NI PASS PROTOCOL (SECONDARY DATA USE)

TITLE:	**EVALUATING SAFETY IN INSULIN-REQUIRING DIABETIC PATIENTS RECEIVING INAVOLISIB PLUS ENDOCRINE THERAPY-BASED REGIMENS IN THE REAL WORLD**
PROTOCOL NUMBER:	GO46271
VERSION NUMBER:	*2*.0
EU PAS REGISTER NUMBER:	To be determined
STUDIED MEDICINAL PRODUCT:	Inavolisib (Itovebi)
AUTHOR:	[redacted] Email: [redacted]
DATE FINAL:	*Version 1.0: 11 September 2025*
***DATE AMENDED*:**	*Version 2.0:* See electronic *signature and* date stamp *on the final page of this document.*

PROTOCOL AMENDMENT, VERSION 2.0: RATIONALE

Protocol version 2.0 has been amended has been amended in accordance with EMA's suggestions to address consistency of US/EU hyperglycemia guidelines, need of an additional data source, extension of observation time window and to increase sample size to 50 patients.

Changes to the protocol are as follows:

- Added milestone of feasibility report (Section 5).
- Updated study duration from 3 years to 3–4 years to meet the minimum study size (Sections 8.1 and 8.5).
- Updated study design to include observation period and an additional data source at the time of feasibility report (Sections 8.1 and 8.5).
- [redacted]
- Sample size is updated from approximately 30 to minimum of 50 patients (Section 8.5).
- Updated research method limitation due to generalizability to address that treatment guidelines and risk minimization measures regarding hyperglycemia are aligned in both US and EU (Section 8.9).
- Updated research method limitation due to low sample size (Section 8.9).
- Synopsis has been updated to include changes from the main protocol.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

ACTIVE SUBSTANCE:	ATC: L01EM06
PRODUCT REFERENCE NUMBER:	006353
PROCEDURE NUMBER:	EMEA/H/C/006353/0000
JOINT PASS	No
RESEARCH QUESTION AND OBJECTIVES:	The research question is to assess safety outcomes in patients with HR+/HER2-, *PIK3CA*-mutated metastatic breast cancer with insulin-requiring diabetes – both type 1 and type 2 – and who receive inavolisib-based regimens in the real world. Safety outcomes are focused on hyperglycemia and other identified adverse events of inavolisib - stomatitis and diarrhea. The primary objectives are: • To describe clinical and demographic characteristics of patients who have insulin-requiring diabetes and receive inavolisib-based regimens in the real world. • To evaluate the incidence, severity, complications, and management of hyperglycemia in patients with insulin-requiring diabetes and who receive inavolisib-based regimens in the real world. The secondary objective is: • To describe the safety and tolerability of inavolisib-based regimens for stomatitis and diarrhea as defined by: • The incidence and management of stomatitis and diarrhea in patients with insulin-requiring diabetes and who receive inavolisib-based regimens in the real world.
COUNTRY OF STUDY POPULATION:	United States of America
MARKETING AUTHORIZATION HOLDER (MAH):	Roche Registration GmbH Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany

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Table of Contents

1. LIST OF ABBREVIATIONS 7
2. RESPONSIBLE PARTIES 9
3. ABSTRACT/SYNOPSIS 10
4. AMENDMENTS AND UPDATES 18
5. MILESTONES 19
6. RATIONALE AND BACKGROUND 19
7. RESEARCH QUESTION AND OBJECTIVES 20
   - 7.1 RESEARCH QUESTION 20
   - 7.2 OBJECTIVES 20
8. RESEARCH METHODS 21
   - 8.1 STUDY DESIGN 21
   - 8.2 SETTING 22
   - 8.3 VARIABLES 23
   - 8.3.1 Patient Characteristic Variables 23
   - 8.3.2 Primary Safety Variables 27
   - 8.3.3 Secondary Variables 31
   - 8.4 DATA SOURCE(S) 32
   - 8.5 STUDY SIZE 32
   - 8.6 DATA MANAGEMENT 33
   - 8.7 DATA ANALYSIS 33
   - [redacted] 33
   - 8.7.2 Other Analyses 35
   - 8.8 DATA QUALITY ASSURANCE AND QUALITY CONTROL 35
   - 8.9 LIMITATIONS OF THE RESEARCH METHOD 36
9. PROTECTION OF HUMAN PATIENTS 37
   - 9.1 INFORMED CONSENT 37
   - 9.2 CONFIDENTIALITY 38
   - 9.3 COMPLIANCE WITH LAWS AND REGULATIONS 38

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 38

11. PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS 39

12. REFERENCES 40

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AI	Aromatase Inhibitors
BC	Breast cancer
BMI	Body Mass Index
CDK	Cyclin-Dependent Kinases
CNS	Central Nervous System
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EHR	Electronic Health Record
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
ER	Estrogen Receptor
ET	Endocrine Therapy
ETR	Endocrine Therapy Resistance
EU PAS	European post-authorization study
FDA	Food and Drug Administration
HbA1c	glycated hemoglobin
HER2	human epidermal growth factor receptor 2
HG	hyperglycemia
HIPAA	Health Insurance Portability and Accountability Act
HR	hormone receptor
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
ICSR	Individual Case Safety Report
IQR	interquartile ranges
IRB	Institutional Review Board
LA	locally advanced
LFT	liver function test
MAH	Marketing authorization holder
mBC	metastatic breast cancer
NI-PASS	non-interventional post-authorization safety study

Abbreviation	Definition
PASS	post-authorization safety study
PFS	progression-free survival
PI3K	phosphoinositide 3-kinase
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (gene name/acronym)
PR	Progesterone Receptor
rwAEs	real world adverse events
RWD	Real World Data
SD	standard deviation
SERD	Selective Estrogen Receptor Degrader
TNM	Tumor Node Metastasis
US	United States of America

2. RESPONSIBLE PARTIES

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3. ABSTRACT/SYNOPSIS

TITLE:	**EVALUATING SAFETY IN INSULIN-REQUIRING DIABETIC PATIENTS RECEIVING INAVOLISIB PLUS ENDOCRINE THERAPY-BASED REGIMENS IN THE REAL WORLD**
PROTOCOL NUMBER:	GO46271
VERSION NUMBER:	2.0
DATE OF SYNOPSIS:	10 September 2025
EU PAS REGISTER NUMBER:	To be registered
STUDIED MEDICINAL PRODUCT:	Inavolisib (Itovebi)
SCIENTIFIC RESPONSIBLE	[redacted]
MAIN AUTHOR	[redacted], Genentech, Roche
PHASE:	IV, non-interventional study
INDICATION:	HR+/HER2- breast cancer
MARKETING AUTHORIZATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Germany

Rationale and Background

Breast cancer (BC) is the most commonly diagnosed cancer in women (Sung et al. 2021, SEER 2023), and hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (HR+/HER2-) BC is the most common breast cancer subtype accounting for approximately 73% of all BCs (American Cancer Society et al. 2022). One of the most common oncogenic drivers in HR+ breast cancer is the upregulation of phosphoinositide 3-kinase (PI3K) pathway activity due to mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (PIK3CA), the gene encoding the alpha isoform catalytic subunit of the PI3K complex (i.e., p110α) (Saal et al. 2005; Stemke-Hale et al. 2008; Fillbrunn et al. 2022). For patients with HR+/HER2- BC, PIK3CA mutations occur in approximately 35-40% of tumors (Anderson et al. 2020, Razavi et al. 2018, Bachman et al. 2005, Samuels et al. 2004; Miron et al. 2010).

