FINAL DRAFT

Study 22262 / BAY 3547926

DOSE ESCALATION PART 1 ONLY

Drug Handling Guidelines for ^{225}Ac-GPC3 ACC (BAY 3547926) and Cold-GPC3-ACC (BAY 3547922) at Study Sites

A multicenter, open label, non-randomized first-in-human phase 1 dose escalation and expansion study to evaluate the safety, tolerability, pharmacokinetics, and anti-tumor activity of BAY 3547926 alone, and in combination with atezolizumab and bevacizumab, in participants with advanced hepatocellular carcinoma (HCC)

Version 0.6 DRAFT
16 SEP 2024

Revision History		
Version Number	**Description of Changes**	**Version Date**
0.6 DRAFT	Initial Handling Guidelines for DOSE ESCALATION PART 1 for ^{225}Ac- GPC3-ACC (BAY 3547926) and Cold-GPC3-ACC (BAY 3547922).	**DRAFT** 16 SEP 2024

TABLE OF CONTENTS

ABBREVIATIONS

ACC	Antibody Chelator Conjugate
ALARA	As Low As Reasonably Achievable
CoA	Certificate of Analysis
CRA	Clinical Research Associate
EOM	End of Manufacturing
CSS&MM	Clinical Study Supply & Medication Manager (previously IMM)
Ph.Eur.	European Pharmacopoeia
GMP	Good Manufacturing Practise
ISF	Investigator Site File
IV	Intravenous
LAF	Laminated Air Flow
M	Molar - mole per litre
mAb	Monoclonal Antibody
MBq	Mega Becquerel
QC	Quality Check
QP	Qualified Person
USP	United States Pharmacopeia

1 INTRODUCTION

These Drug Handling Guidelines (DHG) for study 22262 define handling of study interventions used (see protocol Table 6-1) for Part 1, dose escalation only. They provide a description of the ordering, transport, storage, preparation, handling, and destruction of ^{225}Ac- GPC3 ACC (BAY 3547926) and Cold GPC3 ACC (BAY 3547922)

The radiolabeled study drug should be handled by authorized site staff who are qualified by training and experience in the safe handling of radionuclides. Both local and national regulations for handling of radioactive material must be followed. The Nuclear Medicine Department/Radiopharmacy at the study sites must be licensed to use actinium-225. Further details on radioprotection measures and actinium-225 exposure risks can be found in Appendix 1. Please contact your Clinical Research Associate (CRA) if more details are required.

All site staff with study responsibilities must be trained appropriately before performing any study specific tasks. Training on these guidelines should be documented in the Veeva Study Training System. Site staff working on the study must be listed on the Site Staff Delegation of Authority Log. It should be clearly stated on the log which drug handling activities each person has been delegated.

2 STUDY DRUG

The two study interventions used in Part 1 (Dose Escalation) of this study are BAY3547926 and BAY3547922.

- BAY 3547926 consists of an anti-GPC3-targeted monoclonal antibody (mAb), Glypican 3 (ANTI-GPC3), linked to a macropa to allow chelation of the radioactive alpha-emitter actinium-225 (actinium-225-macropa-anti-GPC3, referred to hereafter as **^{225}Ac-GPC3 ACC.**

- BAY 3547922 (cold (unlabeled) GPC3 antibody-chelator conjugate (Cold GPC3 ACC)), which consists of an anti-GPC3 mAb with a macropa, referred to hereafter as **Cold GPC3 ACC**. The Cold GPC3 ACC is not radiolabelled.

^{225}Ac-GPC3 ACC will be distributed to sites as a sterile, ready-to-use formulation with a sufficient radioactivity concentration for the dose level. Cold GPC3 ACC will be provided as a sterile, lyophilized powder. After proper preparation, the two study interventions are administered in sequence to achieve a total antibody mass dose of ***30***mg. The antibody mass dose received from ^{225}Ac-GPC3 ACC is approximately 15mg, and the Cold GPC3 ACC provides the remaining mass dose. In all participants, the cold GPC3 ACC will be administered as an IV infusion prior to the administration of ^{225}Ac-GPC3 ACC.

The manufacturing process of the study drug is not covered in this document.
Also not covered in this document are drug handling instructions for Dose Expansion (Parts 2 and 3). A separate document will be provided to sites at future date, prior to the start of Dose Expansion.

Further details of the study intervention can be found in the Investigator's Brochure.

3 MEASUREMENT OF ACTINIUM-225

The Nuclear Medicine Department/Radiopharmacy at the study sites must be licensed by the relevant national/local authorities to handle actinium-225.

