PROTOCOL: CA2440008

IZABRIGHT-Breast01: A Randomized, Open-label, Inferentially Seamless Phase 2/3 Study of Izalontamab Brengitecan (BMS-986507) versus Treatment of Physician's Choice in Patients with Previously Untreated, Locally Advanced, Recurrent Inoperable, or Metastatic Triple-negative Breast Cancer (TNBC) or ER-low, HER2-negative BC who are Ineligible for Anti-PD1/PD-L1 Treatment

Compound: BMS-986507(BL-B01D1;iza-bren)

Brief Title:

Study of Izalontamab Brengitecan (BMS-986507) versus Treatment of Physician's Choice in Patients with Previously Untreated, Locally Advanced, Recurrent Inoperable, or Metastatic Triple-negative Breast Cancer Ineligible for anti-PD(L)1-based Treatments

PHARMACY MANUAL
V-2

May 28, 2025

Bristol Myers Squibb
Pharmacy Services
P.O. Box 4000
Princeton, NJ 08543

This pharmacy manual applies to the revised CA2440008 clinical trial protocol and all subsequent amendments unless otherwise noted in the Document History section.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Manual V1	March 25, 2025	Version 1
Manual V2	May 28, 2025	Updated per Protocol Amendment 01 (V. 30APR25) with the following changes: Updated TOC- removed appendix 1 reference Section 3; updated study design schematic, modified protocol language for BMS-986507 dosing (day 8 language) 3.1.2; remove syringe pump reference, updated concentration to 1-9 mg/mL, remove preparation example for syringe pump administration. 3.1.3; updated infusion storage conditions 3.2; updated table as per protocol language, added pegfilgrastim Removed appendix 1; syringe pump preparation

(Document versions must follow the guidelines as outlined in QMS-SOP-30805, Appendix A)

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1 OBJECTIVE

The objective of this Pharmacy Manual is to provide the investigational site with clear and detailed information on the storage, handling, preparation, and administration of clinical product(s) used in the Bristol Myers Squibb CA2440008 protocol.

The information within this Pharmacy Manual is intended to supplement the CA2440008 clinical trial protocol.

2 SPONSOR CONTACTS

If concerns about the quality or appearance of the study drug, or questions regarding product preparation or handling arise, do not dispense the study drug and contact the Sponsor immediately:

General drug supply questions:

Sarah Burchell
Senior Manager, Trial Supplies Management
Bristol Myers Squibb
Email: sarah.burchell@bms.com

Questions regarding drug preparation and pharmacy manual content:

Peter Trimboli, PharmD, R.Ph
Director, Pharmacy Services

Bristol Myers Squibb
Email: Peter.trimboli@bms.com
Alternate Email: pharmacyservices@bms.com

Questions concerning clinical activities and clinical protocol content:

Medical Monitor	**Clinical Scientist/Co-Clinical Scientist**
Daniel Eiger, MD	Julia Spiridigliozzi
Sr. Clinical Trial Physician-Medical Monitor	Sr. Clinical Scientist
Bristol Myers Squibb Company	Bristol Myers Squibb Company
Telephone: +41 – (0)79-560-9762	Telephone : N/A
Email: daniel.eiger@bms.com	Email: Julia.Spiridigliozzi@bms.com

3 STUDY TREATMENT

All components and ancillary supplies used by the investigational site must align with materials as listed in the Investigator's Brochure or this Pharmacy Manual. Specific questions concerning use of a particular component which is not listed may be sent to: pharmacyservices@bms.com.

