due to AE, Grade ≥ 2 stomatitis, diarrhea, neutropenia, thrombocytopenia, and anemia <u>Phase I Study GO39374:</u> Grade ≥ 2 hyperglycemia, any AE of Grade 3 and above, inavolisib dose modification due to AE
No. of Patients (total, and with individual PK)	165 patients for Study GO39374 and 149 for Study WO41554 (with post-hoc PK parameters). Arm F in Study GO39374 was excluded from the safety analysis because anti-hyperglycemic medication was given to all patients in Arm F from Day 1.
Population Characteristics (Table 17, 18;	General <u>Phase III Study WO41554 (n=149):</u> Age median (range): 53.0 [27.0, 77.0] Weight median (range): 62.0 [39.0, 124] 144 (96.6%) female

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Appendix 1 Section 9.1)		57 (38.3%) Asian <u>Phase I Study GO39374 (n=165):</u> Age median (range): 59.0 [31.0, 85.0] Weight median (range): 65.0 [43.0, 159] 164 (99.4%) female 4 (2.4%) Asian; 3 (1.8%) Black or African American; 1 (0.6%) Multiple; 119 (72.1%) White, 38 (23%) Unknown
	Organ impairment	<u>Phase III Study WO41554 (n=149):</u> Hepatic impairment (NCI): normal 108 (72.5%); Mild 41 (27.5%) Renal impairment (CrCL): normal 92 (61.7%); Mild 48 (32.2%); Moderate 9 (6.0%) <u>Phase I Study GO39374 (n=165):</u> Hepatic impairment (NCI): normal 102 (61.8%); Mild group1 58 (35.2%); Mild group2 4 (2.4%); Renal impairment (CrCL): normal 77 (46.7%); Mild 70 (42.4%); Moderate 17 (10.3%)
	Pediatrics (if any)	No pediatric patients were included
	Geriatrics (if any)	<u>Phase III Study WO41554 (n=149):</u> The median (range) age was 53 years (27.0 to 77.0 years), with 13.4% ≥65 years and 2.68% ≥75 years. 144 (96.6%) female <u>Phase I Study GO39374 (n=165):</u> The median (range) age was 59 years (31.0 to 85.0 years), with 26.67% ≥ 65 years and 4.85% ≥75 years. 164 (99.4%) female
Dose(s) Included	Phase III Study WO41554: 9 mg Phase I Study GO39374: 3, 6, 9, 12mg	
Exposure Metrics Explored (range)	The exposure metrics were derived based on the posthoc PK parameters and the nominal dose <u>Phase III Study WO41554(n=149):</u> AUC median (range): 979 [598, 2180] ng·h/mL C _{max} median (range): 65.4 [34.5, 146] ng/mL C _{min} median (range): 22.1 [10.6, 65.5] ng/mL <u>Phase I Study GO39374 (n=165):</u> AUC median (range): 977 [157, 2850] ng·h/mL C _{max} median (range): 57.0 [8.97, 128] ng/mL C _{min} median (range): 25.2 [3.70, 103] ng/mL	
Covariates Evaluated	Include all covariates for the efficacy analysis, plus “Risk factors for Hyperglycemia at Study Entry” and “Steroid PO 10 mg prednisone QD or the equivalent”	
Final Model Parameters	Summary	Acceptability [FDA’s comments]
Model Structure	The relationships between safety and inavolisib exposure were explored using Kaplan-Meier curves and Cox proportional hazard models for the time to event endpoints (time to onset for the AE endpoints), and logistic regressions for the binary endpoints (the AE endpoints). The Firth correction was implemented in the logistic regression when required to reduce the bias of maximum /likelihood estimates where small samples with unbalanced risk factors lead to separation problem	Acceptable
Model Parameter Estimates	<u>Phase III Study WO41554:</u> No exposure-response relationships (both probability and time to onset) were observed for Grade ≥3 AE, Neutropenia Grade ≥2, Hyperglycemia Grade ≥2, Thrombocytopenia ≥2, inavolisib dose Modification due to AE, Diarrhea Grade ≥2, Stomatitis Grade ≥2; positive exposure-response relationship was observed for probability of Anemia Grade ≥ 2 (see Tables 31-48 in Report 1129439). <u>Phase I Study GO39374:</u> Positive exposure-response relationships (both probability and time to onset) were observed for Grade ≥3 AE, hyperglycemia Grade ≥2, and inavolisib dose modification due to AE (see Tables 12-16 in Report 1129439).	Acceptable
Model Evaluation	Same as exposure-efficacy analysis	Acceptable
Covariates and Clinical Relevance	<u>Phase III Study WO41554:</u> Various baseline covariates were identified for the safety endpoints, such as Hemoglobin for Grade ≥2 anemia (probability and time to onset), Neutrophil count for Grade ≥2 Neutropenia (probability and time to	Acceptable

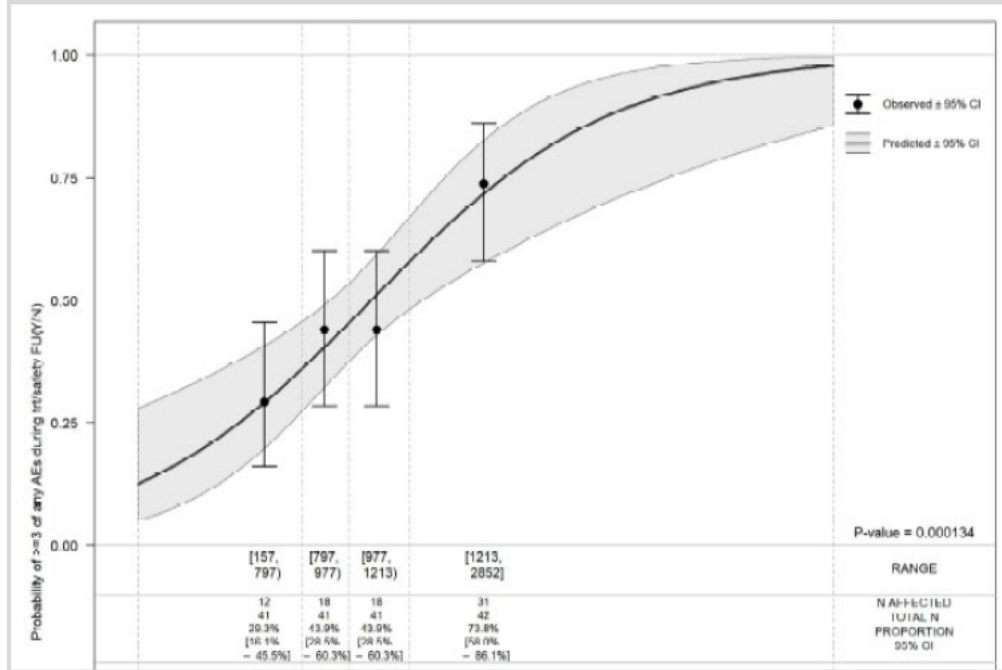
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	onset), and Platelet count for Grade ≥ 2 Thrombocytopenia (probability and time to onset). The identification of those covariates in the model were expected because as lab values they are highly relevant to the respective AE endpoints. Race was also identified as covariate for Grade ≥ 2 Hyperglycemia and Thrombocytopenia (probability and time to onset), and for Grade ≥ 2 anemia and Grade ≥ 3 AE (time to onset), with higher probability or early on-set of those AEs in Asian patients, however, the rate of inavo dose modification or dose reduction in Asian or Chinese patients are comparable to those in the global patients. <u>Phase I Study G039374:</u> Patients with high risk factors for Hyperglycemia at Study Entry (i.e., BMI ≥ 30 or HbA1C $\geq 5.7\%$) are at a higher probability of experiencing an AE Grade ≥ 3 or hyperglycemia Grade ≥ 2 ; this was expected given hyperglycemia is an on-target AE for inavolisib. Patients receiving inavolisib in combination with palbociclib and fulvestrant are also at a higher probability of experiencing an AE Grade ≥ 3 ; this was expected given neutropenia is the most common AE for palbociclib.	
Simulation for Specific Population	Not applicable	N/A
Visualization of E-R relationships	The relationship between inavolisib exposure metric and the AE endpoints (time to onset and probability) were graphically explored using Kaplan-Meier plots and logistic plots.	Acceptable
Overall Clinical Relevance for ER	Although positive relationship between inavolisib exposure and safety endpoints (Grade ≥ 3 AE, hyperglycemia Grade ≥ 2 , and inavolisib dose modification) were revealed in Study G039374, no positive relationship was found for WO41554 (except Anemia Grade ≥ 2). This can be explained by a wider exposure range in study G039374 compared to Study WO41554, broader HbA1c and fasting blood glucose eligibility criteria in Study G039374 compared to Study WO41554, and better AE management in WO41554.	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	(b) (4)	Acceptable with minor edits by the Agency