Results from the pivotal Study WO41554 (INAVO120,) demonstrated robust clinical benefit of inavolisib in combination with palbociclib and fulvestrant in patients with endocrine-resistant, *PIK3CA*-mutated, HR-positive, HER2-negative locally advanced (LA) or metastatic breast cancer (mBC). Addition of inavolisib to the combination of palbociclib and fulvestrant demonstrated a statistically significant and reduced risk of disease progression or death by 57% (stratified hazard ratio$=$0.43 [95%CI:0.32, 0.59], p$<$0.0001) and clinically meaningful improvement in progression-free survival (PFS) (median PFS increased from 7.3 to 15.0 months) in patients with endocrine-resistant *PIK3CA*-mutated, HR+/HER2− LA/mBC; Turner et al. NEJM 2024). Results also showed a statistically significant and clinically meaningful improvement in overall survival (hazard ratio for death: 0.67; 95% CI: 0.48 to 0.94, Jhaveri et al. 2025).

Insulin dependent patients with type 1 diabetes and type 2 diabetes were excluded in the clinical development program of HR+/HER2- mBC patients (Study WO41554, INAVO120), as well as Study GO45322 (safINA), a Phase II, multicenter, single-country, prospective safety study, to assess the safety of inavolisib and inavolisib-associated hyperglycemia in participants with Type 2 diabetes and *PIK3CA*-mutated HR+/HER2− advanced breast cancer treated with the combination of inavolisib plus fulvestrant, with or without palbociclib.

The purpose of this real world data (RWD) study is to evaluate patients with *PIK3CA*-mutated HR+/HER2- mBC and insulin-requiring diabetes, as part of additional pharmacovigilance activities agreed for the E.U. Risk Management Plan during initial Marketing Authorization procedure. Specifically, additional safety data on patients requiring insulin, including both type 1 and type 2 diabetes, who receive inavolisib-based regimens — as these patients were not included in the INAVO120 patient population — were requested. The marketing authorization holder (MAH) will conduct a RWD study to collect these data from the Flatiron Health oncology electronic health record (EHR) system.

Research Question and Objectives

The research objectives for this study are focused on patients with *PIK3CA*-mutated HR+/HER2- mBC and insulin-requiring diabetes as described below.

The primary objectives for this study are as follows:

- To describe clinical and demographic characteristics of these patients who receive inavolisib-based regimens in the real world
- To describe the safety and tolerability of inavolisib-based regimens for hyperglycemia as defined by:
  - The incidence, severity, and management of hyperglycemia *and associated complications (including diabetic ketoacidosis)* in these patients who receive inavolisib-based regimens in the real world.

The secondary objectives for this study are as follows:

- To describe the safety and tolerability of inavolisib-based regimens for stomatitis and diarrhea as defined by
  - The incidence and management of stomatitis and diarrhea in these patients who receive inavolisib-based regimens in the real world

Study Design

The Sponsor proposes a retrospective cohort study of eligible patients receiving inavolisib-based regimens in the Flatiron Health Network over a 3- *to 4-year* period from 01 January 2026 – 31 December *2029 to observe a minimum of 50 eligible patients*. The Flatiron Health Oncology Network comprises secondary data from over 3.5 million US oncology patients in over 280 oncology clinics, primarily in community-based settings, but also includes at least 15%–20% of patients being treated at academic-based centers.

Eligible patients will include *PIK3CA*-mutated, HR+/HER2- mBC, based on secondary use of EHR data as part of Flatiron Health's Oncology EHR network. Information on eligible patients meeting the study's inclusion/exclusion criteria (e.g., age, estrogen receptor [ER]/progesterone receptor [PR]/HER2 status, comorbidities, prior treatments, etc) will be collected for identified safety events over a 3 *to 4*-year study period (01 January 2026 – 31 December *2029*).

Flatiron's OncoEMR captures information on the patient's interactions with the health care system, including but not limited to demographic and clinical characteristics at mBC diagnosis, visit dates and clinical notes, laboratory, biomarker and imaging visits and results, treatment-related information (e.g., administrations, orders, dose and reasons for discontinuation) and other important comorbidities (e.g. diabetes) and concomitant medications (e.g. metformin).

The planned start date of 01 January 2026 will initiate the period of identifying eligible patients who are taking the inavolisib-based regimens in the Flatiron Health network since FDA approval of inavolisib (10 October 2024) and also receiving insulin. The study period will allow for at least 3 years to identify and collect data from eligible patients being treated by physicians in the Flatiron Health network of participating community and academic-based centers. An extension or additional data vendors will be considered if the sample size of eligible patients for the study using the Flatiron Health database is below projections.

This RWD study will focus on the incidence, severity and complications, and management of hyperglycemia, stomatitis and diarrhea, which are identified adverse events (AEs) for inavolisib. Trained abstractors will review the medical records to abstract the relevant data from patients' electronic health records, clinical notes, biomarker results, laboratory values, imaging assessments, procedures and comedications (frequency, type of administration, dose and duration).

Informed Consent: Patients who visit oncologists in the Flatiron Health network consent to have their de-identified and anonymized data included in the Flatiron Health Research database. Hence, no additional consent is required for this observational study using secondary data from electronic health records, which is in accordance with data privacy requirements, institutional review board (IRB) approval waivers and Health Insurance Portability and Accountability Act (HIPAA) guidelines.

