PRODUCT CODE: SAR446523

STUDY CODE: TED18162

STUDY NAME: A first-in-human, open-label, Phase 1 study to evaluate the safety, antitumor activity, pharmacokinetics, and pharmacodynamics of subcutaneous SAR446523, an anti-GPRC5D ADCC-enhanced monoclonal antibody, in participants with relapsed/refractory multiple myeloma

Version N°1.0 Date: 08-JUL-2024

PRODUCT MANAGEMENT MANUAL

DOCUMENT HISTORY

Version	Date	Section	Description	Author
1.0	08-JUL-2024	All	Initial Release	CSSM

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF EQUATIONS

ABBREVIATION LIST

ADCC	Antibody-Dependent Cellular Cytotoxicity
AoD	Acknowledgement Of Destruction
AoR	Acknowledgement of Receipt
AxMP	Auxiliary Medicinal Product
C	Cycle
CAPA	Corrective And Preventive Actions
CSTD	Closed System Transfer Device
CxDx	Cycle X Day X
CSCSM	Clinical Supply Chain Study Manager
D	Day
DL	Doses Levels
DP	Drug Product
Fc	Fragment Crystallizable region
FDA	Food and Drug Administration
FDS	Formulated Drug Product
GPRC5D	G-Protein-coupled Receptor, class C, group 5, member D
GTIN	Global Trade Item Number
IMP	Investigational Medicinal Product (a.k.a. kit or Product)
IRR	Injection Related Reaction
IRT	Interactive Response Technology
ISF	Investigator Study File
IV	IntraVenous
MAD	Maximum Administered Dose
MTD	Maximum Tolerance Dose
ORR	Overall Response Rate
PO	Per Os
PP	PolyPropylene
QW	Once a Week
Q2W	Once every 2 Week
RDR	Recommended Dose Range
ROW	Rest Of the World
RP2D	Recommended Phase 2 Dose
SC	SubCutaneous
SFV	Syringe Fill Volume
TE	Temperature Excursion
TER	Temperature Excursion Report
TMD	Temperature Monitoring Device
Tx	Treatment
US	United States
WFI	Water For Injection

Below instructions refer herein to the products/materials supplied by Sponsor.

This Product Management Manual is the reference regarding instructions for management of products. It could not be replaced by a site document.

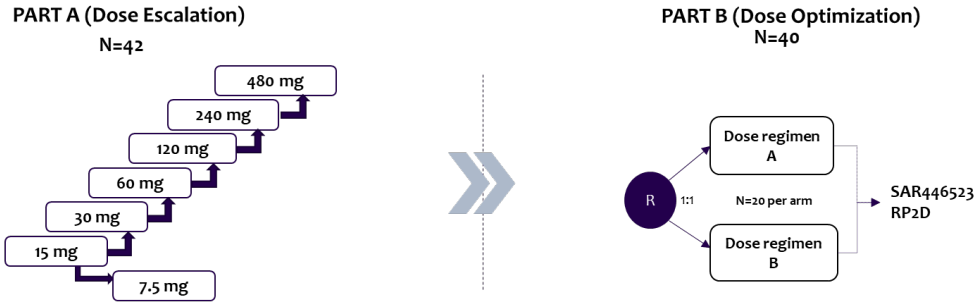
1. PROTOCOL STUDY DESIGN

This is a First In Human (FIH), multicenter, open label, Phase 1 study of SAR446523 conducted in patients with RRMM.

The study consists of two parts:

- Dose escalation (Part A): In this part, up to 6 Doses Levels (DLs) of SAR446523 monotherapy will be explored to determine the MAD, MTD, and RDR of 2 dose regimens which will be tested in the dose optimization part. During Part A, 6 doses of SAR446523 will be tested (DL 1 to DL 6) with the possibility to deescalate to a DL-1. In dose escalation part, the maximum dose increment between DLs is 100%. Based on the Study Board's decision, the dosing schedule may be adjusted to expand a dosing cohort to further evaluate safety, PK, PDy findings and antitumor activity at a given DL or to add cohorts to evaluate additional DLs/dose regimens. The study procedures for these additional participant(s)/cohort(s) will be the same as those described for other study participants/cohorts.
- Dose optimization (Part B): In this part, participants will be randomly assigned in a 1:1 ratio using IRT to either one of the chosen dose regimens of SAR446523 monotherapy (determined from data coming from Part A). The RP2D will be determined by the Study Board based on the efficacy, including the primary endpoint of ORR (assessed as per Investigator) and other secondary endpoints such as overall safety profile, PK and PDy, and biomarkers.

Figure 1 - Graphical study design



SAR446523 dosing schedule: **15-480 mg SC QW C1, Q2W thereafter of every 4 week-cycle**
Dose escalation: *cohort of 3-6 patients*

Abbreviations: C1 = cycle 1; N= number of participants; QW = once a week; Q2W = once every 2 weeks; RP2D = recommended phase 2 dose; SC = subcutaneous.

2. DESCRIPTION OF PRODUCTS

For non-modified marketed products (AxMPs are only concerned, refer to section 2.2), no preparation and administrations instructions will be provided in this document. Please refer to commercialized leaflet for instructions.

Product leaflet/Summary of Product Characteristics (SMPC) in local language are available in eTMF 02,01,11. Site Monitor is to retrieve them and provide them to site(s).

The Table 1 list the IMP used during the study.Table 1 - Investigational medicinal product(s) administered

Table 1 - Investigational medicinal product(s) administered

Intervention name	SAR446523
Intervention description	SAR446523 QW for Cycle 1 and Q2W thereafter
Dose formulation	Powder for solution for injection
Unit dose strength(s)	250 mg
Dosage level(s)	DL 1 to DL 6
Route of administration	SC

Abbreviations: DL = dose level; IV = intravenous; PO = per os; QW = once weekly; Q2W = once every two weeks; SC = subcutaneous.

2.1 Investigational Medicinal Product (IMP)

Nature of IMP(s)

SAR446523 is a monospecific monoclonal antibody targeting human GPRC5D with enhanced ADCC Fc effector function intended for the treatment of Refractory/Relapsed Multiple Myeloma. The drug product is a lyophilized powder for solution for injection at a 250 mg/vial strength. The DP is intended for SC administration in Phase I clinical trial.

SAR446523 is a lyophilized powder in a 20 mL Type 1 clear glass vial (ISO 20R). To ensure an extractable volume of 2.5 mL of the 100 mg/mL reconstituted solution (250 mg extractible), each vial has been overfilled at 6.39 mL of the 50 mg/mL FDS (319.5 mg of SAR446523) before freeze-drying. The composition of the Drug Product is described in the Table 2.

Route of administration: Subcutaneous (SC) administration.

SAR446523 will be provided by the Sponsor.

The Investigational Medicinal Product (IMP) vials **should not be shaken or dropped**. The IMP vials should not be frozen or exposed to temperatures over 25°C. Upon dilution in diluent, the vial or the syringe should not be shaken, dropped or exposed to temperature over 25°C. **Pneumatic tubes for transfer are not allowed.**

Table 2 - SAR446523 Drug Product Composition

Components	Composition of liquid IMP (per vial)	Function
SAR443523	250 mg	Drug substance
Histidine[1]	7.758 mg	Buffering agent
Sucrose	200 mg	Cryoprotectant
Polysorbate 80	2.50 mg	Surfactant/stabilizing agent
EDTA disodium dihydrate	0.0185 mg	Chelator

[1]Mixture of L-histidine and L-histidine hydrochloride monohydrate. Content reported as mg of L-histidine free base (MW 155.16 g/mol), assuming a 20 mM and 3.88 mM L-histidine for 100 mg/mL and 19.4 mg/mL solutions respectively.