See Appendix 1, Section 9.1 for Study G039374 and Table 17 and 18 for Study WO41554 in Report 1129439 for Summary of Baseline Characteristics and Laboratory Values in the exposure-safety analysis Datasets.
See Appendix 2, Section 10.1 for Study WO41554 in Report 1129439 for Covariate Distribution over Quartiles of AUCss, Cmaxss and Cminss for All Subjects Included in the exposure-safety Analysis of Inavolisib.
See Table 12, 13, 14 and Appendix 1, Section 9.18, 9.22, 9.26 for Study G039374 and Table 31-48 for Study WO41554 in Report 1129439 for Parameter Estimates from Final exposure-safety Models of Inavolisib.
See Figure 11-16 and Appendix 1, Section 9.16, 9.17, 9.20, 9.21, 9.24, 9.25 in Report 1129439 for exposure-safety Curves of Inavolisib vs AUCss, Cmaxss or Cminss for Study G039374
See Figure 24, 25 and Appendix 2, Section 10.31-10.37, 10.39-10.45 in Report 1129439 for exposure-safety Curves of Inavolisib vs. AUCss, Cmaxss or Cminss for Study WO41554.

The FDA's Assessment: The Applicant's E-R (safety) analyses are acceptable. As indicated in figures below, positive relationships were identified between exposure parameter (AUC or C_{max}) and the probability of AE grade ≥ 3 , hyperglycemia grade ≥ 2 , inavolisib dose modification due to AE and anemia grade ≥ 2 in study G039374 or WO41554.

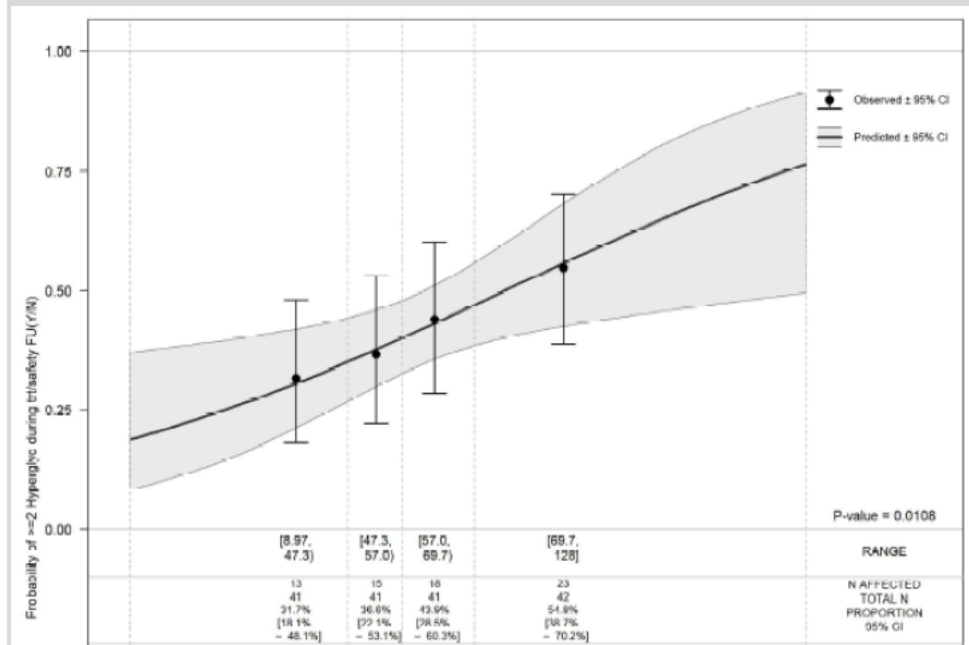
Figure 12: GO39374-Probability of AE Grade ≥ 3 by Quartiles of AUC



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

Source: Adapted from Figure 11 on page 51 of Applicant's Exposure-Response Analysis Report

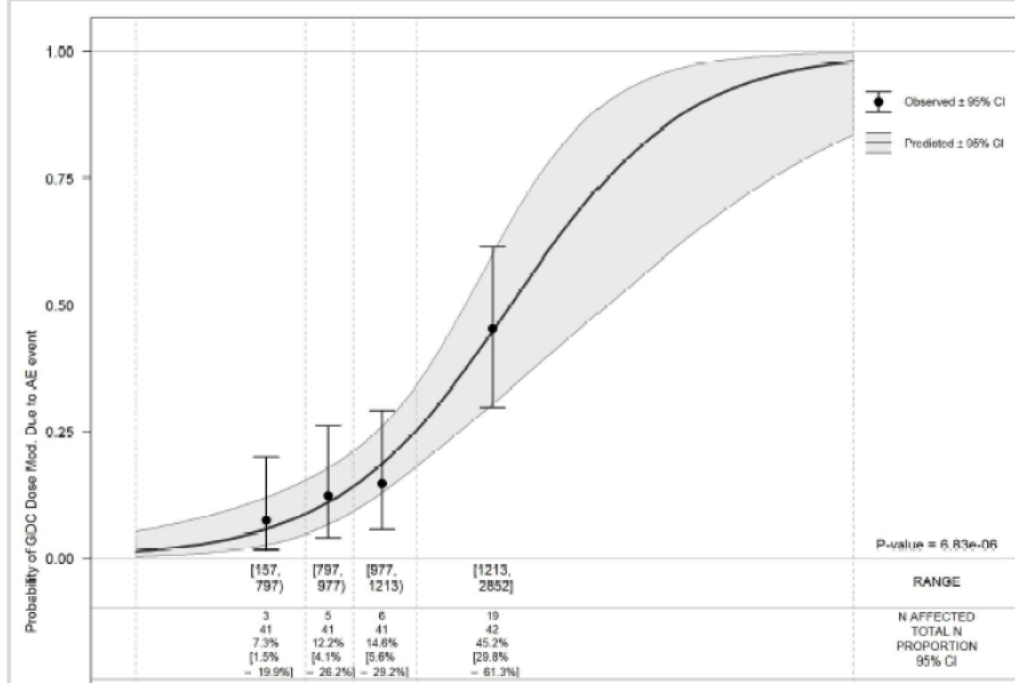
Figure 13: GO39374-Probability of Hyperglycemia Grade ≥ 2 by Quartiles of Cmax



AE= adverse event; CI= confidence interval; Cmax= maximum concentration; N= number of subjects

Source: Adapted from Figure 13 on page 51 of Applicant's Exposure-Response Analysis Report