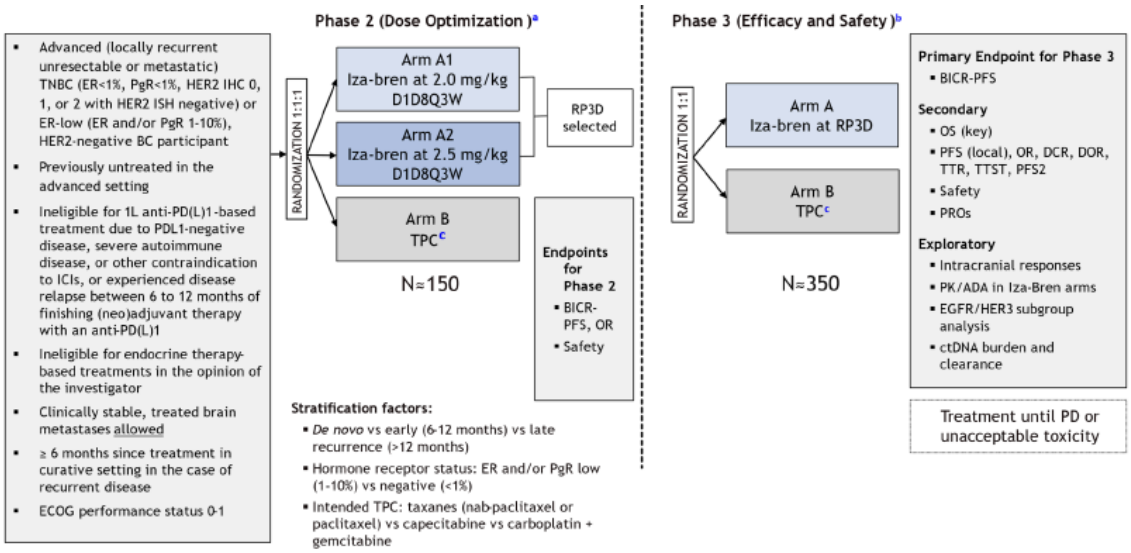
Diluents (i.e., sterile 0.9% sodium chloride), syringes, tubing for intravenous administration, Syringe pumps, Closed System Transfer Devices (if applicable), and filters should be sourced locally by the clinical site.

Overall Study Design:

Study CA2440008 is a Phase 2/3, inferentially seamless randomized, open-label, global clinical trial comparing the efficacy and safety of iza-bren monotherapy versus TPC (paclitaxel, nab-paclitaxel, capecitabine, or carboplatin plus gemcitabine) in approximately 500 participants with previously untreated, locally-advanced, recurrent inoperable or metastatic TNBC or ER-low, HER2-negative BC who are ineligible for an approved anti-PD-1 or an anti-PD-L1-based treatment combination and endocrine therapy-based treatments.

In Phase 2, participants will be randomized 1:1:1 to receive either iza-bren at the dose levels 2.0mg/kg (Arm A1) or 2.5mg/kg (Arm A2) on Days 1 and 8 in a 21-day cycle (D1D8Q3W) or the comparator of TPC (Arm B). After a dose is selected for Phase 3 (RP3D), the selected dose of iza-bren versus TPC will continue to be investigated to confirm efficacy and safety in the Phase 3 part of the study. In the Phase 3 part of the study, participants will be randomized 1:1 to receive either iza-bren RP3D (Arm A) or TPC (Arm B).

Schematic Study Design



[a] Data from the RP3D-containing experimental arm and Arm B will be carried over from Phase 2 to 3 part of the study (approximately 100 participants : Phase 2).

[b] Phase 3 part of the study will continue to randomize approximately 350 participants for a total of 450 participants needed for the Phase 3 analysis, but conside the 50 patients randomized to the sub-optimal experimental arm, the final total sample size will be 500 participants.

[c] TPC (paclitaxel, nab-paclitaxel, capecitabine, or carboplatin plus gemcitabine) is specified prior to randomization by the investigator.

Note: Carboplatin + Gemcitabine is an option only for participants with early recurrence.

Table 7.1-2: Study Arm(s)

Arm Title/Treatment	Intervention Description/ Dosage Levels	Route of Administration
Phase 2 Arms A1 and A2: Iza-bren	2.0 or 2.5 mg/kg on Days 1 and 8 of each 21-day cycle	IV infusion (see Section 7.1.2)
Phase 3 Arm A: Iza-bren	RP3D on Days 1 and 8 of each 21-day cycle	IV infusion (see Section 7.1.2)
Phases 2 and 3 Arm B: Nab-paclitaxel	100 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle	IV infusion per local SoC
Phases 2 and 3 Arm B: Paclitaxel	80-90 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle	IV infusion per local SoC
Phases 2 and 3 Arm B: Capecitabine	1000 to 1250 mg/m^2 BID on Days 1 thorough 14 of each 21-day cycle	Oral
Phases 2 and 3 Arm B: Carboplatin plus Gemcitabine	AUC of 2 mg/mL×min (carboplatin) and at 1000 mg/m^2 (gemcitabine) on Day 1 and Day 8 every 21 days	IV infusion per local SoC

NOTE: Always refer to the study treatment section of latest version of the CA2440008 clinical trial protocol for complete details on treatment and dosing assignments.