Data Sources

The data source is Flatiron Health's Oncology EHR network. The database includes information from more than 280 cancer clinics (community-based cancer treatment clinics and academic centers), over 2330 clinicians, and 3.5 million active cancer patients, representing US cancer patients with geographical and demographical diversity. Flatiron curates data from both structured and unstructured data using technology-enabled abstraction, with many variables having inter-abstractor agreement $>$95% and strong kappa values. Structured data is pre-specified by the software and captured during routine patient care (e.g. age, gender, diagnoses reported by the oncologist, drug administrations and drug orders). Unstructured data is the information that is not pre-specified by the software but entered by the physician as free text notes (e.g. results, complement of information for cancer diagnosis) or scanned/pdf reports (biomarkers tests, dates and results, radiology reports, etc). There are no additional linkages by the Sponsor to external data sources other than Flatiron Health. The Flatiron Health database provides comprehensive and reliable longitudinal view of cancer diagnosis and treatments representative of oncology care, especially community-*based care, in the United States.*

Population

The study population will consist of US patients who are in the nationwide Flatiron Health network and who have *PIK3CA*-mutated, HR+/, /HER2- metastatic breast cancer and are taking inavolisib-based regimens in the real world.

Patients must meet the following criteria for being selected into the study population:

Key Inclusion/Exclusion (I/E) Criteria for INAVO120-based real world population:

Inclusion criteria:

- Diagnosis of breast cancer – ICD-9 (174.x or 175.x) or ICD-10 (C50.xx)
- Diagnosed with metastatic breast cancer (mBC) on or after 11/1/24 (FDA approval of inavolisib on 10 October 2024)
- ≥18 years of age at mBC diagnosis
- HR+/HER2- (includes HER2-low and HER2-equivocal)
- Type 1 and type 2 diabetes patients who *receive* insulin for at least 6 months prior to the index date
- Patients receiving an inavolisib-based regimen, abstracted from the EHR between 01 January 2026 *and* 31 *December 2029 (allowing* for up to *6* cycles of inavolisib to collect rwAE's).

Exclusion criteria:

- Patients with diabetes and end organ damage (clinician notes for diabetic kidney disease, diabetic retinopathy, diabetic neuropathy, diabetic circulatory complications and diabetic foot ulcers)
- Eastern Cooperative Oncology Group score=3+
- Inavolisib-based regimens in 4L or later

Variables

This real world study will collect variables relevant for the research questions and objectives of the study, to the extent they are available in the Flatiron Health Oncology-based EHR, and available in structured and/or unstructured data for abstraction. These variables include patient demographics and clinical characteristics data as well as treatment exposure and safety outcome variables.

Patient Characteristic Variables

Patient demographic and clinical characteristics for this study are as follows, with the time points of assessment listed in the table below:

Demographic variables:

- Age (age at initial breast cancer diagnosis, metastatic breast cancer diagnosis and at initiation of inavolisib-based regimen)
- Sex assigned at birth (male, female)

- Menopausal status as of mBC diagnosis date (defined as postmenopausal if >60 and for patients ≤ 60 yrs, based on clinical notes and oopherectomy status)
- Race/ethnicity (Race: White or Caucasian, Black or African-American, Asian, Other race and Ethnicity: yes/no Hispanic or Latino)
- Practice type (Community, Academic)
- Geographic Region (Northeast, Midwest, South, West)
- Payer category (Medicaid, Medicare, Commercial Health Plan, Workers Compensation, Other Government Program, Patient Assistance Program, Self-pay, Other Payer/Type Unknown)
- Socioeconomic status index (area-level socioeconomic status variable of a patient's residence)

Clinical characteristic variables (at index date)

- Biomarker status (ER, PR, HR and HER2 expression; *PIK3CA* mutation status)
- Diabetes status, type 1 or type 2, duration of disease and age at diagnosis, if available
- Insulin duration, history of dose changes/interruptions in 6 months prior to index date, to the extent data are available
- Stage at diagnosis (e.g., as explicitly documented by the clinician (stage I, II, III or IV); Tumor Node Metastasis (TNM) stage, clinical and pathological stage, where available)
- Recurrent vs. *de novo* disease (derived by Flatiron based on initial stage at diagnosis and time period between initial and mBC diagnosis dates),
- Sites of metastases (at mBC diagnosis date)
- Eastern Cooperative Oncology Group (ECOG) scores at mBC diagnosis and at start of inavolisib-based line of treatment, as available.
- Body mass index (BMI) at mBC diagnosis date and at index date
- Endocrine therapy resistance (ETR) status, derived based on adjuvant endocrine therapy start and end dates (patients who relapsed while on adjuvant endocrine therapy or within 12 months of end of adjuvant treatment)
- Comorbidities (obtained from the EHR as of the mBC diagnosis date)
- Laboratory values (e.g., glucose, glycated hemoglobin [HbA1c])

Treatment Exposure Variables

The treatment exposure variables for this study are as follows, with the time points of assessment listed in the table below:

- Line of therapy regimen names, before, during and after inavolisib-based regimen of interest
- Administrations of anti-cancer agents, such as for fulvestrant

- Visit dates, including telemedicine
- Orals and medication orders with an emphasis on eligible inavolisib-based regimens, insulin and concomitant medications for specified AE's of interest

Primary Safety Variables

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

Secondary Variables

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

Patient data will be collected based on information abstracted from the Flatiron EHR with human abstraction by trained nurses or other health personnel (e.g., safety data that are not well-captured in structured variables) and natural language processing, with the variables and relevant time periods shown below.

Table 1 Key variables and time points of assessments during the study period

Data	Pre-Index date [a]	Index date [a]	Follow-up through end of study period [b]
Dates of diagnosis – initial breast cancer, metastatic breast cancer	X		
Biomarker test results for ER, PR, HR, and HER2 expression, and *PIK3CA* mutation status in the mBC setting and, where available, in the eBC setting	X		
Patient demographics - age at initial diagnosis and at mBC diagnosis, sex, race/ethnicity, menopausal status, geographic region, practice type, insurance type, socioeconomic index	X		
Clinical characteristics - BMI, stage at diagnosis, recurrent vs. *de novo* disease, histology, sites of metastases, ECOG scores	X	X	X
Laboratory values - e.g., HbA1c, glucose, comprehensive metabolic panel labs	X	X	X
Comorbidities – history of diabetes, renal disease, liver disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease	X	X	X
Line of therapy regimens- before, during and after inavolisib-based regimens	X	X	X
Visit dates, including telemedicine, clinic note dates, order dates, episode dates, administration dates, test dates		X	X
Treatment exposure - Administrations, orals and medication orders with an emphasis on inavolisib-based regimens– start and stop dates, dose, discontinuations and if available, reasons for discontinuation		X	X
Safety outcome variables of incidence, severity (using real world surrogate measures with labs, hospitalizations), complications and management (e.g., concomitant medications, inavolisib dose changes, holds & discontinuations), or hyperglycemia stomatitis and diarrhea, where documentation is available in oncologist EHR		X	X
Follow-up information - dates of death, date of last visit, last clinic note date, study end date, loss to follow-up or censoring		X	X

BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; EHR = Electronic Health Record; ER = estrogen receptor, HbA1c = glycated hemoglobin; HR = hormone receptor, HER2 = human epidermal growth factor receptor 2; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (gene name/acronym); PR = progesterone receptor.