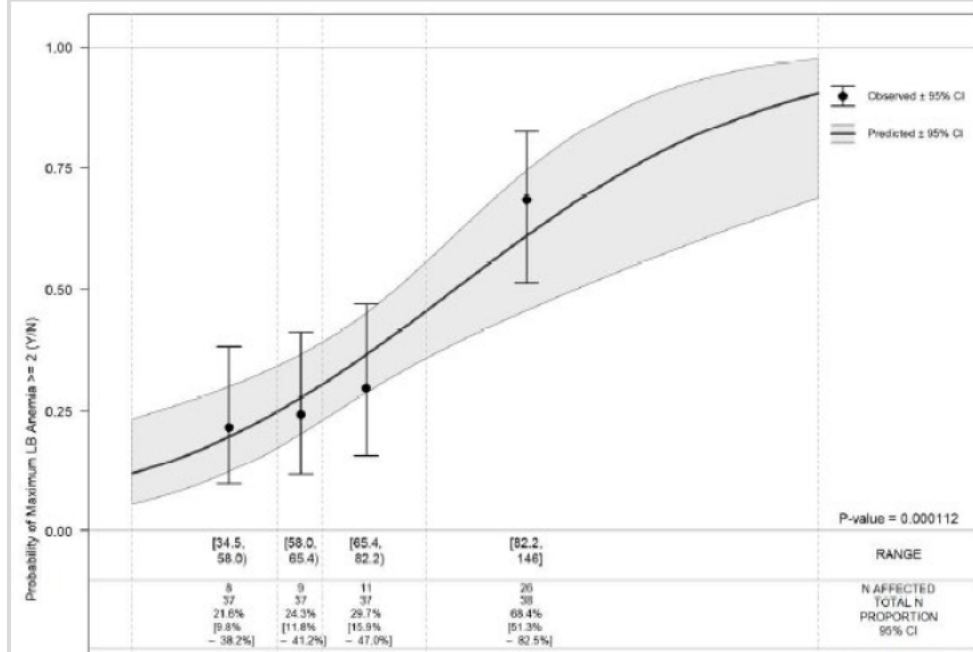
Figure 14: GO39374-Probability of a Inavolisib Dose Modification due to AE by Quartiles of AUC



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

Source: Adapted from Figure 15 on page 57 of Applicant's Exposure-Response Analysis Report

Figure 15: WO41554-Probability of Anemia Grade ≥ 2 by Quartiles of C_{max}



AE= adverse event; CI= confidence interval; C_{max}= maximum concentration; N= number of subjects.
 Source: Adapted from Figure 24 on page 84 of Applicant's Exposure-Response Analysis Report

19.4.3.4. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position: Exposure-efficacy analyses supported 9 mg QD inavolisib as an efficacious dose in the context of the positive topline efficacy results for treatment (Inavo+Palbo+Fulv) versus reference (Pbo+Palbo+Fulv) groups.

Inavolisib exposure was not significantly associated with ORR, BOR, DOR, CBR, PFS, or TFST based on Study WO41554, after adjustment to baseline covariates, indicating that patients benefited similarly across the range of observed exposures following 9 mg QD. For OS, exposures of inavolisib achieved at the 9 mg QD were associated with similar effect on OS with the exception of the upper quartile of C_{min} (Q4) which showed a lower probability of survival. This should be interpreted with caution; indeed, OS was not mature yet and could have been impacted by treatments after study treatment discontinuation.

In Study WO41554, higher inavolisib exposure was associated with a higher risk for Grade ≥ 2 anemia, but not with any of the other AE of interest (i.e., Grade ≥ 2 hyperglycemia, neutropenia, thrombocytopenia, diarrhea, stomatitis; any Grade ≥ 3 AE; inavolisib dose modification due to AE), after adjustment to baseline covariates.

The 9 mg QD dose of inavolisib demonstrated high median relative dose intensity of

inavolisib. Patients with exposure metrics in Q4 were associated with a lower dose intensity, most likely due to dose reduction/dose hold. However, the median value of dose intensity across exposure cohorts were all above or equal to 90%, indicating good tolerability across the exposure range for patients who were administered the 9 mg QD dose.

The FDA's Assessment: FDA agrees that inavolisib 9 mg QD is an effective dosage based on improved PFS for inavolisib + palbociclib + fulvestrant compared to placebo + palbociclib + fulvestrant in patients with HR+, HER2- locally advanced or metastatic breast cancer. However, FDA disagrees that 9 mg QD is an optimized dosage for the targeted indication. See details in section 6.3.2.2.

19.4.4. Physiologically Based Pharmacokinetic Modeling Review

19.4.4.1. Executive Summary

The FDA's Assessment: The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to evaluate the drug-drug interaction (DDI) potential of inavolisib as a precipitant of the CYP3A substrate midazolam.

The Division of Pharmacometrics has reviewed the PBPK report (1129287) and related model summary reports, response to FDA information request dated 15 July 2024 (seq0027), and the modeling supporting files, and concluded that PBPK analysis cannot rule out the induction potential of inavolisib on the sensitive CYP3A substrate midazolam. The magnitude of inavolisib induction on the exposure of substrates of CYP3A cannot be confidently predicted due to the uncertainties about the induction parameters and methodology.