Izalontamab Brengitecan Dosing

(Refer to clinical protocol section 7.1.1 for information on pre-medications)

Phase 2, Arms A1 and A2: iza-bren will be administered at 2.0 and 2.5 mg/kg by IV infusion on Days 1 and 8 in a 21-day cycle.

Phase 3, Arm A: iza-bren will be administered at RP3D selected by IV infusion on Days 1 and 8 in a 21-day cycle.

The first IV infusion duration will be approximately 120 ± 10 minutes. If no infusion reactions have occurred during the first dose, subsequent infusions can be completed in approximately 60 to 120 minutes (infusion time may be extended if requested and agreed with the Medical Monitor).

After the first dose (Cycle 1 Day 1) and second dose (Cycle 1 Day 8), participants must be observed for at least 60 minutes following completion of iza-bren infusion for safety. For subsequent cycles, participants should be monitored for at least 30 minutes after the completion of the infusion. The infusion should be slowed or interrupted if the participant develops infusion-related symptoms or be permanently discontinued in case of severe infusion reactions. Treatment should be continued until disease progression or unacceptable toxicity, whichever occurs first.

The participant's weight at screening (rounded up to the nearest tenth) may be used to calculate the initial dose and following doses unless a weight change of more than ± 10% occurs.

The first dose of iza-bren will establish Cycle 1 Day 1. Day 1 of each subsequent cycle will similarly be established by iza-bren dosing. Iza-bren may be administered within a +3-day window after the planned dose. Dosing may be delayed due to AEs or administrative reasons. Day 1 dosing visits cannot be skipped (see clinical protocol sections 7.4 and 9.5).

Day 8 dosing cannot be administered earlier than 7 days after Day 1 dosing. Day 8 dosing cannot be delayed longer than 3 days. If the delay is longer than 3 days, Day 8 dosing should be skipped and a new cycle started when treatment is resumed. If Day 8 is skipped, the new cycle should not be started earlier than 21 days after the last dose of study intervention. If Day 8 dosing is delayed, a new cycle should not be started earlier than 14 days after the Day 8 dose.

Arm B: Chemotherapy Dosing

TPC options will be prepared and administered per local guidelines as follows:

- Nab-paclitaxel will be given by IV infusion at 100 mg/m^2 on Days 1, 8, and 15 in a 28-day cycle.
- Paclitaxel will be given by IV infusion at 80-90 mg/m^2 on Days 1, 8, and 15 in a 28-day cycle.
- Capecitabine will be given orally at 1000 to 1250 mg/m^2 BID on Days 1 through 14 in a 21-day cycle.
- Carboplatin and gemcitabine combination will be given by IV infusion at 1000 mg/m^2 (gemcitabine) and at AUC 2 (carboplatin) on Days 1 and 8 every 21 days.

For carboplatin, CrCl calculation is based on the Cockcroft-Gault formula and should include the most recent serum creatinine and most recent weight. Note: If calculation of the CrCl by the Cockcroft-Gault formula yields a result of > 125mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min. Carboplatin dose will be calculated based on the Calvert formula:

Carboplatin dose (mg) = target AUC × (CrCl+ 25)

(Refer to clinical protocol section 7.4 for Dosage modifications)

3.1 IZALONTAMAB BRENGITECAN (BMS-986507)

3.1.1 *Product Description*

Product Name	BMS-986507 for Injection, 120 mg/vial
Product description and Packaging	**Packaging:** 4 x vials in a white clinical carton, Each vial will be labelled with a clinical booklet label The outer carton will be labelled with a clinical booklet label **Appearance:** **White to light yellow cake appearance**, no signs of melt back. After reconstitution, a colorless to pale yellow liquid, with a slight opalescence, should not appear turbid.
Product Ingredients	Each vial contains 120 mg of BMS 986507
Storage Conditions	Store vials at 2 - 8 °C (36°F to 46°F), Protect from Light

3.1.2 *Handling and Dose Preparation*

As with all investigational products, care should be taken when handling and preparing BMS-986507. BMS-986507 should be handled following local regulation/guidelines. Handle investigational products using local engineering controls (e.g., biological safety cabinet, laminar or vertical flow hood) and following administrative controls in place for the preparation and administration of hazardous compounds (if so determined), to include standard procedures for the safe handling of sterile products applying aseptic techniques. Gloves are required. If BMS986507 solution comes in contact with the skin or mucosa, immediately and thoroughly wash with soap and water. For additional information, please refer to the Safety Data Sheet (SDS).