[a] index date is start date of inavolisib.

[b] during and after inavolisib treatment period.

Study Size

The retrospective cohort study is planned with a *minimum* sample size of 50 patients with insulin-requiring type 1 or type 2 diabetes and *PIK3CA*-mutated, HR-positive, HER2-negative advanced breast cancer who are part of the Flatiron Health Oncology network. It is estimated that *3 to 4 years will* be required to collect data on this *number* of patients who are suitable candidates for inavolisib-based regimens.

The feasibility of a non-interventional study evaluating diabetic patients requiring insulin treatment (including both type 1 and 2 diabetes) has been conducted by assessing the prevalence of these patients among patients treated with alpelisib from 2019*–2024*, using the Flatiron Health Network of US oncology patients. Although the real world use of inavolisib may *differ* from that of alpelisib, the sponsor believes this provides an initial understanding of a potential sample size for this study. To achieve the committed sample size, the Sponsor will include patients who receive the triplet regimen in 2L and/or 3L as well as other inavolisib-based regimens received in the real world that include inavolisib plus endocrine therapy backbones.

Data Analysis

The primary and secondary objectives of this study are to describe the study population with respect to baseline demographic and clinical characteristics, and to assess the incidence, severity, complications and management of hyperglycemia, stomatitis and diarrhea. All analyses will be descriptive in nature and there are no statistical tests of hypotheses, nor time to event outcomes (see Section 8.7.1).

In the descriptive analyses, distribution and percentages will be reported for categorical variables; medians with interquartile ranges (IQR), means with standard deviations (SD), minimum values, and maximum values will be reported for continuous variables. Missing values will be described as a separate category. The proportion of patients with an observed real world adverse event (rwAE) will be reported for the period of inavolisib-based regimens.

Sensitivity analyses accounting for starting dose of inavolisib, line of therapy, history of diabetes, duration of insulin use and type of diabetes (type 1 versus type 2) will be conducted as able based on sample size (See Other Analyses, Section 8.7.2).

4. AMENDMENTS AND UPDATES

Substantial protocol amendments/updates so far: *amendments and updates are listed in summary of changes.*

5. MILESTONES

Milestone	Planned Date
Registration of protocol in the EU PAS register	TBD
First Data Extraction	*Oct 2026*
Feasibility Report	*Dec 2026*
Last Data Extraction	*Dec 2029* [a]
Final report of study results (CSR)	*Dec 2030* [b]
Registration of the results in the EU PAS register	TBD
Publication submission	TBD

CSR = clinical study report; EU PAS = European post-authorization study; TBD = to be determined.

[a] *Last data extraction may occur as early as December 2028 if minimum requirement of 50 observed eligible patients is met.*

[b] *One year after last data extraction date*

6. RATIONALE AND BACKGROUND

Breast cancer (BC) 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 (Breast Cancer, Facts and Figures 2022-2024). HR-positive, HER2-negative (HR+/HER2-) BC is the most common breast cancer subtype accounting for approximately 73% of all breast cancers (American Cancer Society et al. 2022).

One of the most common oncogenic drivers in HR-positive breast cancer is the upregulation of PI3K pathway activity due to mutations in *PIK3CA*, the gene encoding the alpha isoform catalytic subunit of the PI3K complex (i.e., p110α) (Saal et al. 2005; Stemke-Hale et al. 2008; Fillbrunn et al. 2022). For patients with HR+/HER2- BC, *PIK3CA* mutations occur in approximately 35-40% of tumors, regardless of stage (i.e., early versus metastatic breast cancer (eBC) vs (mBC) [Anderson EJ et al. 2020, Razavi P et al. 2018, Bachman et al. 2005, Samuels Y et al. 2004; Miron A et al. 2010].

Results from the pivotal Study WO41554 (INAVO120) demonstrated robust clinical benefit of inavolisib in combination with palbociclib and fulvestrant in patients with endocrine-resistant, *PIK3CA*-mutated, HR-positive, HER2-negative locally advanced or mBC. Addition of inavolisib to the combination of palbociclib and fulvestrant demonstrated a statistically significant and clinically meaningful improvement in PFS, by reducing the risk of disease progression or death by 57% in patients (Stratified hazard ratio [HR] = 0.43 [95%CI:0.32, 0.59], $p < 0.0001$; Turner et al. 2024). A 7.7-month improvement in median PFS was demonstrated. Overall survival was statistically significant and clinically meaningful (hazard ratio for death, 0.67; 95% CI, 0.48 to 0.94,

Jhaveri et al. NEJM 2025). Robustness of the treatment effect on PFS was confirmed in sensitivity analyses, and consistency in benefit was observed across clinically relevant subgroups and efficacy endpoints (Turner et al. 2024).

The purpose of the proposed real world data (RWD) study is to evaluate safety – focused on hyperglycemia, stomatitis and diarrhea - of patients with insulin-requiring diabetes as part of a post-marketing commitment for the European Medicines Agency. Additional data were requested for patients requiring insulin, including both type 1 and type 2 diabetes, who receive inavolisib-based regimens. Insulin dependent patients with type 1 diabetes and type 2 diabetes were excluded in the clinical development program of inavolisib for HR+/HER2− metastatic breast cancer patients, including the INAVO120 patient population.

The MAH proposed a real world data study to collect these data from an oncology EHR system in the US.

7. RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTION

The research question is to describe safety outcomes in patients with insulin-requiring diabetes - both type 1 and type 2 - and who receive inavolisib-based regimens in the real world. Safety outcomes are focused on hyperglycemia and *associated complications (including diabetic ketoacidosis) and* other identified risks of inavolisib - stomatitis and diarrhea.

7.2 OBJECTIVES

The primary objective for this study is to evaluate patients with *PIK3CA*-mutated HR+/HER2- mBC and insulin-requiring diabetes as follows:

- To describe clinical and demographic characteristics of insulin-requiring patients who receive inavolisib-based regimens in the real world (e.g., inavolisib plus fulvestrant plus palbociclib, inavolisib plus fulvestrant plus ribociclib, inavolisib plus fulvestrant, etc).
- To describe the safety and tolerability of inavolisib-based regimens as it relates to hyperglycemia *and associated complications (including diabetic ketoacidosis)* by describing the following:
  - The incidence, severity, complications, and management of hyperglycemia in patients with type 1 and type 2 diabetes and *PIK3CA*-mutated, HR+, HER2- metastatic breast cancer on long-term insulin treatment, who receive inavolisib-based regimens in the real world.