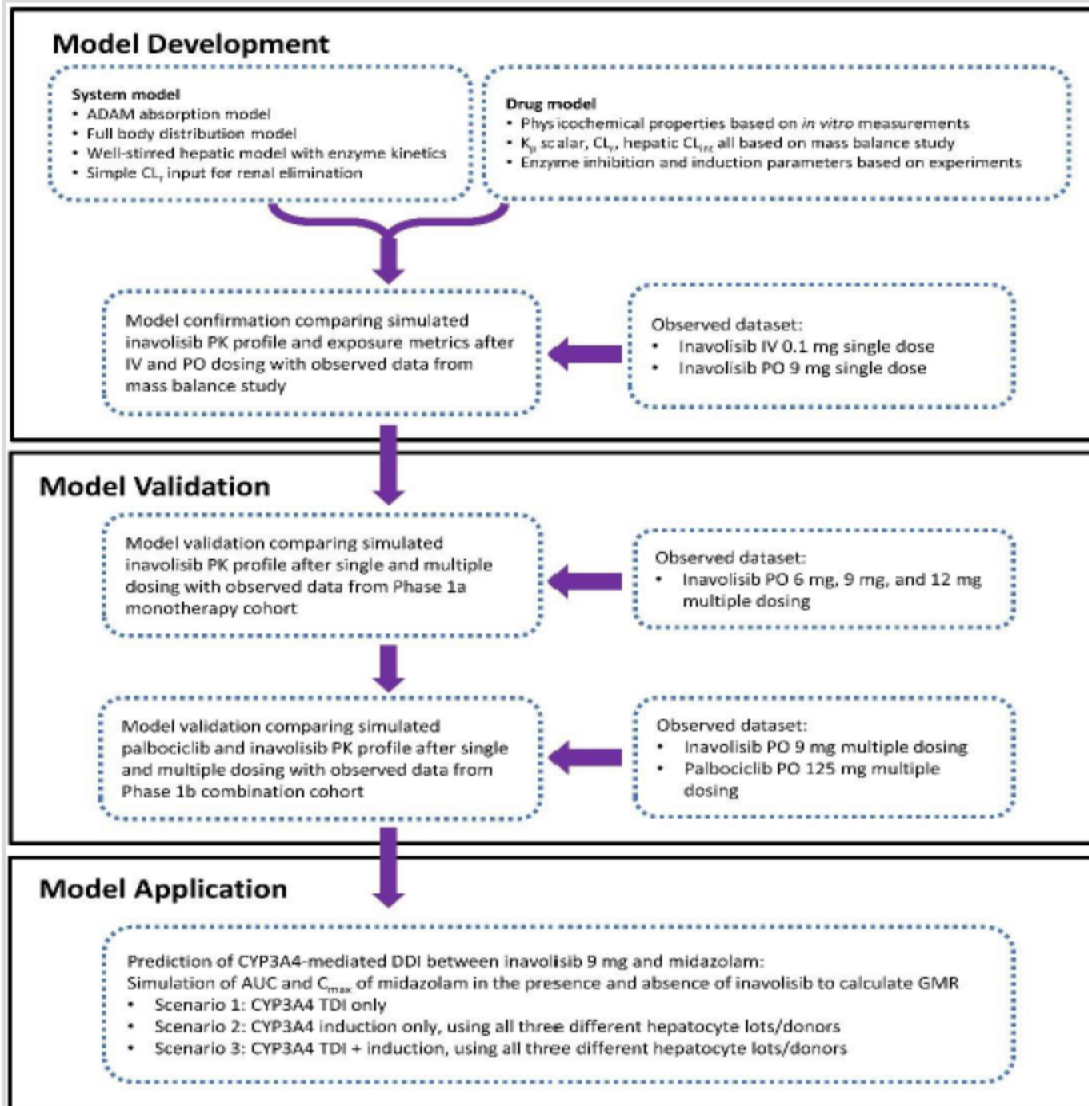
19.4.4.2. Methods

The FDA's Assessment: All simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Versions 22, Certara, Sheffield, UK) with the healthy subject population (sim-Healthy Volunteers) model. Age, sex, subject number, and dosing regimens were consistent with the actual trial design. Ten trials were simulated for each simulation scenario. Schemes of the PBPK modeling and simulation strategy are shown in **Figure 16**, which summarizes the studies used for inavolisib model development and verification, and model applications in predicting DDI of inavolisib as a precipitant of CYP3A4 induction or inhibition. The final model input parameters were summarized in **Table 50**. The inavolisib PBPK model consists of an Advanced Dissolution, Absorption and Metabolism (ADAM) model for describing drug absorption in each gut segment, a full PBPK model (method 3) for distribution, and an enzyme kinetics model and renal clearance for elimination. The Simcyp library models of midazolam, triazolam, itraconazole, rifampin and erythromycin were used without any modification, except for CYP3A4 TDI parameters for erythromycin (see **Results, section 2**).

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A published palbociclib PBPK model (PMID: 27402157) was used to verify the inavolisib interaction parameters. At the reviewer's request (FDA Information Request dated 15 July 2024), the Applicant evaluated the performance of this model using Simcyp version 22, and the results are shown in itraconazole and **Table 51** Predicted and observed palbociclib exposure in the presence and absence of itraconazole and rifampin. In general, the model could capture the effects of itraconazole and rifampin on palbociclib exposure, but it tended to underpredict the C_{max} and AUC_{inf} of palbociclib, especially in the itraconazole study. Thus, the reviewer modified the Applicant's model by increasing the fraction absorbed (fa) from 0.85 to 0.975 and reducing the additional human liver microsome clearance from 37.65 to 20 mL/min/mg protein. As a result, the fraction metabolized by CYP3A4 was changed from 53% to 62%. The performance of this modified model was evaluated and results are summarized in **Figure 17**, **Figure 18** and **Table 51**.

Figure 16: Modeling and simulation strategy



Source: Figure 1 in the PBPK report 129287

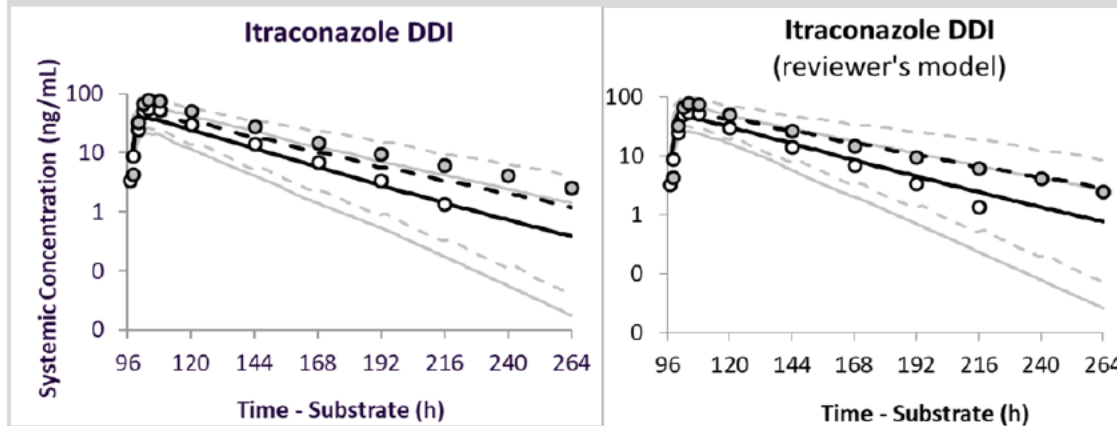
Table 50: Final input parameters in the inavolisib model

Section	Parameter	Unit	Value	References and/or justification
Physicochemical	MW	g/mol	407.4	Measured, data on file
	LogPo:w		0.96	Measured, data on file
	Acid/Base		Monoprotic Base	Measured, data on file
	pKa		3.12	Measured, data on file
	B/P		1.1	Measured, data on file
	f _{u,p}		0.63	Measured, data on file
Absorption	Model Setting		ADAM	
	P _{eff,max}	10 ⁻⁴ cm/s	0.439	Predicted See Appendix 1
	MDCK	10 ⁻⁶ cm/s	2.5	Measured, data on file
	Formulation module		Solid Formulation – Immediate Release – (b) (4)	
	Intrinsic solubility	mg/mL	(b) (4)	Measured, data on file
	Particle size	µm	(b) (4)	d50= (b) (4) µm, data on file
	Micelle partition coefficient		Neutral: 2; Ion: 6	Optimized See Appendix 2
Distribution	Model Setting		Full PBPK	
	V _{ss}		2.65 L/kg	GP42652 CSR
	K _p scalar		6.31	Optimized
Elimination	Model Setting		Enzyme Kinetics	
	CL _r	L/hr	5.54	GP42652 CSR
	CL _{int} – CYP3A4	µL/min/pmol of enzyme	0.00144	GP42652 CSR Retrograde calculation See Appendix 3 and 4
	Additional CL – liver HLM	µL/min/mg protein	2.77	GP42652 CSR Retrograde calculation See Appendix 3 and 4
Interaction	Model Setting		CYP3A4	
	K _{app}	µM	88	16-0806-GNE-In Vitro Report
	K _{inact}	1/hr	4.62	16-0806-GNE-In Vitro Report
	f _{u,mic}		0.984	Measured, data on file
	Ind _{max}		11.1	16-0131-GNE-In Vitro Report and Appendix 5
	IndC ₅₀	µM	5.46	GP42652 CSR 16-0131-GNE-In Vitro Report and Appendix 5
	f _{u,inc}		0.984	Set as equal to measured f _{u,mic}

B/P=ratio of drug concentration in blood over plasma; CL_{int}= intrinsic clearance; CL_r=renal clearance; f_{u,inc}=unbound fraction in the in vitro incubation; f_{u,mic}=unbound fraction in the microsomal incubation; f_{u,p}=fraction unbound in plasma; IndC₅₀ =compound concentration that causes half maximal induction; Ind_{max}=maximal fold induction over vehicle; K_{app}=drug concentration to reach half maximal inactivation rate for the time-dependent inhibition; K_{inact}=inactivation rate of the enzyme; K_p=tissue: plasma partitioning; LogPo:w= the log10 of the coefficient for solvent partitioning between 1-octanol and water; MDCK=Madin-Darby canine kidney; MW=molecular weight; P_{eff,max}=effective permeability of the compound in the human jejunum; pK_a=logarithmic acid dissociation constant; V_{ss}=volume of distribution at steady state.