Visually inspect the drug product vial for particulate matter and discoloration prior to reconstitution. Once reconstituted, do not use the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles (see pharmacy manual section 5; study drug destruction). Do not shake the vial.

IV Infusion Dose Preparation

BMS-986507 can be further diluted in normal saline to a concentration from a range of **1 mg/mL to 9 mg/mL**.

a. Vial Reconstitution for IV Preparation

i. Reconstitute BMS-986507 120 mg/vial (IV); **add 10 mL of Sterile Water for Injection (SWFI) to the BMS-986507 120 mg vial.** Gently swirl the vial and wait approximately 2 minutes for dissolution, to prepare BMS-986507 reconstituted solution**, 12 mg/mL**. Confirm that powder is fully dissolved.

ii. The lyophilized vials are vacuum sealed, which causes a strong suction effect

when reconstituting. It may occur that when inserting a syringe containing, for example, 10cc of sterile water for injection into the vial stopper, the vacuum will pull the syringe plunger, drawing in the diluent forcefully. Allow the syringe plunger to be pulled by the vacuum until manual intervention is required. Due to this vacuum effect, it is recommended to **reconstitute one vial at a time using a single 10 mL aliquot.**

iii. Once a solution is obtained, gently swirl the vial again to ensure homogeneity of contents. DO NOT SHAKE the vial during or after reconstitution is completed.

b. IV Infusion Preparation

Materials

i. BMS-986507 IV infusions are compatible with the following:

- **Diluent(s) or infusion:** 0.9% sodium Chloride (NS; 0.9% NaCl)
- **Materials:** Infusion bags comprised of PVC, EVA, and Polyolefin. Infusion lines comprised of PE (Polyethylene), PUR (Polyurethane), or PVC (Polyvinylchloride). **In-line filters must be used for administration comprised of PES (polyethersulfone) or Nylon**
- **Concentration range**: Prepared infusions must be in a final concentration of/or between **1 mg/mL to 9 mg/mL.**

Preparation for infusion

ii. Calculate the volume (mL) of BMS-986507 required per weight-based dose (mg/kg) and transfer to an IV bag or syringe.

- Withdraw the calculated volume of BMS-986507 12 mg/mL solution from the reconstituted vial(s) and transfer to an IV bag or syringe.
- Further dilute BMS-986507 solution with 0.9% Sodium Chloride (NS) to prepare infusion in a final concentration ranging from **1 mg/mL to 9 mg/mL**
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of BMS-986507.
- **At all times immediately after dose preparation until dose administration is complete, the infusion bag must be protected from room light using a light protective sleeve**.

NOTE: Sites must contact Pharmacy Services prior to the use of CSTDs (Closed System Transfer Devices) to ensure compatibility between the device and the drug product by using the following email address: pharmacyservices@bms.com

The example below has been rounded per practical application of standard syringes used for drug preparation.

Preparation example at 2.5 mg/kg dose for a 72 kg patient:

Dose = 180 mg (72 kg x 2.5 mg/kg)
Concentration using a pre-mixed 50 mL infusion bag: 180 mg/ 50 ml = 3.6 mg/mL (within range)
Infusion preparation: 15 mL of BMS-986507 12 mg/mL solution added to 35 ml of 0.9 % Sodium Chloride (NS) = 50 mL total volume

(Note: When using a pre-mix normal saline infusion bag any overage should be removed in addition to drug volume required according to local site standard)

Administration method: Administer using a standard infusion pump over the protocol defined time