The secondary objective for this study is as follows:

- To describe the safety and tolerability of inavolisib-based regimens as assessed by stomatitis and diarrhea
  - The incidence, severity, and management of stomatitis and diarrhea in type 1 and type 2 diabetes patients on long-term insulin treatment, who receive inavolisib-based regimens in HR+/HER2- *PIK3CA*-mutated metastatic breast cancer patients in the real world.

8. RESEARCH METHODS

8.1 STUDY DESIGN

A retrospective cohort study of patients with *PIK3CA*-mutated, HR+/HER2- metastatic breast cancer (mBC) patients, based on secondary data use of EHR data as part of Flatiron Health's Oncology EHR network. Information on eligible patients meeting the study's inclusion/exclusion criteria will be collected for identified safety events (hyperglycemia, stomatitis and diarrhea) over the study period.

The Sponsor proposes a retrospective cohort study of eligible patients receiving inavolisib-based regimens in the Flatiron Health Network over a 3 *to 4*-year study period from 1 January 2026 - 31 December *2029 to observe a minimum of 50 eligible patients*. The Flatiron Health Oncology Network comprises secondary data from over 3.5 million US oncology patients in over 280 oncology clinics, primarily in community-based settings, but also includes at least 15%–20% of patients being treated at academic-based centers. Flatiron's OncoEMR captures information on the patient's interactions with oncology clinics, including but not limited to demographic and clinical characteristics at metastatic breast cancer (mBC) diagnosis, visit dates and clinical notes, laboratory, biomarker and imaging visits and results, treatment-related information (e.g., administrations, orders, dose and reasons for discontinuation) and other important comorbidities and concomitant medications (e.g., diabetes and metformin).

The planned start date of 01 January 2026 will initiate the period of identifying eligible patients who are taking an inavolisib-based regimen in the Flatiron Health network after FDA approval. The study period will allow at least 3 years to identify and collect data from *a minimum of 50* eligible patients *to meet the commitments for this post-authorization safety study (PASS). An update on the need for an extended observation period or an additional data source will be provided at the time of the feasibility report (Section 5).* An extension *of the observation period will be prioritized over the use of an additional data source to allow for a single set of more precise estimates, rather than two sets of less precise estimates coming from two distinct data sources.*

The study will focus on the incidence, severity and complications, and management of hyperglycemia, stomatitis and diarrhea, which are identified adverse events (AE's) for inavolisib. Trained abstractors will abstract the relevant data from patients' electronic

health records with respect to demographic and clinical characteristics (e.g., ages at eBC and mBC diagnosis, stage at diagnosis, menopausal status, endocrine resistance status, biomarker results, etc), treatment information (e.g., dose, duration and type of administration) and outcomes of interest (e.g., dates of new onset of hyperglycemia, stomatitis and diarrhea) as well as other important information to contextualize the safety outcomes (e.g., other comorbidities, comedications, laboratory results, visit frequency, etc).

8.2 SETTING

This study will be conducted in Flatiron Health network patients in the US who have insulin-requiring diabetes and have *PIK3CA*-mutated, hormone receptor positive (HR+), HER2 negative (HER2-) metastatic breast cancer and are receiving inavolisib-based regimens in the real world.

Patients must meet the following criteria for inclusion into the analysis:

Key Inclusion/Exclusion (I/E) Criteria for INAVO120-like real world population:
Inclusion criteria:

- Diagnosis of breast cancer – ICD-9 (174.x or 175.x) or ICD-10 (C50.xx)
- Diagnosed with metastatic breast cancer (mBC) on or after 11/1/24 (FDA approval of inavolisib on October 10, 2024)
- ≥18 years of age at mBC diagnosis
- HR+/HER2- (includes HER2-low and HER2-equivocal)
- Insulin-requiring diabetes (taking insulin for at least 6 months prior to index date)
- Patients receiving an inavolisib-based regimen between *1 January 2026 and 31 December 2029.*
  - Label-approved INAVO120 regimen, inavolisib plus palbociclib plus fulvestrant.
  - Off-label regimens combining inavolisib and endocrine-based therapies in the real world which are being investigated in trials by the Sponsor for metastatic HR+/HER2- breast cancer patients: inavolisib plus fulvestrant; inavolisib plus fulvestrant plus abemaciclib; inavolisib plus fulvestrant plus ribociclib; inavolisib plus CDKi plus oral SERDs; inavolisib plus CDKi plus aromatase inhibitors (AIs).

Exclusion criteria:

- Patients with diabetes and end organ damage (clinician notes for diabetic kidney disease, diabetic retinopathy, diabetic neuropathy, diabetic circulatory complications and diabetic foot ulcers)
- Eastern Cooperative Oncology Group score = 3+
- Inavolisib-based regimens 4L or later

8.3 VARIABLES

This real world study will collect variables relevant for the research questions and objectives of the study, to the extent they are available in structured and unstructured components of the EHR. These variables include patient characteristics such as demographics and clinical characteristics as well as treatment exposure and safety outcome variables.

8.3.1 Patient Characteristic Variables

Patient demographic and clinical characteristics for this study are listed below. Each variable is important for descriptive purposes, as predictors or as confounders. The time points of assessment for each set of variables are also listed in the table below:

Demographic variables:

- Age at clinical milestones:
  - Age at initial breast cancer diagnosis
  - Age at metastatic breast cancer diagnosis
  - Age at initiation of inavolisib-based regimen

    Since only birth year is provided, a patient's age at metastatic diagnosis will be calculated by subtracting the year of metastatic diagnosis (ignoring the month/day) from the year of birth
- Sex at birth (male, female)
- Menopausal status as of mBC diagnosis date and as of index date
- Race, Ethnicity (Race: White or Caucasian, Black or African-American, Asian, Other race and Ethnicity: yes/no Hispanic or Latino)
- Practice type (Community, Academic)
- Geographic Region (Northeast, Midwest, South, West, defined based on states in the region:
  - Northeast: CT, ME, MA, NH, RI, VT, DE, NJ, NY, PA
  - Midwest: IL, IN, MI, OH, WI, IA, KS, MN MO, NE, ND, SD
  - South: FL, GA, MD, NC, SC, VA, DC, WV, AL, KY, MS, TN, AR, LA, OK, TX, Puerto Rico
  - West: AZ, CO, ID, MT, NV, NM, UT, WY, AK, CA, HI, OR, WA)
- Payer category (Medicaid, Medicare, Commercial Health Plan, Workers Compensation, Other Government Program, Patient Assistance Program, Self-pay, Other Payer/Type Unknown)
- Socioeconomic index (based on patient's block during 2015-19 and most recent residence, classified as a relative score from 1-5)