Source: Table 1 in the PBPK report 129287

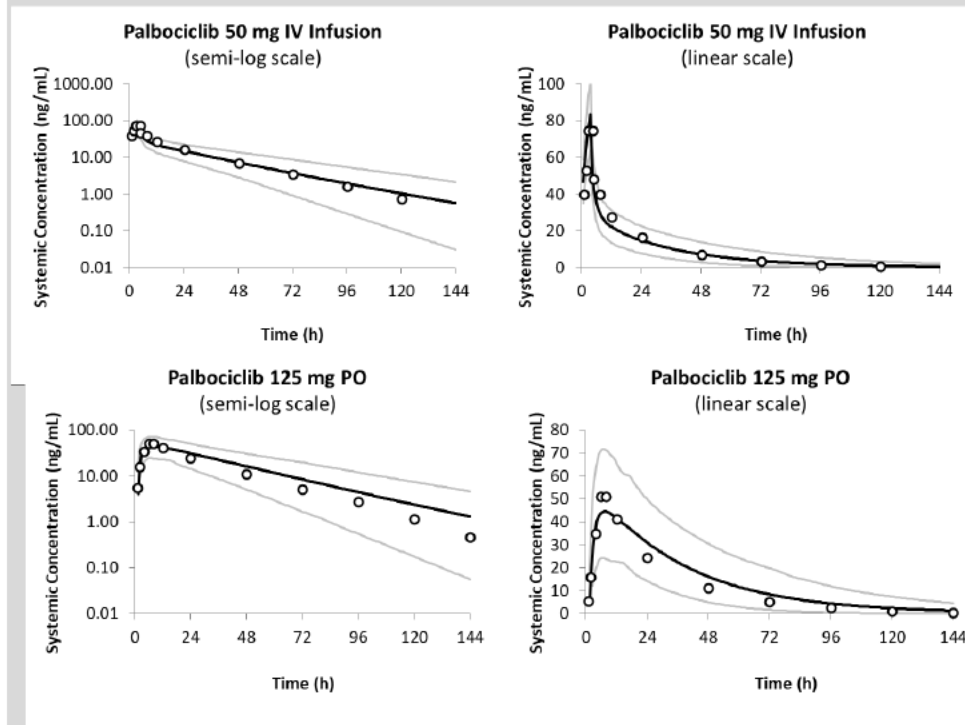
Figure 17: Simulated and observed plasma concentration-time profiles of palbociclib after a single 125-mg oral dose with or without coadministration of itraconazole



The white and gray circles represent observed palbociclib PK data following a single dose of 125 mg of palbociclib on Day 5 in the absence and presence of itraconazole (200 mg QD orally from Day 1 to Day 11), respectively. The solid lines and dashed lines represent the simulated palbociclib profiles in the absence and presence of itraconazole, respectively; black lines represent the simulation mean, gray lines represent the 5th and 95th percentiles of the simulations.

Source: Figure 2 in clinical-information-amendment.pdf (seq0027) and reviewer's analysis

Figure 18: Simulated and observed plasma concentration-time profiles of palbociclib following oral or intravenous administration of a single dose of palbociclib



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The white circles represent observed palbociclib PK data following a single oral dose of 125 mg of palbociclib or a single 50 mg intravenous infusion, respectively (digitalized from PMID: 27402157). The solid lines represent the simulated palbociclib profiles; black lines represent the simulation mean, gray lines represent the 5th and 95th percentiles of the simulations. Simulations were performed using the palbociclib model modified by the reviewer.
Source: reviewer's analysis

Table 51: Predicted and observed palbociclib exposure in the presence and absence of itraconazole and rifampin

Precipitants		C _{max} (ng/mL)	C _{max,inh} (ng/mL)	C _{max} Ratio	AUC _{inf} (ng/mL.h)	AUC _{inf,inh} (ng/mL.h)	AUC _{inf} ratio	Model
itraconazole	Observed	60	80	1.4	1864	3482	1.85	
	Predicted	37	49	1.33	1377	2015	1.46	Applicant
	Pred/obs	0.61	0.61	0.99	0.74	0.58	0.78	
	Predicted	44	59	1.36	1831	2895	1.58	Reviewer
	Pred/obs	0.74	0.74	1.01	0.98	0.83	0.85	
rifampin	Observed	55	16	0.30	1657	247	0.15	
	Predicted	36	12	0.34	1376	284	0.21	Applicant
	Pred/obs	0.66	0.79	1.13	0.83	1.15	1.38	
	Predicted	44	14	0.32	1830	332	0.18	reviewer
	Pred/obs	0.79	0.9	1.08	1.1	1.35	1.21	

Source: clinical-information-amendment.pdf (seq0027) and reviewer's analysis

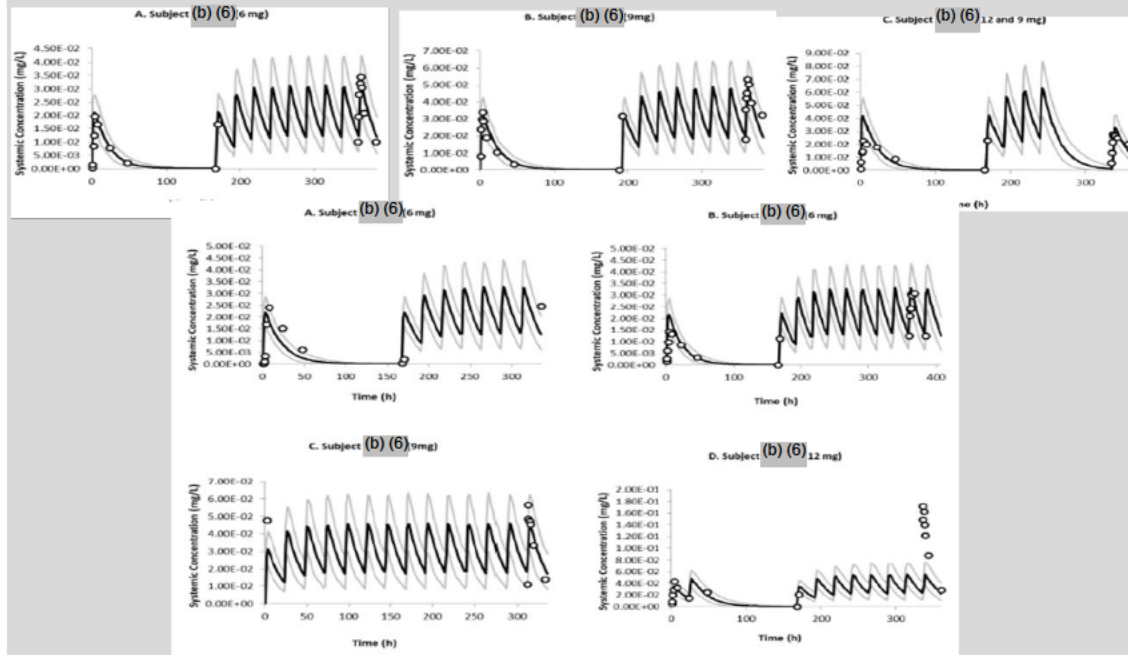
19.4.4.3. Results

The FDA's Assessment:

1. Can the PBPK model adequately describe the PK profiles of inavolisib?

Yes. The model could reasonably well describe the plasma concentration-time profiles of inavolisib following single and multiple oral doses of inavolisib in patients with cancer, and the model-estimated AUC and C_{max} were mostly within 0.8- and 1.25-fold of the observed values. Simulated and observed inavolisib PK profiles and parameters are summarized in **Figure 19** **Figure 20** and **Table 52**.