IV Infusion Dose Administration

BMS-986507 will be administered by IV infusion on Day 1 and Day 8 in a 21-day cycle. The first IV infusion duration will be 120 minutes ± 10 minutes; if no infusion reactions have occurred during the first dose, subsequent infusions can be completed in 60 to 120 minutes (unless agreed or requested by the investigator, time can be extended). **BMS-986507 for IV infusion should be administered using a compatible 0.2 micron in-line filter (see section 3.1.2). BMS-986507 should be dosed per subject assignment as outlined in the study drug dosing section of the clinical protocol CA2440008. The infusion bag must be protected from light during storage and administration.**

3.1.3 Product Storage and Stability

Storage for vials;

Vial containing BMS-987507 must be stored refrigerated at 2 - 8 °C (36°F to 46°F) and must be protected from light

Storage for Infusion;

The product does not contain a preservative. After preparation, prepared/dispensed BMS-986507 infusions may be stored:

at 2 - 8 °C (36°F to 46°F) for 24 hours with a maximum of 4 of the 24 hours at room temperature (including administration time). **Infusions must be protected from light.**

3.2 ADDITIONAL PRODUCT(S)

3.2.1 Product Description(s)

Product Description/ Class and Dosage Form	**Contents**	**Packaging**
Nab-paclitaxel Powder for dispersion for Infusion	100 mg/vial	1 vial per carton
Paclitaxel Concentrate for Solution for Infusion	100 mg/vial (6 mg/mL)	1 vial per carton
Capecitabine Film Coated Tablets	150 mg per tablet or 500 mg per tablet	Cartons containing blister packs of 60 tablets each
Carboplatin Concentrate Solution for infusion	10 mg/mL (450 mg/vial)	1 vial per carton
Gemcitabine Concentrate for Solution for infusion or Powder for solution for infusion	38 mg/mL or 1 or 2 g/vial	1 vial per carton
Pegfilgrastim solution for injection	6 mg/0.6 mL	1 vial per carton

These products may be provided by the sponsor or obtained by investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. **These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC).** Potency, packaging, and storage conditions may vary for China. Storage conditions will be indicated on label.

3.2.2 Handling and Dose Preparation

All product should be handled as per clinical label and according to local regulations, policies, and/or procedures outlining the proper handling for hazardous medications, if so determined.

For injectable drugs, care should be taken when handling and preparing product(s) for intravenous use. All products intended for parenteral use should be prepared using local regulation/guidelines regarding engineering (e.g., a biological safety cabinet, laminar or vertical flow hood) and the administrative controls required for the preparation and administration of hazardous compounds (if so determined), including standard procedures for the safe handling of agents applying aseptic techniques. For additional information, please refer to the Safety Data Sheet (SDS), **SmPC, or package insert.**

Inspect parenteral drug products visually for particulate matter and discoloration prior to administration. Product sourced locally or supplied by BMS (or designee) should be prepared as per the product specific package insert or SmPC. For additional information or with questions on the preparation and handling of products supplied by BMS that are not addressed by the SmPC or package insert please contact Pharmacy Services (pharmacyservices@bms.com).

3.2.3 Product Storage and Stability

Store product as per the package insert, SmPC, or clinical label.

4 SITE TEMPERATURE EXCURSIONS AND TRANSIT

Formulated products (e.g., vials, bottles, kits, etc.) must be stored under the proper conditions as listed on the product label. If any temperature excursions are encountered during on-site storage or during transport, please report these to BMS for assessment. Depending on the type of temperature excursion (on-site or in-transit), use the appropriate form and process for reporting the excursion to BMS, following instructions in the Bristol Myers Squibb, *Job Aid - Investigational Medicinal Product (IMP) Handling at Investigational Sites*.

Proper storage conditions must be maintained during any movements of inventory within an investigational site. Storage conditions must be maintained throughout transport with supporting documentation maintained at the site. Where controlled storage conditions (e.g., temperature, relative humidity, light, etc...) are required during transit, the necessary environmental controls must be in place to ensure that the drug product remains within the acceptable temperature range. Temperature monitoring devices such as min/max device should be implemented during transit.