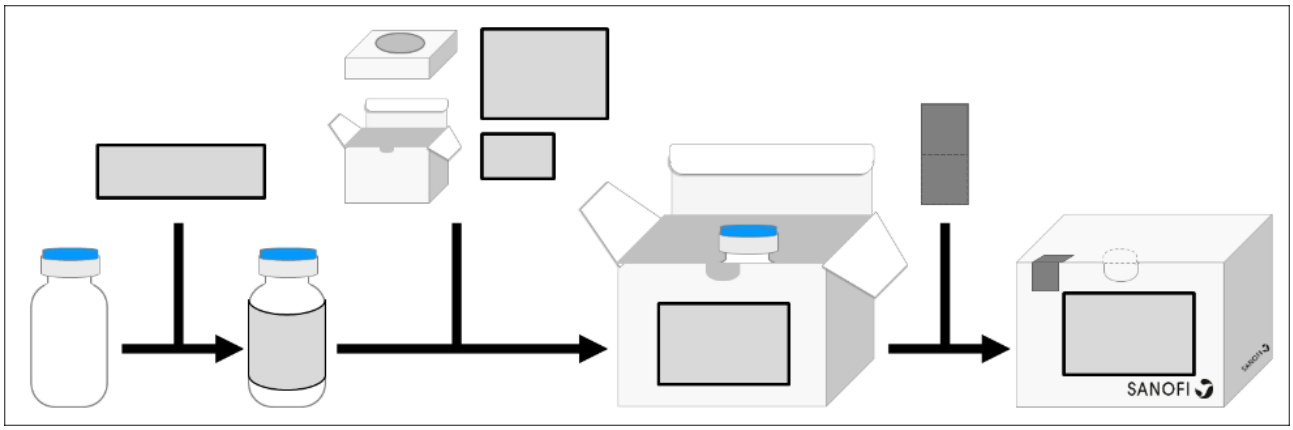
Packaging:

SAR446523 drug product (DP) is a lyophilized powder for solution for injection in 20R ISO vial (1A1).

Each vial is labelled with a booklet label and 1 vial is put in a box. The box is labelled with both a booklet label (fixed mentions), a single label (variables mentions) and tamper sealed.

The size of box is 84 x 53 x 33 millimeters.

Figure 2 - Schema of packaging: SAR446523



Note 1 : The labelling text may not be an exact representation.

Vials and boxes are labelled with multilingual booklet label covering all the countries involved in the study.

Note 2 : Pictures/photos are for illustration only, and may not be an exact representation of the product/label

Handling of IMPs (e.g., storage, traceability) is covered in applicable sections.

Labelling:

The label of SAR446523 will include the following pictograms as presented below:

Pictogram		Explanation
REF	REF	Study Code *
SN	SN	Treatment/Dose Number
LOT	LOT	Packaging/Batch number
	EXP	Expiry date
		Investigator name
#		Subject number

* Terminology “Trial Reference” may also be used in some documents.

Note 1: The labelling text may not be an exact representation.

Note 2: Pictures are for illustration purposes only and may not be an exact representation of the product/label.

The data matrix applied on Sanofi’s Investigational Medicinal Products is compliant with the GS1 Standard for the Identification of Investigational Medicinal Products.

GS1 Data matrix is a barcode that contains Global Trade Item Number (GTIN), Trial Reference, Packaging/Batch Number and, if applicable, Treatment Number. In case your clinical site uses the GS1 code, the GS1 Data matrix can be used to record the kits in your system by scanning them. The inventory logs must be available for Site Monitor for review and a copy must be in the ISF.

Figure 3 - SAR446523 250 mg labels example

2.2 Auxiliary Medicinal Product (AxMP)

AxMP will not be supplied centrally. For more information, please refer to the study protocol.

The order of premedication administration is the following: montelukast, dexamethasone, acetaminophen/paracetamol, and then diphenhydramine.
SAR446523 IRRs/ISRs premedication is to be given prior each administration of SAR446523 for the first 4 administrations in Cycle 1. After 4 administrations, the continuation of this premedication (except for montelukast which is to be administered only on Cycle 1) is to be left as per Investigator choice based on previous episodes of IRRs/ISRs. This premedication is to be given 15 to 60 minutes prior to SAR446523 administration, except for montelukast. This premedication comprises montelukast 10 mg PO (or equivalent) given 2 hours prior to the first SAR446523 administration (at C1D1, C1D8, C1D15, and C1D22 only), acetaminophen (paracetamol) 650 to 1000 mg PO or IV, diphenhydramine 50 mg PO (or equivalent) or diphenhydramine 25 to 50 mg IV (or equivalent), dexamethasone 20 mg PO or methylprednisolone 100 mg IV. Please refer to the protocol for more information.

Table 3 - Auxiliary medicinal product administered

Intervention name	Montelukast 10 mg PO	Dexamethasone PO	Methylprednisolone IV	Diphenhydramine PO or IV	Acetaminophen PO or IV
Intervention description	PO	PO	IV	PO or IV	PO or IV
Dose formulation	Film-coated tablet	Tablet	Powder for solution for injection	Tablet or solution for IV administration	Tablet or solution for IV administration
Unit dose strength(s)	10 mg	20 mg	20 to 120 mg	50 mg (tablets and solution)	650 to 1000 mg
Dosage level(s)	10 mg, 2 hours prior SAR446523 administration on Cycle 1 Day 1, 8, 15, and 22.	20 mg, 30 to 60 min prior SAR446523 administration on Cycle 1 Day 1, 8, 15, and 22 (except for participants in SAR446523 + dexamethasone arm in Part C, where dexamethasone is administered as IMP).	100 mg, IV 30 to 60 min prior SAR446523 administration on Cycle 1 Day 1, 8, 15, and 22 if PO dexamethasone not feasible (except for participants in SAR446523 + dexamethasone arm in Part C, where dexamethasone is administered as IMP).	50 mg, PO or 25 to 50 mg IV, 15 to 60 min prior SAR446523 administration on Cycle 1 Day 1, 8, 15, and 22.	150 to 1000 mg, PO or IV, 15 to 60 min prior SAR446523 administration on Cycle 1 Day 1, 8, 15, and 22.
Route of administration	PO	PO	IV	PO or IV	PO or IV

Abbreviations: IMP = investigational medicinal product; IV = intravenous; PO = per os.

2.3 Material used for product preparation and/or administration.

Examples of ancillaries: preparation and administration ancillaries/devices (infusion pumps, syringes, needles, etc.)
All these materials are provided locally (by sites or by the IPMs).

Table 4 - List of materials for reconstitution and/or administration

Material	Composition	Description
Syringes	Polypropylene (PP)	Disposable syringes of appropriate size (Luer-Lock recommended)
Needles	Stainless steel	21G needles for reconstitution and withdrawal. 24G to 27G for injection
CSTD BD Phaseal Optima	Polypropylene[a]	Protector-P20-O, vial adaptator, ref: 515064
	Polypropylene[a], stainless Steel[a], silicone[a]	Injector-N35-O, syringe adaptator, ref 515052
	Polypropylene[a]	Connector-C35-O, connection to needle, ref 515070

[a]in direct contact with product, according to supplier documentation

3. INITIAL SHIPMENT OF PRODUCTS

Once all regulatory requirements are met, the first product shipment to a study site may be generated.

To initiate the first shipment, the study site has to be activated in IRT database by a Sponsor study team member.

The Sponsor sends an initial supply of SAR446523 to sites after the site is activated in IRT and when the first study participant screened.

All products are shipped in qualified boxes that ensure correct temperature conditions as per labelled storage conditions.

Site staff signs the Acknowledgment of Receipt section of the form included in the shipment and acknowledge the shipment in IRT immediately upon receipt.

4. RESUPPLY OF PRODUCTS

Resupply shipments are sent throughout the study as necessary according to IRT set up. All shipments should be immediately confirmed in IRT upon receipt.

It is essential to register receipt of products (as per section “Receipt of Product”) in IRT Acknowledgement of Receipt function and to always register medication allocation to the study participant in IRT to ensure an adequate supply of IMP and AxMP (AxMP if serialized meaning: labelled with a treatment number) at the clinical site. The AxMPs are not included in the study, as they are not supplied globally.

IRT automatically processes re-supply shipments for the clinical sites to cover upcoming study participants visits and/or when the level of inventory for buffer stock goes below the trigger level (pre-determined by the IRT set up).