Gamma emissions from actinium-225 and its daughters allow the use of standard instruments for measuring product activity with dose calibrators and detecting spills with survey meters or contamination monitors.

Before using actinium-225 radiopharmaceuticals provided by Bayer, each study site must determine the proper dial setting or calibration factor of their dose calibrator(s). This allows for accurate measurements of actinium-225 activity, including dose verification.

To determine the dial setting for each calibrator, the study site facility will receive actinium-225 standard reference material provided by Bayer along with instructions to perform an actinium-225 specific dial setting and an approval form for dial setting of dose calibrators. The form must be completed by the study site for each dose calibrator and returned to Bayer for approval (see Appendix 2 for full instructions).

As required by institutional policy and local regulations, suitability tests of the dose calibrator should be performed (e.g., constancy, linearity, etc.). If these routine suitability tests are maintained, the established dial setting can be used for all Bayer investigational clinical studies using actinium-225. The dial setting procedure should be repeated if maintenance or repair is performed on an existing approved dose calibrator or if a new calibrator is planned to be used. Furthermore, the dial setting procedure will need to be repeated if there are any changes to the actinium-225 standardization triggered by metrology institutes involved.

Please ensure a copy of the ***Approval Form for Dial Setting of Dose Calibrators*** (Appendix 2) for all dose calibrators is filed in the ISF.

4 COLD GPC3 ACC (BAY 3547922)

4.1 BAY 3547922 Packaging

Cold GPC3 ACC lyophilizate vials are shipped to sites in a temperature controlled (2-8 °C) shipping box. A temperature logger will be included with the temperature controlled (2-8 °C) shipment. 1 box (1 unit) = 1 vial. The vial labels and carton labels have a kit number but are not participant specific.

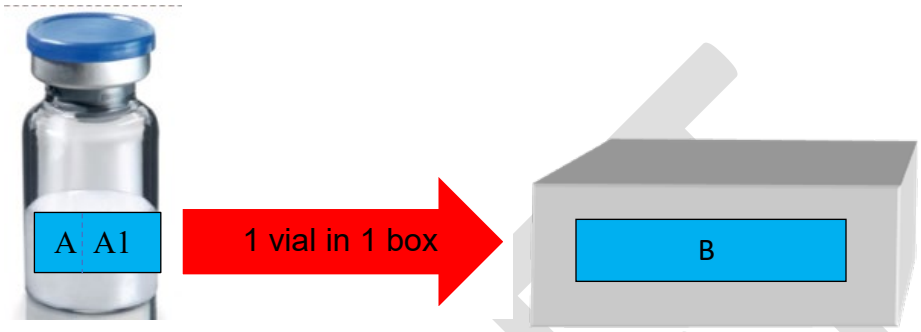


Table 1 Label Detail

1 vial containing BAY 3547922 LYO 125 mg (12.5 mg/mL when reconstituted)	
Label A (blue)	Affixed to vial
Label A1 (blue)	Tear off label
Label B (blue)	Affixed carton label

The consignment will also contain the following:

1. Dispatch Order Form
2. Delivery note or equivalent
3. Temperature logger

4.2 Ordering

Bayer is responsible for supplying Cold GPC3 ACC lyophilizate as described above to the study site. The site, however, maintains full responsibility for the on-site stock management of supply of the Cold GPC3 ACC lyophilizate.

The ***Drug Order Form for Cold GPC3 ACC (BAY 3547922***) must be used to order Cold GPC3 ACC (see Section 13, Appendix 3b) and should be submitted **at least 10 calendar days prior to the planned administration**. The initial order will be based upon site recruitment activity. It is recommended to order multiple vials with first participant so that an adequate stock is onsite for future participants/dosing. Please note, the vial labels and carton labels are not participant specific. Therefore, existing stock and planned participant dosing should be evaluated when considering the need to re-order Cold GPC3 ACC lyophilizate for new participants. Resupply orders should be submitted on demand and orders should be based upon Site activity.

The Drug Order Form for Cold GPC3 ACC lyophilizate must be completed, ensuring that the required information is entered clearly and accurately, and sent to the email addresses listed on the Drug Order Form for Cold GPC3 ACC. Bayer Clinical Supply Team will send a confirmation of receipt to the ordering personnel by email and initiate the shipment.