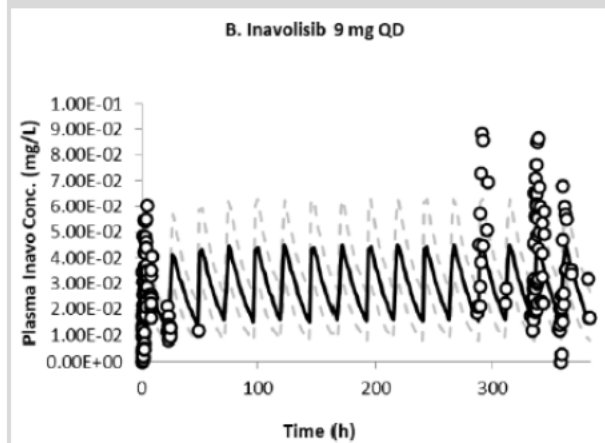
Figure 19: Predicted and observed plasma concentrations of inavolisib after single and multiple doses of inavolisib in breast cancer patients from the monotherapy Arm A (GO39374 CSR)



The simulation results after 6 mg, 9 mg, and 12 mg oral dosing of inavolisib are overlaid with individual observed data (n=7 subjects) shown in open circles. The median simulation profile is shown in the solid black line with 90% prediction intervals (5th and 95th percentile of the predictions) shown in grey lines. Only patients with normal renal function (CRCL $\geq$ 90 mL/min) were included for model validation. Subject (b) (6) initially took 12 mg and then reduced to 9 mg..

Source: Figure 4 and Appendix 7 in the PBPK report 129287

Figure 20: Predicted and observed plasma concentrations of inavolisib after multiple oral doses of inavolisib in breast cancer patients from the combination therapy Arm B (inavolisib/palbociclib/letrozole) (GO39374 CSR)



The simulation results of inavolisib at dose of 9 mg QD are overlaid with observed data shown in open circles. The median simulation profile is shown in the solid black line with 90% prediction intervals shown in dashed grey lines.

Source: Figure 5 in the PBPK report 129287

Table 52: Simulated and observed pharmacokinetic parameters of inavolisib after single- or multiple-dose administration in cancer patients in the FTIH study (D3610C00001)

	Pharmacokinetic parameters	Observed	Predicted	Pred/Obs
Single dose	AUC _{0-inf} /Dose (ng*hr/mL/mg)	80.7	76.8	0.95
	C _{max} /Dose (ng/mL/mg)	3.1	3.6	1.17
	T _{max} (hr)	4.3	3.1	0.73
Steady state	AUC _{0-24h} /Dose (ng*hr/mL/mg)	89.9	80.2	0.89
	C _{max} /Dose (ng/mL/mg)	6.1	5.1	0.84
	T _{max} (hr)	1.8	2.9	1.58

†Geometric mean values are calculated by the reviewer based on the data submitted in clinical-information-amendment.pdf (seq0027). Individual inavolisib exposure was normalized to the dose shown in Figure 4 before geometric means were calculated

Source: clinical-information-amendment.pdf (seq0027)

2. Can PBPK analyses be used to estimate the effects of inavolisib on the CYP3A substrate midazolam?

The potential induction effect of inavolisib on the sensitive CYP3A substrate midazolam following oral administration of inavolisib 9-mg QD cannot be ruled out for the reasons discussed below.

In vitro, inavolisib is a time-dependent inhibitor and inducer of CYP3A. Following oral administration of single and multiple doses of inavolisib, inavolisib AUC increased approximately proportional to the dose. The clinical DDI study of inavolisib with midazolam in patients with cancer has not been conducted. The available clinical PK data are insufficient to differentiate the CYP3A inhibition or induction of inavolisib, thus the CYP3A inhibition and induction parameters of inavolisib cannot be independently verified. In addition, the ability of PBPK modeling to accurately predict complex DDI has not been demonstrated. A study conducted by the Innovation and Quality (IQ) Induction Working Group showed that, for compounds that were both in vitro time-dependent inhibitors and inducers of CYP3A, prediction of the DDI trended toward an overprediction of the inactivation or a net effect of no interaction (PMID: 23995268). The inhibition or induction effects of this type of compound should be evaluated separately.

Inhibitory Effect of inavolisib on CYP3A

The time-dependent inhibition studies were conducted in human liver microsomes (HLM) using testosterone and midazolam as probe CYP3A substrates and in primary human hepatocytes using midazolam as a substrate (Study 16-0806). The Applicant used the k_{inact} and K_i values estimated from the HLM data in the inavolisib model for predicting its inhibitory effect on midazolam. In the HLM study, the k_{inact} and K_i values could only be estimated from the data generated using midazolam, while values could not be determined using testosterone because

the maximum inactivation rate was not achieved under the experimental condition. In this study, erythromycin was used as a positive control and its k_{inact} and K_I values were also generated using midazolam as a substrate. To examine the ability of the in vitro TDI parameters of inavolisib to predict DDI, the k_{inact} and K_I values in the SV-erythromycin model was replaced with the one generated by the Applicant, and simulations of clinical DDIs of erythromycin with midazolam or triazolam were performed. The effects of erythromycin were reasonably predicted (Table 53), which provides some confidence in predicting CYP3A inhibition using parameters generated under the same experimental condition. When simulating the DDI effect of inavolisib on midazolam using only the k_{inact} and K_I values from the HLM study, inavolisib was predicted to increase midazolam AUC and C_{max} by 17% and 10%, respectively. This result suggests that inavolisib is expected to have a minimal inhibitory effect on midazolam exposure. Therefore, the effect of inavolisib on midazolam exposure, if any, could be mainly driven by the induction effect of inavolisib.

Of note, in the IC50 shift assay, greater shift and lower IC50 were observed when testosterone was used as a CYP3A substrate, suggesting that testosterone may be more sensitive to inavolisib inhibition. If this is the case, the inhibitory effect of inavolisib on CYP3A may potentially be underestimated.

Table 53: Predicted and observed effects of erythromycin on single dose pharmacokinetics of CYP3A substrates

Dosing regimen		Observed Ratio		Predicted/observed		References
Erythromycin	CYP3A substrates	AUC _{inf}	C _{max}	AUC ratio	C _{max} ratio	PMID
500 mg tid 7d	MDZ 15 mg 2h after, D3	4.43	2.7	1.15	0.91	8453848
	MDZ 0.05 mpk IV, D6	2.17	-	1.09	-	
500 mg bid 2d	TZM 0.125 mg 1 h after, D2	3.65	1.77	0.5	0.77	9757151
	TZM 0.5 mg 2h after, D3	2.06	1.46	1.07	1.03	3771812

MDZ, midazolam; TZM, triazolam; IV, intravenous; D, Day; mpk, mg per kg.

Source: reviewer's analysis

Induction effect of inavolisib on CYP3A

Inavolisib increased mRNA and activity of CYP3A in hepatocytes from three donors (namely, FOS, 1198 and 1421, report 16-0131). The induction parameters of inavolisib were estimated based on the response of mRNA expression in these hepatocytes to inavolisib, and then calibrated to the induction parameters of rifampin generated from the same hepatocytes (Table 54). Using the calibrated parameters, inavolisib was predicted to have a weak induction effect on CYP3A based on the parameters generated from lot FOS (Table 54). However, there is uncertainty about using the calibrated parameters to estimate induction effect. Although the induction calibration method was published by Simcyp (PMID: 27026679), in the Simcyp PBPK models of CYP3A inducers except for phenobarbital, CYP3A induction parameters optimized with clinical DDI data were used instead of calibrated parameters published in the aforementioned paper, indicating that clinical DDI data were needed to adequately predict the induction effects of CYP3A inducers.