Nevertheless, site staff should physically check if there is sufficient product supply for upcoming study participants. If there is a concern about the level of inventory at the clinical site, please contact the Sponsor’s Site Monitor.

5. RECEIPT OF PRODUCTS

Upon receipt of a shipment at site, the study site personnel responsible for products management (e.g., Investigator/Pharmacist or a Delegate) should unpack the shipping box as soon as possible and check the content of the package for any issues with the shipment such as Temperature Excursions, incorrect number of kits or damaged kits.

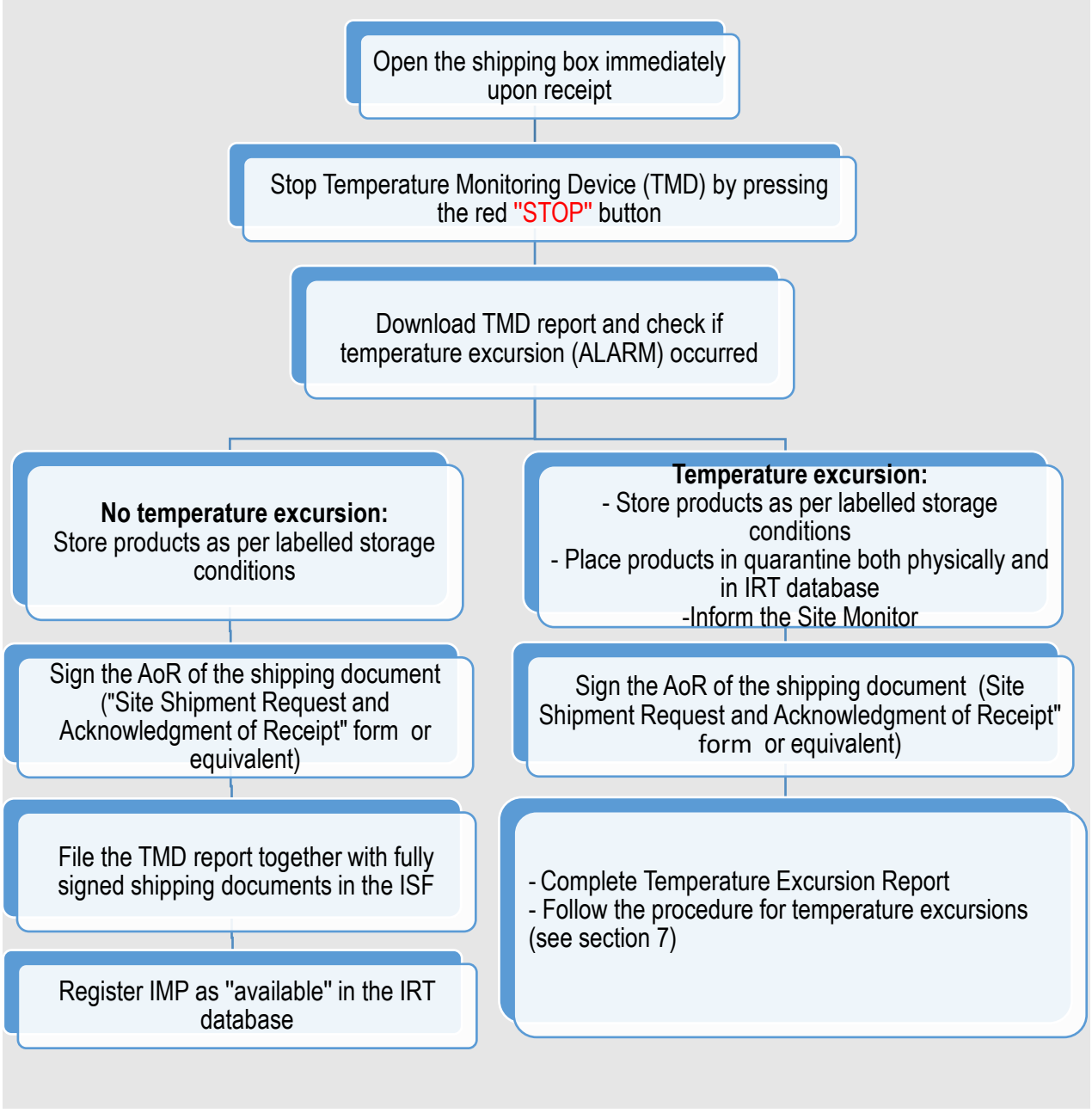
In case of damaged products, please refer to section 13 on Product Complaints.

The study site personnel responsible for products management must verify that the shipment was received as stated on the “Site Shipment Request and Acknowledgement of Receipt" or equivalent form included in the shipment box (batch number, quantity, treatment number and expiry date if applicable) by signing and dating the AoR form. Completed original forms should be filed and maintained as part of the ISF to document the receipt of the products.

Upon receipt of a shipment the following procedures are to be followed by the study site personnel responsible for products management.

5.1 IRT receipt procedure

Figure 4 - Acknowledgement of Receipt procedure at site with IRT.



Any cases of missing temperature record (temperature data not available such as missing TMD) also need to be reported to the Sponsor. Site staff will have to complete TER.

6. STORAGE AND TEMPERATURE MONITORING CONDITION OF PRODUCTS

The study site must have suitable facilities for product storage. Products must always be stored in a secure location in accordance with local regulations, labeling specifications, policies and procedures.

The Investigational Medicinal Product (IMP) vials **should not be shaken or dropped**. The IMP vials should not be frozen or exposed to temperatures over 25°C. Upon dilution in diluent, the vial or the syringe should not be shaken, dropped or exposed to temperature over 25°C. **Pneumatic tubes for transfer are not allowed.**

IMP name	Storage conditions
SAR446523	Between +2°C to 8°C Protected from light

The site must monitor the refrigerator temperature using a calibrated TMD or a validated temperature monitoring system.

Temperature monitoring records must be available and easily retrievable for monitoring activities all along the study duration and stored at the study site. If you use electronic data logger, readable extract should be available.

Then, in case raw data must be printed (such as logs related to a temperature excursion), they should be signed and dated for validated central monitoring system & reports.

Any changes to the site storage of the products (such as pharmacy location move, use of a different refrigerator, change in TMD) or change in site personnel responsible for management of products throughout the study must be reported to the Sponsor's Site Monitor and fully documented in the ISF, Pharmacy section (if applicable).

I**n case of products supplied by sites**, refer to the product information (commercialized leaflet) for required storage conditions.

7. TEMPERATURE EXCURSION MANAGEMENT OF PRODUCTS

7.1 Temperature Excursion

For the receipt of products please refer to Figure 4 in section 5.

If a Temperature Excursion occurs:

- The affected products must be placed in quarantine immediately with a clear sign of "quarantined" and clearly separated from the rest of the supplies. In addition, the affected products must be stored under proper conditions as per storage requirements and temperature monitored,
- For studies with IRT, additionally, the affected kits must be placed in ''quarantine'' status in the system, to avoid potential allocation to study participant. Please refer to section 8 and to the IRT documentation for more details on this action,
- The Sponsor's Site Monitor must be informed about the Temperature Excursion within one business day of discovery.

Any cases of missing temperature record (temperature data not available such as missing TMD) also need to be reported to the Sponsor. Site staff will have to complete a TER.

In order to report the Temperature Excursion, the study site Investigator/Pharmacist (or Delegate) provides the Sponsor's Site Monitor with the following information:

- Fully completed TER in WORD format (Appendix I)
- Temperature Logs provided must cover:
  - in case of Temperature Excursion during shipment: temperature records until receipt on site and the placement in the appropriate storage conditions,
  - in case of Temperature Excursion during storage on site: at least, the last value before the Temperature Excursion occurred and the first value after the Temperature Excursion period, showing the temperature within the range (under correct storage requirements).

Products affected by a Temperature Excursion must not be dispensed to study participants under any circumstances. The concerned products must stay quarantined until the Sponsor has completed the assessment to determine whether there is a quality impact on the products or not. Refer to section 8 Products quarantine.