Clinical characteristic variables

- Biomarker status (positive, negative, unknown, indeterminate) for each of the following biomarkers:
  - ER, PR, HER2 status
  - *PIK3CA* status
  - If a patient has multiple biomarker assessments in their patient journey, the Sponsor will collect all those data but determine the classification based on their biomarker status closest to the time of the inavolisib-based regimen
- Stage at initial diagnosis
  - Group stage – I, II, III, IV, other or unknown;
  - Tumor Node Metastasis (TNM) stage, including clinical and pathological TNM stage, where available
- Recurrent vs. *de novo* disease
  - For recurrent patients, the time between initial and metastatic diagnosis will be calculated.
- Histology
- Sites of metastases (at mBC diagnosis date) which are recorded as:
  - Bone, Lung, Liver, Brain, central nervous system (CNS) site*, Distant Lymph Node(s), Thyroid, Peritoneum, Soft tissue, Spleen, Bone marrow, Pleura, Skin, Ovary, Adrenal, Kidney, Pancreas, Other

    *CNS site includes metastases to the: leptomeninges, spinal cord, cerebrospinal fluid, cauda equina, cranial nerves, pituitary gland, pineal gland, craniopharyngeal duct, and eye.

    *CNS site excludes: spinal column (bone)

    Locoregional lymph nodes are not captured.
- Eastern Cooperative Oncology Group (ECOG) scores at mBC diagnosis and at start of inavolisib-based lines of treatment
  - The ECOG result closest to the metastatic diagnosis date will be used. If there are multiple tests on the closest date, use the highest status. ECOG will be categorized as: 0, 1, 2+, missing
- Body mass index (BMI) at mBC diagnosis date and index date
- Endocrine therapy resistance (ETR) status as of mBC diagnosis date (primary resistance, secondary resistance):
  - Primary ETR, defined as:

    Patients who had <2 years of adjuvant endocrine therapy (ET) and relapsed while on ET or

    Patients who had <2 years of ET and relapsed within 1 year from last ET end date
  - Secondary ETR, defined as:

Patients who have received ≥ 2 years of endocrine treatment in the adjuvant setting, but relapsed while on treatment

or

Patients who have received ≥ 2 years of endocrine treatment in the adjuvant setting, relapsed within 1 year from last ET end date

- Endocrine therapy sensitive will include patients of the following:
  - Patients who had $\geq$ 5 years of ET and relapsed $>$1 year from last ET end date

  or
  - Patients with $<$5 years of ET and relapsed $>$1 year from the last ET date; these are patients who are not adherent to the adjuvant ET treatment guideline
- Comorbidities
  - Comorbidities, as of the mBC diagnosis date, are obtained from the EHR by using concomitant medications and unstructured data (e.g., clinical notes). The following comorbidities will be captured, where available:
    - Myocardial infarction
    - Congestive heart failure
    - Peripheral vascular disease
    - Cerebrovascular disease
    - Mild chronic liver disease
    - Moderate or severe chronic liver disease
    - Diabetes with end organ damage (an exclusion criteria)
    - Moderate to severe renal disease

Treatment Exposure Variables

The treatment exposure variables for this study are as follows, with the time points of assessment listed in the table below:

- Line of therapy information:
  - Names of combination partners in inavolisib-based regimen
  - Regimen prior to inavolisib-based regimen
  - Regimen subsequent to inavolisib-based regimen
- Dose:
- Starting dose & dose changes of inavolisib
- Starting dose & dose changes of inavolisib combination partners
- Administrations, such as for fulvestrant:
  - Name of treatment
  - Frequency of administration

  - Dosing
- Health care interactions including:
  - Visit dates
  - Telemedicine dates
  - Laboratory dates
- Orals and medication orders for:
  - Inavolisib-based regimen
- Concomitant medications to treat (see Section 8.3.2 and Section 8.3.3 for more detail, Primary Safety and Secondary Safety Variables):
  - [redacted]
  - [redacted]
  - [redacted]

Patient data will be collected based on information abstracted from the Flatiron EHR with human abstraction by trained health personnel (e.g., safety data that are not well-captured in structured variables) and natural language processing, according to the schedule below.

Table 2 Key variables and time points of assessments during the study period

Data	Pre-Index date [a]	Index date [a]	Follow-up period [b]
Dates of diagnosis – initial breast cancer, metastatic breast cancer	X		
Biomarker test results for ER, PR, HR, and HER2 expression, and *PIK3CA* mutation status in the mBC setting and, where available, in the eBC setting	X		
Patient demographics - age at initial diagnosis and at mBC diagnosis, sex, race/ethnicity, menopausal status, geographic region, practice type, insurance type, socioeconomic index	X		
Clinical characteristics - BMI, stage at diagnosis, recurrent vs. *de novo* disease, histology, sites of metastases, ECOG scores	X	X	X

Table 2 Key variables and time points of assessments during the study period (cont'd)

Data	Pre-Index date [a]	Index date [a]	Follow-up period [b]
Laboratory values - e.g., HbA1c, glucose, comprehensive metabolic panel labs	X	X	X
Comorbidities – history of diabetes, renal disease, liver disease, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease	X	X	X
Line of therapy regimens- before, during and after inavolisib-based regimens	X	X	X
Visit dates, including telemedicine, clinic note dates, order dates, episode dates, administration dates, test dates		X	X
Treatment exposure - Administrations, orals and medication orders with an emphasis on inavolisib-based regimens– start and stop dates, dose, discontinuations and if available, reasons for discontinuation		X	X
Safety outcome variables of incidence, severity (using real world surrogate measures with labs, hospitalizations, complications and management (e.g., concomitant medications, inavolisib dose changes, holds & discontinuations), or hyperglycemia stomatitis and diarrhea, where documentation is available in oncologist EHR		X	X
Follow-up information - dates of death, date of last visit, last clinic note date, study end date, loss to follow-up or censoring		X	X

BMI = body mass index; eBC = early breast cancer; ECOG = Eastern Cooperative Oncology Group; EHR = Electronic Health Record; ER = estrogen receptor; HbA_{1c} = glycated hemoglobin; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; mBC = metastatic breast cancer; *PIK3CA* = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform; PR = progesterone receptor.

[a] index date is the start date of inavolisib.

[b] during and after inavolisib treatment period.