4.3 Receipt at study site

Study sites will receive Cold GPC3 ACC lyophilizate in temperature-controlled packaging material to maintain 2-8 °C. A ***Dispatch Order Form for Cold GPC3 ACC (BAY 3547922)*** (see Section 13, Appendix 5b) and a temperature logger will be included with each shipment. Upon receipt, site staff should open the package, immediately stop the temperature logger, and move the Cold GPC3 ACC lyophilizate vials into a suitable 2-8 °C storage unit which is monitored for temperature excursion.

Detailed instructions on how to stop and to interpret the temperature logger can be found on the ***Dispatch Order Form for Cold GPC3 ACC (BAY 3547922)*** (see Section 13, Appendix 5b). Cold GPC3 ACC can only be used if no alarm icon is shown on the temperature logger.

If an alarm icon is present and occurred during transit, the Cold GPC3 ACC must be quarantined at 2-8 °C .The ***Dispatch Order Form for Cold GPC3 ACC (BAY 3547922)*** (see Section 13, Appendix 5b) must be completed, indicating a temperature excursion, and emailed to the recipients as instructed on the Dispatch Order Form for Cold GPC3 ACC. It is the shipment recipient's responsibility to check the temperature logger and to notify the recipients as stated on the form immediately of the excursion. The drug cannot be used until further assessment and approval for use from the recipients as stated on the Dispatch Order Form for Cold GPC3 ACC has been received.

A Temperature Excursion at Site Report form for Cold GPC3 ACC needs to be completed only in the event of a temperature excursion while in storage at the site (see Section 4.4).
Complete the ***Drug Accountability Log for Cold GPC3 ACC (BAY 3547922)*** (Section 13, Appendix 8b) for all vials received.

The temperature loggers contained in the shipment are disposable and can be discarded only after the actions specified above are completed.

4.4 Storage at Study Site

Cold GPC3 ACC lyophilizate vials must be stored at 2-8 °C, protected from bright light.
It is the site's responsibility to monitor and record the refrigerator temperature (manually on paper or electronic logger) while study materials are stored at the site.

- If there is a temperature excursion while study materials are in storage at the study site, then a ***Temperature excursion at study site Report form (TESR)*** (Section 13, Appendix 11) must be completed and emailed along with any supporting temperature data to the Bayer recipients as instructed on the TESR.
- In case of a storage issue at the site, then a ***Storage issue at study site report*** (Section 13, Appendix 12) must be completed and emailed along with any supporting documentation to the Bayer recipients as instructed on the form.

The affected drug should be placed into quarantine and cannot be used until further assessment and approval for use from Bayer's Clinical Study Supply & Medication Manager (CSS&MM) and/or Quality Function (where required) has been received.

4.5 Cold GPC3 ACC preparation for infusion

As stated above, the total ACC mass dose to be administered is 30mg. The mass dose received from ^{225}Ac-GPC3 ACC is approximately 15mg, and the Cold GPC3 ACC provides the remaining mass dose.

Cold GPC3 ACC lyophilizate vials must be reconstituted and then further diluted prior to administration. Reconstitution and subsequent dose preparation must be performed by qualified site staff using aseptic techniques in an ISO Class 5/Grade A laminar flow workstation (LAFW).

Appropriate materials must be used in the reconstitution, dilution, preparation, and administration of Cold GPC3 ACC. Please see the compatible materials and required supplies listed in ***Materials Tested for Compatibility (BAY 3547926 and BAY 3547922)*** in this study (Section 13, Appendix 4). Note: Because of the small volumes being administered, IV extension sets with minimal priming volume (i.e., microbore) are required.

When preparing a dose of Cold GPC3 ACC, please complete the ***Drug Preparation form for Cold GPC3 ACC (BAY 3547922)*** (Section 13, Appendix 6b) and ***Drug Accountability Log for Cold GPC3 ACC (BAY 3547922)*** (Section 13, Appendix 8b) to document the vials used.

4.5.1 Reconstitution of Cold GPC3 ACC Lyophilizate:

a) Remove a vial of Cold GPC3 ACC lyophilizate from the refrigerator.

b) Per local procedures, disinfect all items to be used for dose preparation and place them in an ISO Class 5/Grade A laminar flow workstation (LAFW).

c) After arranging all relevant materials in the LAFW, disinfect the vial septa with sterile 70% isopropyl alcohol.

d) At the start of reconstitution, assign a 4 hour beyond use date (BUD). NOTE: if a delay in administration occurs, the BUD may be extended if the Cold GPC3 ACC is stored under refrigerated conditions (2-8 °C). Please see Section 4.5.3 (check section) for additional information.