For IRT MANAGED PRODUCTS:

- If the Sponsor assesses that there is NO IMPACT on the quality of products, the status of "quarantined" products in IRT has to be changed to "available". The products can be available again for further dispensing to study participants,

If the Sponsor assesses that there is AN IMPACT on the quality of products, the status in IRT has to be changed to "damaged". Kits must remain physically quarantined and kept in a quarantined area until authorization for destruction is received from the Sponsor.

- A comment must be made on the Product Inventory Form (Appendix C) at site level that kits were "affected by Temperature Excursions and not fit for use".

Documentation related to Temperature Excursions (TER, relevant temperature records, Sponsor's assessment) are filed in the ISF.

Note: As AxMPs are supplied by the site, it must be stored as per product information and labelling, handled per institutional policies and procedures. No assessment of Temperature Excursions is performed by the Sponsor.

Refer to section 9.4 for the stability of prepared IMP.

7.2 Rounding rules

Rounding rules are defined according to international rules for rounding. All temperature readings are rounded to the nearest whole number prior to application of Temperature Excursion specifications.

In all situations, temperature rounding rules apply as follows:

Rules	Examples
If the figure after the decimal point is 5 or greater, the result is rounded up to the next higher digit and the decimal is removed.	1.5°C becomes 2°C, 14.6°C becomes 15°C, 29.8°C becomes 30°C - 14.5 becomes - 15°C - 30.6 becomes - 31°C
If the figure after the decimal point is less than 5, the result is rounded down and the decimal is removed.	8.4°C becomes 8°C, 0.4°C becomes 0°C - 14.4°C becomes – 14°C

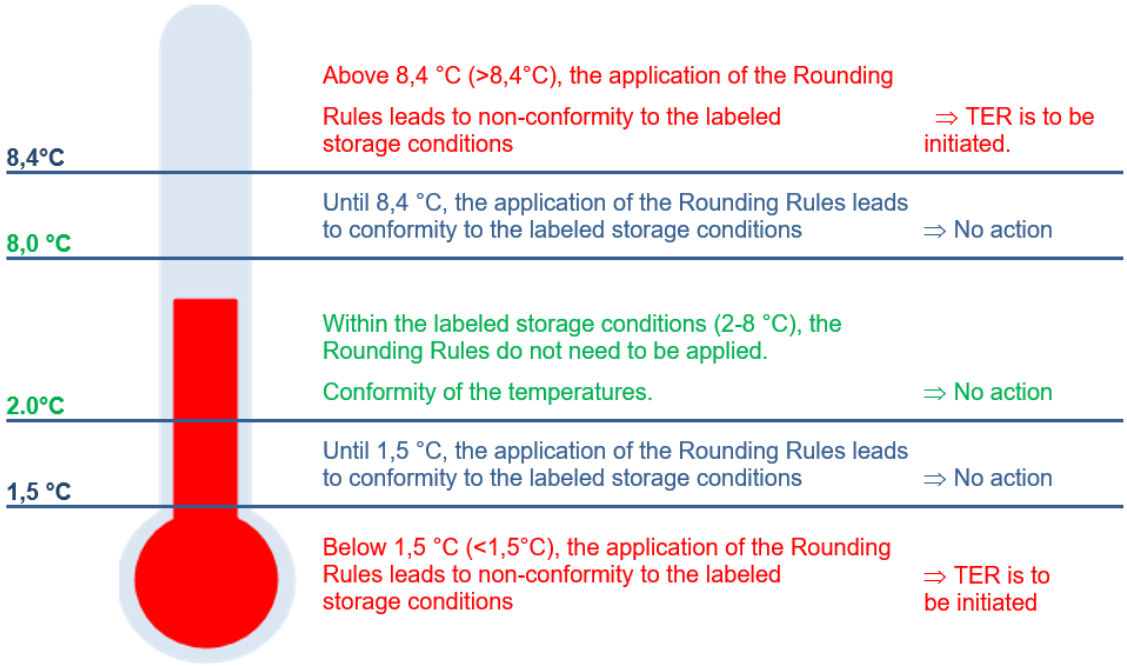
Note: Rules apply if there are 2 digits after the decimal point (e.g., 1.45°C becomes 1°C). The study site personnel should apply the rounding rules prior to the application of the specifications:

First, apply the rounding rules for TE decision making.

7.3 Temperature Excursion for cold chain products

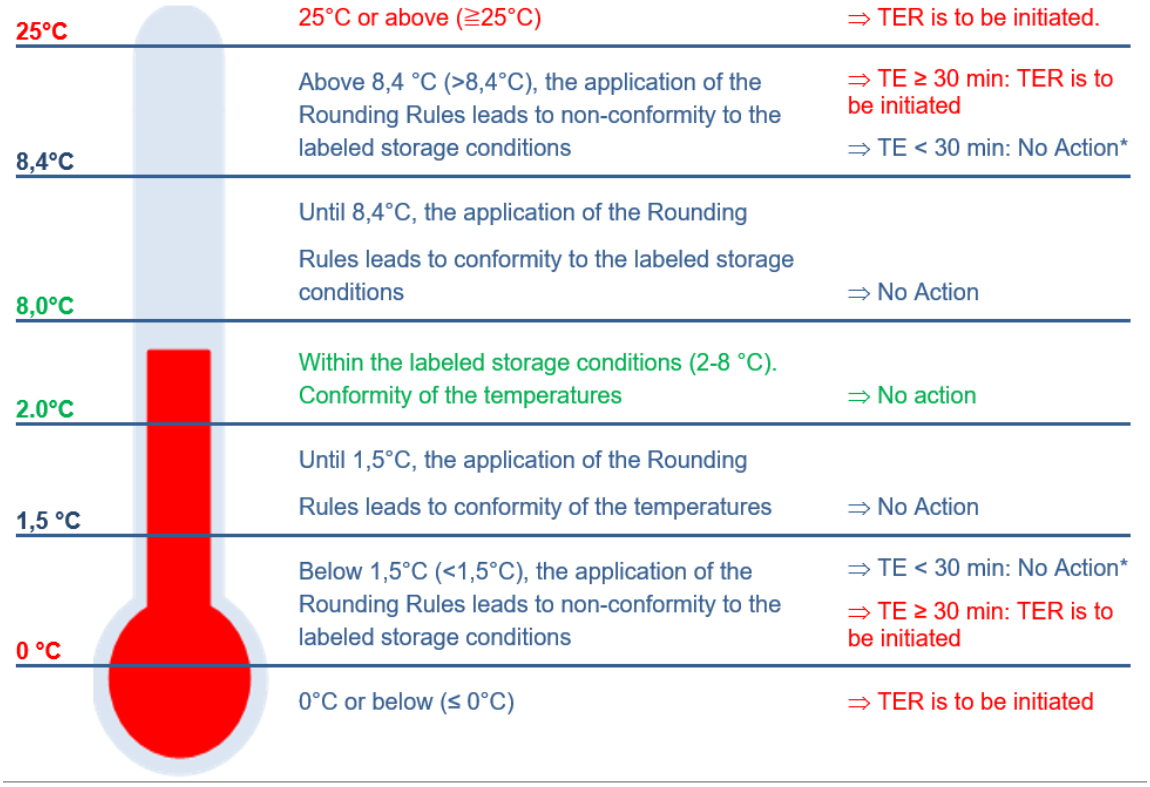
Any non-compliant temperature must be reported as per instructions below:

7.3.1 Temperature Excursion during shipment for products requiring refrigerated storage (products labeled between 2°C and 8°C)



7.3.2 Temperature Excursion during storage at clinical site only* for products requiring refrigerated storage (products labeled between 2°C and 8°C)

*Except if stated differently in provided instructions (e.g., unstable product)



*Frequent occurrences of such events less than 30 minutes (can be cumulative) in a day but equal or more than 3 in 1 month, need further investigation and if applicable, to implement a Corrective Actions and Preventive Actions (CAPAs) when the root-cause is identified.