5 PRODUCT RECEIPT, ACCOUNTABILITY, AND DESTRUCTION

RECEIPT

Shipment Inspection Instructions

1. Open box **immediately** upon receipt.
2. Carefully inspect shipment to ensure all of the supplies were received in good condition, and compare shipment contents to the packing slip, confirm that a correct quantity was delivered, and that all of the listed container ID numbers were received.
3. Sign and date (date of receipt) packing slip and file with study-specific documents.
4. Log all supplies from each shipment in the appropriate Clinical Supplies Inventory Form (provided separately).
5. *The following apply only if an IRT (Interactive Response Technology) system is used*
    a. Log into the IRT system to acknowledge receipt and condition of the supplies.
    b. If receipt of not confirmed in the IRT system, these supplies will *not* be available for dispensing.
    c. For more information, please consult the IRT user manual. For studies which require resupply, the IRT system will automatically coordinate re-supply shipments for all drugs supplied by IRT system to the site.

NOTE: Please maintain the IRT system confirmation emails and other relevant correspondence with your study-specific documents. If you have any issues with not receiving all your IRT system confirmations/emails, then please contact the IRT system helpdesk or your study monitor immediately.

ACCOUNTABILITY

As per the clinical protocol and BMS policy, it is the responsibility of the investigator to ensure that a current disposition record of investigational product accountability and reconciliation is maintained at each investigational site where study drug is inventoried and dispensed.

In addition, records or logs must comply with applicable country/local regulations and guidelines and should include:

- Amount received and placed in storage area
- Amount currently in storage area
- Label ID number or batch number
- Amount dispensed to and returned by subject, including unique subject identifiers
- Amount transferred to another area/site for dispensing or storage
- Non-study disposition (e.g., lost, wasted)
- Amount destroyed at investigational site, if applicable
- Amount returned to the Sponsor, if applicable
- Dates and initials of person responsible for Investigational Product (IP)
- Dispensing/accountability, as per the Site Signature and Delegation Log.

The Sponsor (or designee) can provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

DESTRUCTION

Study Drug Destruction

Study drugs (those supplied by BMS or sourced by the site/investigator) can be destroyed on site if local policies allow it. It is the Investigator's responsibility to ensure that arrangements have been made for the disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate documentation of the disposal must be maintained by the investigational site. **Unused investigational product may be destroyed only following BMS (or designee) inspection, reconciliation, and approval by the responsible Study Monitor (or designee)**.

If required by local country/hospital regulations, drug can be returned to an off-site drug destruction vendor but should only be completed with your Study Monitor (or designee) while they are on site. All drug destruction whether performed on or off site should be documented using the Investigational Product Return Form or local form if approved by Study Monitor (or designee).

Product Quality

Issues that call into question IMP safety, purity, potency, quality and identity (e.g., evidence of suspected tampering of product) must be reported as soon as possible to your study Clinical Trial Monitor and/or Clinical Trial Manager or designee. Report an issue or concern with all BMS supplied IMP and non-IMP suspected to have occurred before the product was transferred to the responsibility of the clinical site (e.g., during manufacturing, packaging and labeling, storage, and/or distribution). For detailed reporting instructions, please refer to the Bristol Myers Squibb, *Job Aid - Investigational Medicinal Product (IMP) Handling at Investigational Sites*.

This includes suspected quality issues for IMP device/drug combination products, and medical devices released for clinical use in Clinical Trials and comparator/marketed product used as an IMP in a clinical study sourced by BMS or vendor.

In the event of a suspected product quality issue, the immediate action to be taken by site is to quarantine the affected product. Do not dispose of the product unless retention presents a risk to personnel (e.g., cytotoxic, risk of injury from broken glass or sharps).

6 IRT AND DATA COLLECTION

For studies utilizing an IRT system, study drug will be assigned to participants via the IRT system. Separate training materials will be sent to each site with regard to IRT usage. All changes, manual drug assignments, and product dispositions must be documented within the IRT system as outlined in the separately provided IRT Site User Manual.

For all studies, site personnel will have the overall responsibility of coordinating the collection of data, completing the electronic Case Report Form (eCRF) and dosing log, and for ensuring that adequate and accurate participant records are available for all procedures for each participant, as required by the clinical team.

The data reported in the eCRF must be in agreement with the information in the participant's source documents (i.e., medical records).

If required, source documents must provide documentation of all data points in eCRF, to include but not limited to: drug preparation details, date/time of study drug administration, dose of study drug delivered, site of administration, date and location of assessment.