In the clinical trial GO39374, palbociclib was co-administered with 9-mg QD inavolisib along with letrozole. The steady state PK parameters of palbociclib in this study were mostly within 30% of the values published in the Palbociclib FDA Clinical Pharmacology Review (NDA 207103 Review, 2014). During inavolisib model verification, the Applicant simulated palbociclib PK in this study using the induction parameters generated from lot 1198 together with CYP3A TDI parameters generated in human liver microsomes. The ability of the simulations to capture the steady state palbociclib PK profile was used as the evidence that the CYP3A interaction parameters were adequately established (Figure 21). The reviewer performed additional simulations to examine the effects of inavolisib on palbociclib PK when inavolisib behaved as a CYP3A inducer. These simulations were performed using the Applicant’s palbociclib model or the reviewer-modified model (see Methods) and the induction parameters generated from lot FOS but without the CYP3A TDI parameters. The results showed that the steady-state palbociclib PK profiles and parameters were not significantly changed (Figure 21 and Table 55) even when inavolisib was predicted to reduce midazolam AUC close to 50% under these conditions (Table 56). Therefore, capturing the steady state palbociclib PK profiles is not sufficient evidence to verify the CYP3A interaction parameters.

Of note, although cytotoxicity was not observed in hepatocytes from lot 1198 and lot 1421, crystallization was observed from cell morphology at 100 µM inavolisib, which may be the potential reason for the reduced response observed at 100 µM compared to 10 µM, the second highest concentration (Report 16-0131). The maximum induction responses of the hepatocytes from lot 1198 and lot 1421 to inavolisib were not reached, which may affect the accuracy of induction parameter estimation.

Taken together, the effect of inavolisib on CYP3A substrates cannot be confidently predicted. The potential induction effect of inavolisib on CYP3A cannot be ruled out.

Table 54: Induction parameters of inavolisib and rifampin and predicted effects of inavolisib on midazolam exposure

Hepatocyte lots	Inavolisib		Rifampin		Inavolisib calibrated		Predicted GMR of MDZ	
	E_{max}	EC_{50} (µM)	E_{max}	EC_{50} (µM)	Ind_{max}	EC_{50} (µM)	AUC_{inf}	C_{max}
Lot 1198	44.39	6.66	65.77	0.39	11.12	5.46	0.9	0.93
Lot 1421	52.07	12.54	52.00	0.75	16.02	5.35	0.86	0.9
Lot FOS	33.55	3.75	73.28	1.81	7.87	0.66	0.63	0.72

MDZ, midazolam; GMR, geometric mean ratio; Ind_{max} , the maximum fold induction, and EC_{50} , the concentration that gives half maximal fold induction; $E_{max} = Ind_{max} - 1$

Source: Table 5 and Appendix 5 in the PBPK report 129287

Table 55: Comparison of observed steady state palbociclib pharmacokinetic parameters in the presence of inavolisib (9 mg QD) with those predicted using various induction parameters of inavolisib

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Pharmacokinetic parameters	Ind _{max}	EC ₅₀	AUC _{0-24h} (ng/mL.h)	T _{max} (h)	C _{max} (ng/mL)	C _{min} (ng/mL)	Palbociclib model
Observed	NA	NA	1650	8.00	97.0	48.3	
Predicted/ observed	7.87	0.66	0.92	0.68	0.85	0.84	Applicant's
	7.87	↓ 30%	0.85	0.67	0.79	0.77	
	7.87	↓ 40%	0.82	0.67	0.77	0.73	
	7.87	0.66	1.31	0.72	1.16	1.26	Reviewer's
	7.87	↓ 40%	1.13	0.7	1.03	1.06	

↓, reduced; Ind_{max}, the maximum fold induction, and EC₅₀, the concentration that gives half maximal fold induction; TDI, time-dependent inhibition parameters; NA, not applicable.

Source: Table 5 in G039374 interim CSR, sim-output-figure5.xlsx, and reviewer's analysis

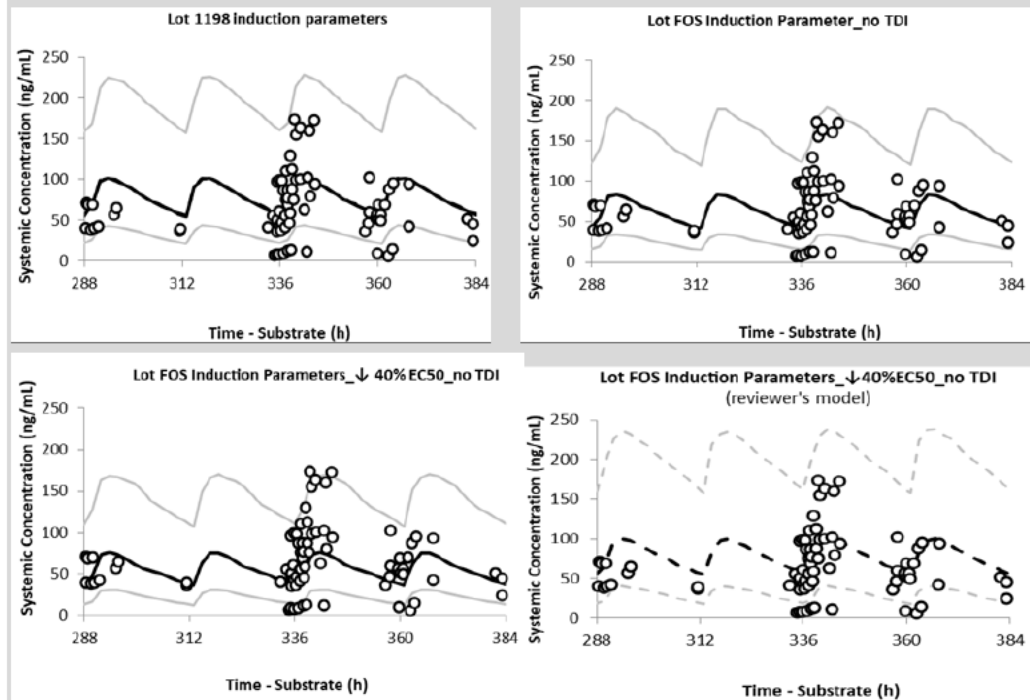
Table 56: Sensitivity analyses of inavolisib CYP3A induction parameters* on midazolam interaction

Hepatocytes	Inavolisib induction parameters		Geometric mean ratios of midazolam	
	Ind _{max}	EC ₅₀	AUC _{0-inf}	C _{max}
Lot FOS	7.87	0.66	0.63	0.72
	↔	↓ 30%	0.55	0.65
	↔	↓ 40%	0.51	0.61

↓, reduced; ↔, unchanged; Ind_{max}, the maximum fold induction, and EC₅₀, the concentration that gives half maximal fold induction. *All simulations were performed without the CYP3A time-dependent inhibition parameters of inavolisib

Source: reviewer's analysis

Figure 21: Predicted and observed plasma concentrations of palbociclib after multiple oral doses of inavolisib in breast cancer patients from the combination therapy Arm B (inavolisib/palbociclib/letrozole) (GO39374 CSR)



The simulation results of palbociclib at 125 mg QD as a CYP3A4 substrate are overlaid with observed data shown in open circles. The median simulation profile is shown in the solid black line with 90% prediction intervals shown in grey lines. Source: Figure 5 in the PBPK report 129287 and reviewer's analysis

19.4.4.4. Conclusion

The FDA's Assessment: PBPK analysis cannot rule out the induction potential of inavolisib on the sensitive CYP3A substrate midazolam. The magnitude of inavolisib induction on the exposure of substrates of CYP3A cannot be confidently predicted due to the uncertainties about the induction parameters and methodology.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

FDA conducted an analysis to review major adverse cardiac events (MACE) in both treatment arms based on the expanded 5-point MACE criteria (Table 57). The 5-point MACE criteria includes acute myocardial infarction (AMI), stroke, cardiovascular death, unstable angina and heart failure.