8. PRODUCTS QUARANTINE

Products that have been placed in quarantine for any reason are stored in accordance with the storage conditions:

- Cold chain: a bag or box clearly signed with “quarantined” in a separate area of the refrigerator/freezer designated for quarantined products or in a different refrigerator for cold chain products. If the quarantined products are stored in a different refrigerator, an additional Temperature Log must be maintained for this refrigerator,
- Until the impact on the products is assessed by the Sponsor, quarantined products must not be dispensed to study participants under any circumstances nor destroyed.

If confirmation is received by the Sponsor that the quarantined products are considered safe for administration, the products can be returned to the released stock area for further dispensing to study participants.

For IRT managed product, the quarantined kits are still considered as part of the site’s stock (even if they cannot be allocated to any study participant). Therefore, no automatic shipment to replace the affected kits will be triggered as long as kits are under quarantine status. In that case, contact Site Monitor. Please refer to the IRT Manual for more details.

9. TREATMENT ALLOCATION, PREPARATION, DISPENSATION AND ADMINISTRATION

9.1 Treatment allocation

Reminder, there is no randomization in part A. Patient are involved in the DL being included. For part B a randomization is performed.

Before enrolling a study participant the Investigator or Delegate should ensure that the participant fulfills all Inclusion/Exclusion criteria.

A randomized subject is defined as a subject who signed the informed consent, fulfills all inclusion/exclusion criteria and has been assigned a randomization number and treatment number on Day 1, in a preplanned order, following the randomization list generated by IRT.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once only. For more precisions, please refer to the study protocol.

In part B, the participants are randomized in an open label fashion to receive either one of chosen dose regimens of SAR446523 monotherapy in a 1:1 randomization ratio.

Table 5 - Schedule of IMP dispensation and administration

	Intervention period (28 days per cycle)					
	Cycle 1				Cycle 2 and beyond	
Visit	D1	D8	D15	D22	D1	D15
Study treatment administration						
SAR446523 administration	X	X	X	X	X	X
SAR IMP dispensation (Number of kits allocated by IRT)	Depending on DL (see Table 6)					

Table 6 - NUMBER OF VIALS OF SAR446523 250 MG PER DOSE LEVEL

Dose Level	Dose (mg)	Number of SAR446523 vial(s) (250 mg/vial)
DL-1	7.5	1
DL1	15	1
DL2	30	1
DL3	60	1
DL4	120	1
DL5	240	1 or 2[a]
DL6	480	2

[a]The number of vials allocated will differ if the site has declared that it is using the authorized CSTD.

Intermediate doses may be defined during the course of the study. In this case, Equation 1 can be used to calculate the volume of IMP associated with a given dose (mg). IMP concentration is dependent on the DL range, refer to Table 10.

IRT system will be used to allocate treatment kit(s) to the study participants. The Investigator or Delegate will dispense the study participant with the treatment kit(s) allocated by IRT during the allocation visits.

A treatment kit cannot be administered to a study participant if the kit is not allocated via an IRT transaction, unless confirmation is given by the Sponsor prior to treatment administration.

Treatment kit replacement: If the treatment allocated to a study participant must be replaced (e.g., due to damaged IMP, etc.), the Pharmacist or Delegate will allocate a replacement IMP kit for this study participant by using the IRT functionality.

Study Participant replacement:
Patient replacement is not planning to replace the randomized patients who have / not have started their treatment, or who prematurely ends their treatment period for whatever reasons.

The Product Accountability Form must be updated accordingly after each treatment allocation. Consistency will be checked by the Study Site Monitor between the treatment kit number allocated and the treatment kit number reported on the Product Accountability Form.

After allocation, a dispensing process has to ensure the correct product, kit number, correct dose is dispensed to the study participant.

9.2 Infusion materials or other supporting material with compatibilities

Any materials not listed in Table 7 and Table 8 need to be submitted and approved to the Sponsor before use.

Table 7 - List of materials for reconstitution

Material	Composition	Description
Syringes	Polypropylene (PP)	Disposable syringes of appropriate size (Luer-Lock recommended)
Needles	Stainless steel	21G needles for reconstitution and withdrawal. 24G to 27G for injection

Table 8 - List of materials for preparation of the syringes and/or administration

Material	Composition	Description
Syringes	Polypropylene (PP)	Disposable syringes of appropriate size (Luer-Lock recommended)
Needles	Stainless steel	21G needles for withdrawal. 24G to 27G for injection
CSTD BD Phaseal Optima	Polypropylene[a]	Protector-P20-O, vial adaptator, ref: 515064
	Polypropylene[a], stainless Steel[a], silicone[a]	Injector-N35-O, syringe adaptator, ref 515052
	Polypropylene[a]	Connector-C35-O, connection to needle, ref 515070

[a]in direct contact with product, according to supplier documentation

The use of a CSTD is not recommended for the following mains reasons:

- The SAR tested is not cytotoxic,
- The SC route of SAR administration does not require CSTD use[1]
- Loss of IMP in the dead volume of the device,
- Frequent contamination with subvisible particles[2] and no in-line filter for SC administration.

Nevertheless, if internal guidelines of a given study site requires it, the CSTD listed in Table 8 is the only tested and compatible with SAR446523 within the 7.5 mg – 480 mg range of SAR446523 dose per SC administration. **For reconstitution, CSTD is not allowed.**

9.3 Preparation steps

Refer to the Preparation Worksheet if applicable. The IMP Preparation Worksheet is an example of the suitable preparation documentation and is provided to ensure preparation is well documented. It is also a guide for the preparation steps.

9.3.1 Procedure overview

The SAR446523 solution for SC administration is prepared for each participant based on their assigned dose level. SAR446523 powder for solution for injection is used to prepare SAR446523 solution for SC administration in a multi-step procedure which is described in detail for doses from 20 mg to 480 mg in Section 9.3.2.3.2 Reconstitution of Lyophilizate for SC administration at 100 mg/mL. For doses lower than 20 mg, the procedure is described in Section 9.3.2.3.1 Reconstitution of Lyophilizate for SC administration at 19.4 mg/mL. Table 9 provides the limiting parameters for SC administration of SAR446523.

1 NIOSH List of Antineoplastic and Other Hazardous Drugs in Healthcare Settings, 2016

2 Characterization of Silicone from Closed System Transfer Devices and its Migration into Pharmaceutical Drug Products. J. Pharm. Sci. 113 (2024) 419−426

Table 9 - Limiting parameters for SC administration

Items	Description
Concentration in syringe	19.4 or 100 mg/mL pending dose range
Volume injected	From 0.2 to 4.8 mL (up to 3 injections and up to 2.5 mL per injection) by manual push
Stability	4 hours at room temperature (15-25°C) from the reconstitution to the end of injection

9.3.2 SAR446523 preparation for SC administration

9.3.2.1 Dose calculation for SC administration

Dose levels and treatment regime for study participants is as follows in Table 10.

Table 10 - Dose levels and treatment regime for SC administration

Study Treatment	Dosage level(s)	Route of Administration	IMP concentration	Administration Volume	Number of injection
SAR446523	7.5 mg - < 20 mg	SC	19.4 mg/mL	0.77 mL - < 1 mL	1
SAR446523	20 mg – 480 mg	SC	100 mg/mL	0.2 mL – 4.8 mL	1 to 3 injections (up to 2.5 mL/injection)[a]

[a]Depends on the administration area, please refer to Section 9.6.

Equation 1 can be used to calculate the volume of IMP associated with a given dose (xg). Please refer to Table 10 for applicable concentration.

Equation 1 - Calculation of volume of SAR446523 required for a given dose

$$Volume_{DP}\ (mL) = \frac{Dose\ (mg)}{IMP\ concentration\ (\frac{mg}{mL})}$$

9.3.2.2 Instructions for SAR446523 - lyophilizate for subcutaneous injection - 250 mg - preparation by dose level

DL to be administered to the patient described in the Table 11 are based on the Briefing Package and Full Protocol for SAR446523 (IND 170364) submitted to the FDA on Friday, 03 May 2024.