8.3.2 Primary Safety Variables

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Primary Safety Variables

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8.3.3 Secondary Variables

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8.4 DATA SOURCE(S)

The data source for this study uses data collected in Flatiron Health's Oncology EHR network. The database includes information from more than 280 cancer clinics (community-based cancer treatment clinics and academic centers), over 2330 clinicians, and 3.5 million active cancer patients, representing US cancer patients with geographical and demographical diversity. Flatiron data represents both structured and unstructured data, with many variables having inter-abstractor agreement >95% and strong kappa values. Structured data is pre-specified by the software and captured during routine patient care (e.g. age, gender, diagnoses reported by the oncologist, drug administrations and drug orders). Unstructured data is the information that is not pre-specified by the software but entered by the physician as free text notes (e.g., results, complement of information for cancer diagnosis) or scanned/pdf reports (biomarkers tests, dates and results, radiology reports, etc). There are no additional linkages by the Sponsor to external data sources. The Flatiron Health database provides comprehensive and reliable longitudinal view of cancer diagnosis and treatments representative of oncology care, especially community-based care, in the US.

8.5 STUDY SIZE

The retrospective cohort study is planned with a sample size of *minimum of* 50 patients with insulin-requiring type 1 or type 2 diabetes and *PIK3CA*-mutated, HR- positive, HER2-negative advanced breast cancer who are part of the Flatiron Health Oncology network. It is estimated that *approximately 3 to 4 years will* be required to collect data on this *number* of patients who are suitable candidates for inavolisib-based regimens.

The feasibility of a non-interventional study evaluating diabetic patients requiring insulin treatment (including both type 1 and 2 diabetes) has been conducted by assessing the prevalence of these patients among patients treated with alpelisib from 2019-*2024*, using the Flatiron Health Network of US oncology patients. Although the real world use of inavolisib may vary from that of alpelisib, the Sponsor believes this provides an initial understanding of a potential sample size for this study. The real world use of the inavolisib triplet regimen may vary as it is a front-line regimen where testing is less common than in later lines, or if other combination partners are preferred or if the competitive landscape of treatment options changes for patients with *PIK3CA* mutations from 2026-28. To achieve the committed sample size, the Sponsor will include patients who receive the triplet regimen in 2L and/or 3L, as well as other inavolisib-based regimens received in the real world that include inavolisib plus endocrine therapy backbones.

The study period will allow at least 3 years to identify and collect data from a minimum of 50 eligible patients to meet the commitments for this post-authorization safety study (PASS). An update on the need for an extended observation period or an additional data source will be provided at the time of the feasibility report (Section 5). An extension of the observation period will be prioritized over the use of an additional data source to

allow for a single set of more precise estimates, rather than two sets of less precise estimates coming from two distinct data sources.

8.6 DATA MANAGEMENT

The data will be transferred electronically to the MAH, and the MAH's standard procedures will be used to handle and process the electronic transfer of these data.

8.7 DATA ANALYSIS

The primary and secondary objectives of this study are to describe the study population with respect to baseline demographic and clinical characteristics, and to assess the incidence, severity, complications and management of hyperglycemia, stomatitis and diarrhea. All analyses will be descriptive in nature and there are no statistical tests of hypotheses, nor time to event outcomes (see Section 8.7.1).

In the descriptive analyses, frequencies and percentages will be reported for categorical variables. Missing values will be described as a separate category. For proportions of patients with an observed rwAE, the analyses will be conducted in several ways, by including: 1) all patients at baseline (defined as the start of the inavolisib-based regimen); 2) patients who have at least 2 visits during the inavolisib-based regimen; 3) patients who are followed up (e.g., have health care visits) during the entire inavolisib-based regimen. Medians with IQR, means with SD, minimum values, and maximum values will be reported for continuous variables.

Sensitivity analyses accounting for starting dose of inavolisib, line of therapy, history of diabetes, duration of insulin use and type of diabetes (type 1 versus type 2) will be conducted, as is feasible based on sample size. (See Other Analyses, Section 8.7.2)

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8.7.2 Other Analyses

Stratified, sub-group and sensitivity analyses may be considered for the following subsets of the study population, sample size permitting:

- Type 1 vs. type 2 diabetes
- Line of therapy of inavolisib
- Starting dose of inavolisib
- Duration on inavolisib-based regimen

Some data may only be available for small samples, and in those cases descriptive analyses will be performed to contextualize the rwAEs with important confounding and prognostic factors such as those listed below:

- Duration of diabetes prior to index date, where available
- Duration of insulin-dependence prior to index date, where available
- Renal impairment
- History of gestational diabetes, where available

8.8 DATA QUALITY ASSURANCE AND QUALITY CONTROL

The MAH must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms (if applicable), and documentation of IRB/EC and governmental notification (if required).

The Marketing Authorization Holder shall ensure that the datasets and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

Data not held within MAH systems will be periodically transferred electronically from Flatiron Health to the MAH. Flatiron Health will comply with the MAH procedures regarding content, archiving and records management of process documents.

Retention of Records

Archiving at the study site has to be for at least five years after final study report or first publication of study results, whichever comes later; or according to local regulation.

Records and documents pertaining to the conduct of this study must be retained by the Genentech, Roche for at least 25 years after completion of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Genentech, Roche. Written notification should be provided to the Genentech, Roche prior to transferring any records to another party or moving them to another location.

8.9 LIMITATIONS OF THE RESEARCH METHOD

There are several limitations that can be considered as listed below:

- **Generalizability:** The dataset is drawn from a large sample of community-based and academic centers in the US, *representing* practice patterns *at these centers* in the *United States. While these* may *differ from specific* ex-US *delivery models,* the *guidelines and measures for the management of hyperglycemia with inavolisib are similar across regions (USPI, EU SmPC). Furthermore, the incidence of hyperglycemia associated with inavolisib due to on-target MOA on the insulin signaling pathway is expected to be consistent across regions While the specific* sequence of anti-*hyperglycemic agents* used *may vary based on local availability, the clinical thresholds for hyperglycemia intervention and dose modifications of inavolisib remain globally aligned.*
- **Unmeasured confounders**: The Sponsor will attempt to collect important predictors and potential confounders to contextualize the reporting of safety-related outcomes, though it is likely there will be unmeasured confounders. Hence, one needs to be cautious in interpreting results (e.g., if patients who have HbA1c levels at baseline are different from those who do not have HbA1c levels at baseline in terms of access, it could be related to the severity and management of AE's). The extent of information available in the dataset also depends on the quality of information entered into the EHR by the clinician, which is a challenge with EHR-based or most observational RWD. For example, the Sponsor will attempt to capture gestational diabetes as a potential risk factor for hyperglycemia, but it may not be uniformly recorded by oncologists.
- **Missing data**: One challenge with EHR data is the potential for missing, inaccurate or incomplete data. Like any real world data source that captures routine health care interactions, there is missing data on important variables of interest. Missing data will be evaluated by using the patient characteristic table to evaluate the extent of missingness in the covariates and the association of missingness with our key variables of interest.
  - Missing data will be reported as a separate value for all variables.