Table 57: Major Adverse Cardiac Events (MACE) in INAVO120

	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	Grade 1-5 n (%)	Grade 3-4 n (%)	Grade 1-5 n (%)	Grade 3-4 n (%)
Any MACE	7 (4.3)	1 (0.6)	8 (4.9)	1 (0.6)
General disorders and administration site conditions				
Chest pain	4 (2.5)	0	7 (4.3)	1 (0.6)
Cardiac disorders				
Acute coronary syndrome	2 (1.2)	1 (0.6)	0	0
Cardiac arrest	0	0	1 (0.6)	0
Nervous system disorders				
Cerebrovascular accident	1 (0.6)	0	0	0

Source: NDA 219249 adsl.xpt,adae.xpt datasets

FDA Reviewers Comment: There were few cases of MACE on INAVO120. There is no clear increase of MACE on the inavolisib treatment arm. Of note, there were no specific cases of unstable angina or heart failure. Chest pain was included in the analysis for Table 57, however, it is not clear that those are all cases of unstable angina.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Haw-Jyh Chiu, PhD	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☒ Approved
	Signature: Haw-jyh Chiu -S Digitally signed by Haw-jyh Chiu -S Date: 2024.10.02 14:17:23 -04'00'			
Nonclinical Acting Team Leader	Nikolett Biel, PhD	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☒ Approved
	Signature: Nikolett M. Biel -S Digitally signed by Nikolett M. Biel -S Date: 2024.10.02 14:39:07 -04'00'			
Clinical Pharmacology Reviewer	Hairat Sabit, PhD	OCP/DCPII	Sections: 6, 19.4.1	Select one: ☒ Authored ☐ Approved
	Signature: Hairat Sabit -S Digitally signed by Hairat Sabit -S Date: 2024.10.02 14:48:22 -04'00'			
Pharmacometrics Reviewer	Fang Li, PhD	OCP/DPM	Sections: 6, 19.4.2, 19.4.3	Select one: ☒ Authored ☐ Approved
	Signature: Frank Li -S Digitally signed by Frank Li -S Date: 2024.10.02 15:43:10 -04'00'			
PBPK Reviewer	Ying-Hong Wang, PhD	OCP/DPM	Sections: 19.4.4	Select one: ☒ Authored ☐ Approved
	Signature: Ying-hong Wang -S Digitally signed by Ying-hong Wang -S Date: 2024.10.02 16:56:09 -04'00'			

NDA Multi-disciplinary Review and Evaluation {NDA 219249}
 ITOVEBI (inavolisib)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Genomics Reviewer	Jielin (Jillian) Sun, PhD	OCP/DTPM	Sections: 6	Select one: ☒ Authored ☐ Approved
	Signature: Jielin Sun -S Digitally signed by Jielin Sun -S Date: 2024.10.03 09:55:10 -04'00'			
Clinical Pharmacology Team Leader	Lauren Price, PharmD	OCP/DCPII	Sections: 6, 19.4	Select one: ☒ Authored ☒ Approved
	Signature: Lauren Price -S Digitally signed by Lauren Price -S Date: 2024.10.04 15:30:30 -04'00'			
Pharmacometrics Team Leader	Jingyu (Jerry) Yu, PhD	OCP/DPM	Sections: 6, 19.4.2; 19.4.3	Select one: ☒ Authored ☒ Approved
	Signature: JINGYU YU -S Digitally signed by JINGYU YU -S Date: 2024.10.03 10:19:16 -04'00'			
PBPK Team Leader	Manuela Grimstein, PhD	OCP/DPM	Sections: 19.4.4	Select one: ☒ Authored ☒ Approved
	Signature: Manuela D. Grimstein -S Digitally signed by Manuela D. Grimstein -S Date: 2024.10.03 11:01:54 -04'00'			
Genomics Team Leader	Jeffrey Kraft, PhD	OCP/DTPM	Sections: 6	Select one: ☒ Authored ☒ Approved
	Signature: Jeffrey B. Kraft Jr -S Digitally signed by Jeffrey B. Kraft Jr -S Date: 2024.10.03 11:14:17 -04'00'			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer	Haley Gittleman, PhD	OB/DBV	Sections: 1, 8.1, 8.3, 8.4	Select one: ☒ Authored ☐ Approved
	Signature: Haley R. Gittleman -S Digitally signed by Haley R. Gittleman -S Date: 2024.10.03 11:25:11 -04'00'			
Statistical Team Leader	Joyce Cheng, PhD	OB/DBV	Sections: 1, 8.1, 8.3, 8.4	Select one: ☒ Authored ☒ Approved
	Signature: Joyce Cheng -S Digitally signed by Joyce Cheng -S Date: 2024.10.03 11:56:16 -04'00'			
Clinical Reviewer	Suparna Wedam, MD	OOD/DO1	Sections: 1, 2, 3 4, 7, 8, 9, 10, 11, 12	Select one: ☒ Authored ☐ Approved
	Signature: Suparna B. Wedam -S Digitally signed by Suparna B. Wedam -S Date: 2024.10.03 15:52:26 -04'00'			
Associate Director for Patient Outcomes	Vishal Bhatnagar, MD	OCE	Sections: 8	Select one: ☐ Authored ☒ Approved
	Signature: Vishal Bhatnagar -S Digitally signed by Vishal Bhatnagar -S Date: 2024.10.03 16:20:50 -04'00'			
Associate Director for Labeling	William Pierce, PharmD, MPH	OCE	Sections: 11, Prescribing Information, Patient Information	Select one: ☒ Authored ☒ Approved
	Signature: William F. Pierce -S Digitally signed by William F. Pierce -S Date: 2024.10.04 09:14:16 -04'00'			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Cross-Disciplinary Team Leader (CDTL)	Preeti Narayan, MD	OOD/ DO1	Sections: All	Select one: ☒ Authored ☒ Approved
	Signature:			
Nonclinical Acting Deputy Division Director	Tiffany Ricks, PhD	OOD/DHOT	Sections: 5	Select one: ☐ Authored ☒ Approved
	Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K. Ricks -S Date: 2024.10.04 09:21:43 -04'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman, PhD	OCP/DCPII	Sections: 6, 19.4	Select one: ☐ Authored ☒ Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2024.10.04 10:21:07 -04'00'			
Division Director OB	Shenghui Tang, PhD	OB/DBV	Sections: 1, 8.1, 8.3, 8.4	Select one: ☐ Authored ☒ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2024.10.04 14:31:41 -04'00'			
Division Director	Laleh Amiri-Kordestani, MD	OOD/DO1	Sections: All	Select one: ☒ Authored ☒ Approved
	Signature:			

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DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Deputy Director	Paul Kluetz, MD	OCE	Sections: All	Select one: ☒ Authored ☐ Approved
	Signature:			

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/s/

PREETI NARAYAN
10/09/2024 02:05:08 PM

LALEH AMIRI KORDESTANI
10/09/2024 02:06:23 PM

PAUL G KLUETZ
10/09/2024 03:41:04 PM