Table 11 - Instructions for SAR446523 - lyophilizate for subcutaneous injection - 250 mg - preparation by dose level

Dose level (mg)	No of required vial	Solution and volume of reconstitution	IMP concentration (mg/mL)	Total volume to be injected (mL)	Syringe volume (recommended in mL)
7.5	1	NaCl 0.9% for injection 16 mL	19.4	0.39	0.5
15	1	NaCl 0.9% for injection 16 mL	19.4	0.77	1
30	1	Water for injection 2.8 mL	100	0.30	0.5
60	1	Water for injection 2.8 mL	100	0.60	1
120	1	Water for injection 2.8 mL	100	1.20	2
240	1 or 2[a]	Water for injection 2.8 mL	100	2.40 (1 or 2 syringes)[b]	3 or 5
480	2	Water for injection 2.8 mL	100	4.8 (2 or 3 syringes)[b]	3 or 5

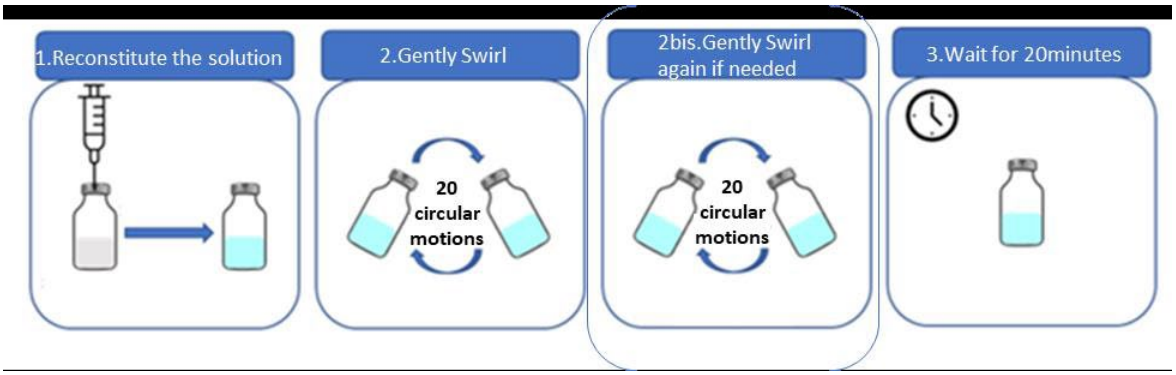
[a]Depending if clinical site uses or not a CSTD: 1 syringe without and 2 with CSTD
[b]Depending on the injection area, please refer to Section 9.6.

As a reminder, dead volume of CSTD BD Phaseal Optima is 0.2 mL.

If necessary, depending on the syringe used, the Sponsor recommends rounding the volume of IMP to be administered to the nearest value with a maximum differential of +/- 0.1 mL.

9.3.2.3 Reconstitution of Lyophilizate for SC administration

Figure 5 - Reconstitution of SAR446523 for SC administration



Note: reconstitution step should be performed in clean conditions, in agreement with nursing and hospital practices for subcutaneous injection as per local rules.

9.3.2.3.1 Reconstitution of Lyophilizate for SC administration at 19.4 mg/mL

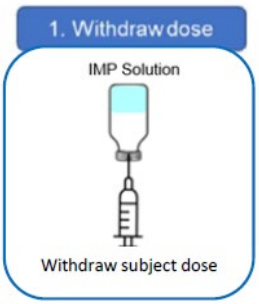
- Remove the cap from 1 vial.
- Draw 16 mL of NaCl 0.9% for injection at room temperature with an 21G needle and an appropriate sized syringe.
- With the vial placed upright on a flat surface, insert the needle in the middle of the stopper and transfer the NaCl 0.9% slowly, directing the stream at the side of the vial containing the powder.
- Gently swirl in 20 circular motions. In case of need, i.e., undissolved powder remaining stuck to the surface of the vial, repeat the operation until no solid are visible and let the vial sit. The vial should not be shaken, inverted, or vigorously swirled.
- The reconstituted solution should stand for 20 minutes before withdrawal and administration to the patient
- The obtained reconstituted solution of SAR446523 at 19.4 mg/mL should be a colorless and clear. The vials are for single use only. Some foam might remain at the surface.
- Reconstituted solution vial must be withdrawn just after the end of 20 minutes to prepare the syringe
- End of administration within 4 hours after the reconstitution (addition of NaCl 0.9%) at room temperature.

9.3.2.3.2 Reconstitution of Lyophilizate for SC administration at 100 mg/mL

- Remove caps from Number of Vials IMP (Table 11). For each vial:
- Draw 2.8 mL of WFI at room temperature with an 21G needle and an appropriate sized syringe.
- With the vial placed upright on a flat surface, insert the needle in the middle of the stopper and transfer the WFI slowly, directing the stream at the side of the vial containing the powder.
- Gently swirl in 20 circular motions. In case of need, i.e., undissolved powder remaining stuck to the surface of the vial, repeat the operation until no solid are visible and let the vial sit. The vial should not be shaken, inverted, or vigorously swirled.
- The reconstituted solution should stand for 20 minutes before withdrawal and administration to the patient
- The obtained reconstituted solution of SAR446523 at 100 mg/mL should be a colorless and clear. The vials are for single use only. Some foam might remain at the surface.
- Reconstituted solution vial must be withdrawn just after the end of 20 minutes to prepare the syringe
- End of administration within 4 hours after the reconstitution (addition of water) at room temperature.

9.3.2.4 Drug product syringe for administration

Figure 6 - First step for administration of prepared IMP: withdrawing the subject dose



One syringe per injection (max 2.5 mL) is to be prepared, with a number of syringes according to Equation 2 for injection if either abdomen or thighs. Equation 3 must be used for injection in upper arms.

Equation 2 - Calculation for syringe number to be prepared for manual push administration in abdomen or thighs

$$N = \left(\frac{Volume_{DP}(mL)}{2.5}\right) \textit{ rounded up to the nearest whole number}$$

Equation 3 - Calculation for syringe number to be prepared for manual push administration in upper arms

$$N = \left(\frac{Volume_{DP}(mL)}{2}\right) \textit{ rounded up to the nearest whole number}$$

- Visually inspect each of the vials to be used for any discolorations, particles, or other unexpected changes. Only use vials that pass visual inspection.

  If no CSTD's are being used:
  - From the number of IMP vials prepared (see section 9.3.2.1):
  - Use 21G needle and syringe(s) to:
  - Withdraw in each syringe the sufficient volume per injection + excess volume[3] needed for injection preparation. Repeat the operation for each of the syringes (refer to Equation 2 or Equation 3).

  If CSTD's are being used
  - Place a vial adaptor (protector) on each of the IMP vial(s) (prepared per Section 9.3.2.3).
  - Place the injector on each syringe, connect the injector + syringe to each vial + adaptor (or protector).
  - Withdraw the subject dose/syringe content as described above. Take also into account the dead volume of the CSTD. Keep the injector on each syringe. Dead volume of the CSTD (injector + connector) is around 0.2 mL according to supplier documentation.

  For this step, you can either add the connector now, or just before administration (see Section 9.6.1), depending on your local procedures.
  - Place the luer lock convertor (connector) on each injector or, depending on your local procedures, just before administration, see Section 9.6.1.

[3]Dead volumes of syringes and needles are not described since they depend on the used materials references. Withdrawing procedures involve withdrawing a little more than necessary before adjusting the volume to be injected, as per local procedures.

- Remove air bubbles from the syringe and secure the needle (if no CSTD's are being used) with cap per local clinical site protocols.

9.4 Storage and shelf life of prepared product

The reconstituted product is prepared at room temperature, and **the reconstituted solution should stand for 20 minutes before withdrawal and administration to the patient.** The maximum time between the addition of the reconstitution solution and the end of administration should not exceed 4 hours at room temperature.

If the prepared product is not stored according to the above guidance or the prepared product is no longer within its recommended shelf life, the product cannot be used and has to be discarded. A proof of disposal/destruction needs to be documented.

9.5 Transfer of prepared product

The IMP vials should not be shaken or dropped. The IMP vials should not be frozen or exposed to temperatures over 25°C. Upon dilution in diluent, the vial or the syringe should not be shaken, dropped or exposed to temperature over 25 °C. Pneumatic tubes for transfer are not allowed.