- The distribution of missingness will be evaluated according to important baseline patient demographic and clinical characteristics.
- Missing data on treatment-related information will be reported and sensitivity analyses will be conducted in subsets of the data with complete data on treatment-related information (e.g., dose and duration of inavolisib).
- Missing data on safety-related information will be reported and sensitivity analyses will be conducted in subsets of the data with more complete information, such as:
  - At least one HbA1c value
  - At least two glucose values
  - Concomitant medications to treat the AE of interest (name)

    Missing data on safety-related outcomes is an important consideration for AE's in this study. Stomatitis and diarrhea, especially in less severe cases, can be managed with over-the-counter medications. Hence less severe cases of stomatitis and diarrhea may not be well captured in the EHR. Patients may also seek care with their primary care physician for more severe reactions. The reported incidence would be too low for less severe cases, and the observed severity for these AE's could be biased towards a higher prevalence of more severe cases.

- **Incomplete follow-up:** This occurs for patients who migrate outside the EHR network, so the incidence and management of rwAEs could be missing for these patients.
- **Low sample size:** Based on *initial* feasibility *evaluations*, there is likely to be a low prevalence of insulin-requiring diabetes among patients receiving PI3K inhibitors in the real world. The small sample size *may* limit interpretation of the results and *attribution of* causal *relationships*.

9. PROTECTION OF HUMAN PATIENTS

9.1 INFORMED CONSENT

This study will be conducted in patients who take inavolisib-based regimens in the Flatiron Health Network, as part of real world interactions with their health care providers. Patients who visit oncologists in the Flatiron Health network consent to have their de-identified and anonymized data included in the Flatiron OncoEMR database. Hence, no additional consent is necessary for this observational study, which is in accordance with data privacy requirements, IRB approvals and HIPAA guidelines. There will be no direct involvement of patients and patients will receive no direct benefit

from participating in the study. The study will entirely be using de-identified, anonymized secondary data from electronic health records.

For this study, it is not necessary, or possible/practical to obtain informed consent for use of secondary data. However certain precautions will be taken, including:

- Ensuring data are anonymized / pseudonymized
- Ensuring final analysis data are anonymized / pseudonymized
- Ensuring possibility of linkage back to individual identified patients is impossible or tightly controlled

9.2 CONFIDENTIALITY

The MAH maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique study-specific patient identification number (real world patients are already anonymized by Flatiron Health as part of accessing their data). This means that patient names are not included in datasets that are transmitted to any MAH location. Roche will maintain high standards of confidentiality and protection of patient personal data. The data will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Patient medical information obtained by this study is confidential. and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, MAH monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

9.3 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for Good Pharmacoepidemiological Practice published by the International Society of Pharmacoepidemiology and the laws and regulations of the country in which the research is conducted.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a non-interventional post-authorization safety study (NI-PASS) involving the use of secondary data and the reporting of adverse reactions in the form of ICSRs is not required.

All adverse events extracted from the data source for the study as specified in the protocol will be summarized as part of any interim safety analyses and in the final study report and final publication.

11. PLANS FOR DISSEMINATION AND COMMUNICATION OF STUDY RESULTS

Regardless of the outcome of NI-PASS, the MAH is dedicated to openly providing information on the NI-PASS to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The MAH will comply with all requirements for publication of study results.

12. REFERENCES

American Cancer Society. (2022). Breast cancer facts and figures, 2022-2024. Retrieved from https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/2022-2024-breast-cancer-fact-figures-acs.pdf

Anderson, EJ, Mollon, LE, Dean, JL, et al. A systematic review of the prevalence and diagnostic workup of *PIK3CA* mutations in HR+/HER2- metastatic breast cancer. International Journal of Breast Cancer, 2020, 3759179. https://doi.org/10.1155/2020/3759179

Bachman, K. E., Argani, P., Samuels, Y., et al. (2004). The *PIK3CA* gene is mutated with high frequency in human breast cancers. Cancer Biology & Therapy, 3(8), 772–775. (Erratum: Cancer Biology & Therapy, 4(2), 133, 2005).

Fillbrunn, M., Signorovitch, J., André, F., et al. (2022). *PIK3CA* mutation status, progression and survival in advanced HR+/HER2- breast cancer: A meta-analysis of published clinical trials. BMC Cancer, 22(1), 1002–1013.

Jhaveri, K., Im, S., Saura, C., et al. Overall survival with inavolisib in *PIK3CA*-mutated advanced breast cancer. The New England Journal of Medicine. 2025. Advance online publication. https://doi.org/10.1056/NEJMoa2501796

Miron, A., Varadi, M., Carrasco, D., et al. *PIK3CA* mutations in in situ and invasive breast carcinomas. Cancer Research. 2010 70(14), 5674–5678. https://doi.org/10.1158/0008-5472.CAN-08-2660

Razavi P, Chang MT, Xu G, et al. The Genomic Landscape of Endocrine-Resistant Advanced Breast Cancers. Cancer Cell. 2018 Sep 10;34(3):427-438.e6.

Saal LH, Holm K, Maurer M, et al. PIK3CA mutations correlate with hormone receptors and PTEN loss in human breast carcinoma. *Cancer Res.* 2005;65(7):2554-2559.

Samuels Y, Wang Z, Bardelli A, et al. High frequency of mutations of the PIK3CA gene in human cancers. Science. 2004 Apr 23;304(5670):554.

SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. (2023, April 19). Surveillance Research Program, National Cancer Institute. Retrieved April 25, 2023, from https://seer.cancer.gov/statistics-network/explorer/

Stemke-Hale K, Gonzalez-Angulo AM, Lluch A, et al. Integrative analysis of PIK3CA, PTEN, and AKT mutations in breast cancer. *Cancer Res.* 2008;68(15):6084-6091.

Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates. *CA Cancer J Clin.* 2021;71(3):209-249.

Turner NC, Im SA, Saura C, et al. Inavolisib-Based Therapy in *PIK3CA*-Mutated Advanced Breast Cancer. N Engl J Med. 2024 Oct 31;391(17):1584-1596. doi: 10.1056/NEJMoa2404625. PMID: 39476340.

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System identifier: RIM-CLIN-1197918

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Second Approval	[redacted] Deputy EU QPPV 24-Mar-2026 17:01:14 GMT+0000