- **Transfer within the same building (except for pneumatic tubes):**
  - Prepared product must be stored and transported according to the storage condition (cold or ambient temperature). The vial or the syringe should not be shaken, dropped or exposed to temperature over 25 °C.
  - Transfers within the same building with a short time frame (5-20 minutes) will be taken into account of the allowed time window from end of preparation till the end of administration. For this type of transfer, the use of a temperature-controlled validated box is not required.
  - Avoid excessive shaking and box drops during transfer.
  - The use of pneumatic tube systems are not allowed.
- **Transfer between buildings of the same clinical site (including transport across a city from preparation site to administration site):**
  - Prepared product must be stored and transported according to the storage condition (cold or ambient temperature). The vial or the syringe should not be shaken, dropped or exposed to temperature over 25 °C.
  - Prepared product must be transported in temperature-controlled validated boxes.
  - Avoid excessive shaking and box drops during transfer.
  - Prepared product is stable up to from end of preparation till the end of administration.

In both cases, an internal transfer form or equivalent should be completed (Appendix J).

Transfer of prepared product between clinical sites and transfer to study participant's home are not allowed without Sponsor's approval.

If the prepared product is not transferred according to the above guidance, the product cannot be used and has to be discarded. A proof of disposal/destruction needs to be documented.

9.6 Treatment dispensation and administration

All SAR administration takes place on site. The administration process is to be documented in the source document worksheet or within the Administration/Dosing Logs.

In case a transfer of IMP (not prepared) is needed, please check specifics in section 12.

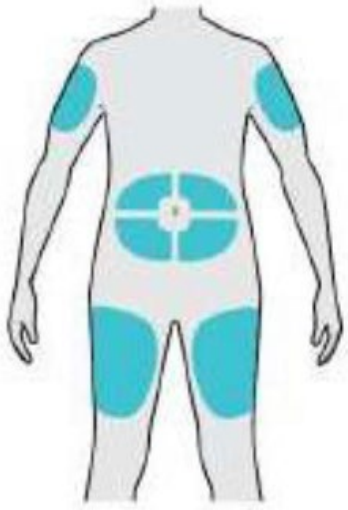
General rules: All patients receiving IMP will receive pre-medications (AxMP) to prevent or reduce incidence or severity of infusion reactions as per study protocol. If an injection reaction is observed, please refer to the protocol for IRRs management guidelines.

Prepared IMP in syringe will be administered subcutaneously in the abdominal area at least 2 cm from the belly button, waist, flank and the 2 cm area around the navel should be avoided (see Figure 7). Injections should alternate between four quadrants of the abdomen, thighs (**up to 2.5 mL** per injection if either abdomen or thighs) or upper arms (**up to 2 mL** per injection in case injection in the upper arm).

Rotation is needed in case of multiple injections for a single dose (on single timepoint) and between each administration (at different timepoint, meaning for instance admin site has to be different at C1D1 and C1D8) Even when administration will be every 2 weeks site, should still follow this rotation guidance.

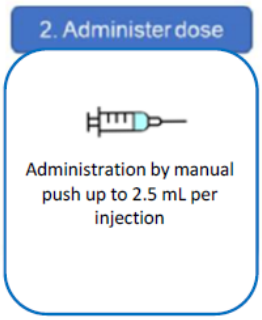
Injection site should be clear of any tenderness, redness, ecchymosis, skin break down, scars, tattoos or other lesions, which may otherwise result in poor injection tolerability. At higher SC dose levels, several injections may be needed (up to 3), and they should be administered at separate sites in the abdomen or thigh.

Figure 7 - Subcutaneous administration area



9.6.1 For subcutaneous administration with manual administration (from 0.2 mL to 4.8 mL)

Figure 8 - Administration of prepared IMP via manual SC administration



- Draw up the total volume inside the syringe

  If no CSTD's are being used:
  - Replace the tranfer needle (21G) with a 24G to 27G needle for injection.

  If CSTD's are being used for IMP preparation:
  - If connector has not be attached previously (Section 9.3.2.4), attach it
  - Attach the 24G to 27G needle for injection to the syringe + injector + connector.

- Remove the cover from the injection needle, prime the syringe and needle with the IMP according to local procedures and discard solution until the adequate volume for dose is left in the syringe. Do not touch the injection needle.
- Inject subject subcutaneously as per site protocol.
- The entire volume in the syringe must be injected, i.e., up to the "0" graduation, to the participant (1 to 3 syringes = participant dose).
- Total time from reconstitution (addition of WFI or NaCl 0.9%) to end of administration must not exceed 4h.

10. PRODUCTS TRACEABILITY, ACCOUNTABILITY AND RECONCILIATION

10.1 Definitions

- Study participant accountability refers to:
  - product allocated, dispensed and administered (if any) to a study participant,
  - product returned by the study participant to verify the compliance (in case of home administrated product by study participant or caregiver).

  This information is used to assess and document that IMP and AxMP have been used according to the protocol.

- Product inventory refers to management of product at site level. This involves products received, products dispensed/ administered at site level and destroyed/returned to depot for destruction.
- Site Reconciliation refers to product balance calculated at site level based on the product inventory. The balance should be equal to zero or discrepancy investigated and justified. Reconciliation must verify that any kit received by site, whether it has been dispensed or not to a study participant, is either disposed/destroyed at site or returned to the depot for destruction.

10.2 Investigational Medicinal Product

Products inventory, study participant accountability and reconciliation at site level must be performed by the Investigator or the Pharmacist or any Delegate. An accurate record for products received, dispensed, discarded and returned or destroyed at the investigator site must be maintained:

- on the Product Inventory and Study Participant Accountability Forms at site level (see example and template in the appendix A, B, C, D)
- on the IRT system
- Site's own forms can be used either as paper or in electronic format if assessed as acceptable by the Sponsor.

For on site preparation and administration (SAR446523 SC): Empty or partially used vials are disposed of immediately after preparation. A final reconciliation is performed on all accountability documentation at the end of the study by the Sponsor's Site Monitor together with the site personnel responsible for product management (Investigator/Pharmacist or Delegate) who signs the final page of the Accountability and Inventory Forms at the bottom of the forms.

Discrepancies are to be documented and explained on the logs and the Sponsor's Site Monitor must be notified upon discovery. Examples of discrepancies:

- Any discrepancies related to kits dispensed but not taken as expected,
- Any information in case a complaint or Temperature Excursion is reported.

The original Products Accountability and Inventory Forms must be filed in the ISF (see pre-filled exemple in appendix B and D).

IRT Accountability Module

In addition to the Investigational Product Dispensing and Reconciliation Form, (Accountability/Inventory Forms), IRT will be used to help maintain study inventory and accountability. IRT Accountability Module will provide a tool to complete the overall accountability for the study IMP/study interventions. The IRT accountability can be completed on an ongoing basis for doses being dispensed or damaged. Prior to any IMP/study interventions return, all IMP/study interventions to be included in the return must be marked as accounted for in IRT.

Details on the operations of IRT can be found in the IRT Study User Guide related to the study.

10.3 Auxiliary Medicinal Product (AxMP)

Appropriate system and documentation have to be in place to allow adequate traceability of product movements from first product receipt up to dispensation at site or prescription to the study participant (in case this is not dispensed at site) to ensure rapid location identification in case of recall.

An internal traceability must be conducted as per local regulation and site's own practices. AxMP traceability to allow adequate reconstruction of AxMP movements and administration.

For non-authorized AxMP supplied by Sponsor, study participant accountability, product inventory and site reconciliation are required. For authorized AxMP supplied by Sponsor, product inventory and site reconciliation are required. Moreover, AxMP administration data should be recorded in the study participant source document (batch number, dose, date...).

For AxMP locally supplied by sites (with or without reimbursement from Sanofi), a site traceability must be conducted as per local regulation and site's own practices.

11. DESTRUCTION AND RETURN OF PRODUCTS

This section is applicable to:

- Used and unused IMP

Products can be destroyed for many reasons, including (but not limited to): expired batch, study completion, project stopped, obsolete labelling, physically damaged, rejected due to quality considerations (e.g., Temperature Excursion, complaint) ...

Product destruction can take place:

- At Investigational Site if approved by the Sponsor.
- At Sponsor (local/regional depot) or at a Sponsor's third-party vendor after a return, if product destruction cannot take place at Investigational Site. A Return Form is issued (in case of return to Sponsor or to a Sponsor's third-party vendor). It is initiated by the Investigational Site (the Sponsor's Site Monitor will provide the correct form to use) and validated with Sponsor.

Return to Sponsor or to a Sponsor's third-party vendor or destruction at Investigational Site can only occur after:

1. Study Participant accountability, product inventory and reconciliation have been performed and documented correctly at Investigational Site (after products are returned from study participant's home to site, in case of home administration). Copies of study Participant Accountability and Product Inventory forms/system (see related section) have to be provided to Sponsor's Site Monitor to allow for accountability check and reconciliation. Any discrepancies must be investigated and satisfactorily explained.
2. An Authorization of Destruction (AoD) has been obtained from the Sponsor's Site Monitor for the following materials:

Type of kit	
Unused kits - Not dispensed	
Used kits with remaining units*: allocated manually or by an IRT and dispensed * A remaining unit is a unit not used for preparation nor administration/intake	

For the following materials, Authorization of Destruction from Sponsor is **NOT** needed.

- Completely Used kits (= empty box): box can be kept for compliance purposes and must be destroyed according to local practices.
- Partially used units: waste disposal of partially unit(s) should be done according to local practices.
- For Hazardous medical material (such as gloves, syringes…) - this material must be discarded at site level and not sent back to the depot.

Technical items such as insulated bags, backpack, gel/ice pack, sharp container supplied by Sponsor and used for the study must be destroyed at site at the end of the study.

Product Removal from storage condition:

Storage conditions must be kept until Sponsor Authorization of Destruction has been given. However, expired materials can be removed out of their storage conditions before AoD to avoid accidental dispensing to study participant.If materials are not destroyed directly, they must be stored in a dedicated quarantine area, until physical destruction, with a clear sign of "quarantine".

In order to combat counterfeiting, it is requested to make empty boxes unusable at the time of destruction processing, resulting in making the label unreadable and unusable (e.g., torn or strike out the labels).

Product destruction at Investigational Site

After destruction/disposal is performed:

- Study Participant Accountability, Product Inventory Form/system must be updated.
- For unused kits, or used kits with remaining units, a dated certificate of destruction or receipt for destruction (pick-up by qualified vendor in charge of destruction who acknowledge the receipt of the material and certify that the product will be destroyed according to applicable contract) must be provided to the Sponsor's Site Monitor. This document should be accompanied with the list of individual kit numbers destroyed (if there are treatment numbers on the kits).
- Destruction documentation must be filed in ISF: Authorization of Destruction, a dated certificate of destruction or receipt for destruction, list of individual kit numbers destroyed, local regulatory documentation if applicable.

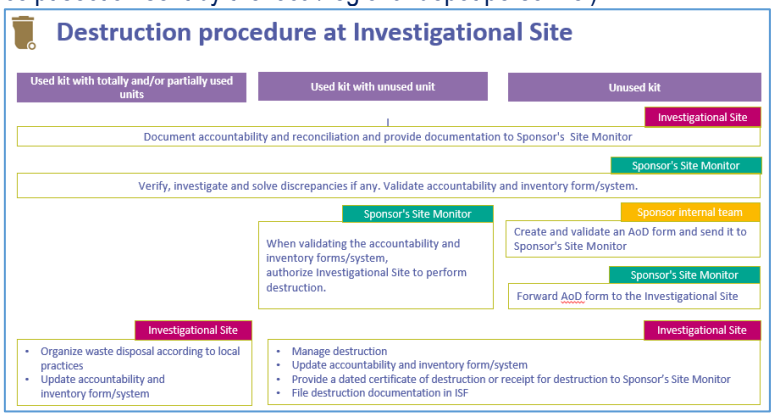
Product return to Sponsor or to a Sponsor's third-party vendor when applicable

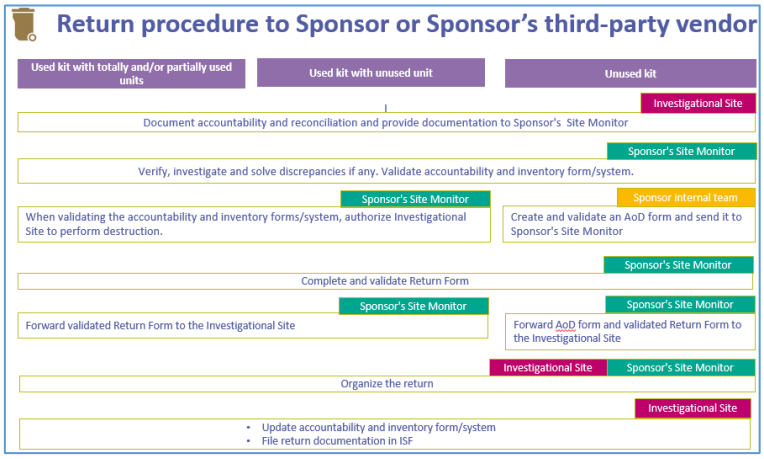
After Return Form is obtained:

- The Sponsor's Site Monitor organizes the return with the Investigational Site. The responsible person at the Investigational Site packages the products for the return.
- The content of the return parcel is checked by two people at Investigational Site and immediately sealed ready for pick up.

After the return is performed:

- Study Participant Accountability and Product Inventory Form/system must be updated.
- Return documentation must be filed in ISF: proof of pick-up of the products at Investigational Site, Return Form (including Acknowledgement of Receipt section sent by the local/regional depot personnel)





12. PRODUCTS TRANSFER

12.1 Transfer within same clinical site

If the product is received at one location (e.g., pharmacy) and stored at another location (e.g., department) the process and the documentation used to perform the transfer from the receipt to the storage location is checked by the Site Monitor to ensure that the storage conditions are always within the required range. In case of transfer IMP from receipt location to storage location:

For cold chain products, a validated cooling box is to be used. Time out of temperature range has to be documented. Any internal tranfer should be documented and should follow Sponsor requirements. Refer to Appendix "Internal Transfer".

An Internal Transfer Form or equivalent should be completed (see Add reference to apprendix)

12.2 Transfer between clinical sites

This kind of transfer should remain an exception and must be initiated/authorized by the Sponsor.

Instructions to perform such transfer should be clearly provided by the Sponsor and followed by the study site staff with records maintained accordingly.

13. PRODUCTS COMPLAINTS

Any technical issues related to the products provided by the Sponsor must be reported to the Sponsor's Site Monitor within 1 business day. A Product Complaint Form must be completed by the Sponsor's Site Monitor. (Appendix K)

Once completed, the Product Complaint Form is sent in WORD format to the Sponsor R&D Complaint Officer or delegate by email to MP-Quality-Complaints@sanofi.com. All defected IMP must be put in quarantine in IRT and physically. The defected IMP may be sent back to the Sponsor for further investigation if requested by the R&D Quality Operations (QO) Complaint Officer. AoR is sent to the originator by the R&D Complaint Office including details concerning sample return of the defective product.

14. APPENDICES

Please find below list of forms that your Sponsor's Site Monitor will provide you with the latest version to be used.

- Appendix A: PMM appendix_study Participant Accountability Form,
- Appendix B: PMM appendix_study Participant Accountability Form with pre-filled examples,
- Appendix C: PMM_appendix_Product Inventory Form
- Appendix D: PMM appendix_Product Inventory Form with pre-filled examples
- Appendix E: PMM appendix_Preparation Worksheet for products requiring reconstitution and further dilution
- Appendix X: Return for Destruction – Inventory Form,
- Appendix G: "Study Product Cold Chain Transportation Instructions for Site Staff"
- Appendix H: Material Safety Data Sheet
- Appendix I: WW-Temperature Excursion Report
- Appendix J: Internal Transfer Document,
- Appendix K: WW-Investigational Product Complaint Form.

End of Document