e) Following aseptic technique, use a 10 mL syringe to add 10.0 mL sterile water for injection (WFI) to each vial of Cold GPC3 ACC lyophilizate to provide a final concentration of 12.5mg/mL. NOTE: the vial septum should not be pierced more than once during reconstitution.

f) Gently swirl the vial to dissolve the lyophilised solid. NOTE: do not heat or vigorously shake the vial as damage to the protein may occur.

g) Allow to settle for one minute to let bubbles rise to the surface.

h) Visually inspect the vial to ensure no undissolved substance is present. If so, repeat the gentle swirling and settling procedure.

i) After the lyophilizate is completely dissolved, inspect the vial visually for discoloration and/or particulate matter. The solution should be colourless to slightly yellowish. The reconstituted

solution should only be used after complete dissolution of the Cold GPC3 ACC lyophilizate and only if the obtained solution is free of visible particles (no magnification).

4.5.2 Dilution and Preparation of Cold GPC3 ACC Participant Doses:

The volume of reconstituted cold GPC3 ACC to be withdrawn from the vial will vary based on the time from end of manufacture of ^{225}Ac-GCP3 ACC to the day of administration. Because of this variation, the site radiopharmacy team will need to communicate the date of manufacture of ^{225}Ac-GPC3 ACC to the IDS pharmacy team.
Based on the time elapsed from manufacturing to administration, prepare each participant dose as described in the table below.
Please consider, the vial septum should not be pierced more than once for the withdrawal of reconstituted Cold GPC3 ACC solution.

Table 2 Participant Dose

Day of Dosing	1	2	3	4	5	5.5*
Volume of cold ACC (mL)	1.4	1.2	1.2	1.0	1.0	1.0
Mass dose from cold ACC (mg)	17.5	15.0	15.0	12.5	12.5	12.5

* Day 5.5 represents the start of day 6 until manufacturer's expiration

a) Use a 10mL syringe to withdraw the volume of reconstituted cold GPC3 ACC solution specified in the table according to the day of preparation. NOTE: Day 0 is the day of manufacture.
b) Immediately after, dilute the cold GPC3 ACC solution in the syringe with a sufficient volume of saline to achieve a final volume of **5mL** of diluted cold GPC3 ACC for administration.
c) Invert the dose syringe multiple times to ensure proper mixing.

Any remaining amount of cold GPC3 ACC in the vials must be discarded.

4.5.3 Instructions for labels and forms:

a. Affix the vial tear off label to the ***Drug Preparation form for Cold GPC3 ACC (BAY 3547922)*** (see Section 13, Appendix 6b)

b. Create 2 copies of the syringe label. One copy should be affixed to the syringe, and the other copy should accompany the dose to the administration suite for use by the administration staff. At minimum, the label should state:

- *Protocol number (e.g. BAY 3547926 / 22262)*
- *Participant number*
- *Date prepared and BUD (date/time)*
- *Study drug name (e.g., BAY 3547922 / Cold GPC3 ACC)*
- *Dose (mg)*
- *Volume (ml)*
- *Additional information may be added per local requirements.*

c. Ensure the ***Drug preparation form for Cold GPC3 ACC (BAY 3547922)*** (see Section 13, Appendix 6b) is completed for each dose prepared, even if it is prepared but not administered.

The prepared dose of cold GPC3 ACC should be administered completely within four hours of the start of preparation when kept at room temperature. If not used immediately, the prepared solution must be stored at 2 – 8°C (36°F to 46°F). Following refrigeration, allow the product to adapt to room temperature for approximately 30 minutes before administration. The total time exceeding 2-8°C must not surpass four hours, including preparation and administration. The overall handling time including refrigeration of prepared solution must not exceed 24 hours. The product temperature should not exceed 30°C.

Due to the inherent sensitivity of protein products, until further studies indicate otherwise, exposure of solutions to bright light (e.g., sun light) and freezing of the reconstituted Cold GPC3 ACC should be avoided.

4.6 Transfer of syringe(s) to the person(s) who will administer the Cold GPC3 ACC

On the day of the ^{225}Ac-GPC3 ACC administration, the person performing the administration will receive the following from the person preparing each syringe:

- Labelled syringe containing prepared dose of Cold GPC3 ACC
- A copy of each syringe label for all syringes prepared, to affix to ***Drug Administration forms*** (see Section 13, Appendix 7a and 7b).

The person who collects the syringe should sign the ***Drug Preparation form(s) for Cold GPC3 ACC (BAY 3547922)*** (see Section 13, Appendix 6b) as a confirmation of receipt of the syringe.

5 ^{225}Ac-GPC3 ACC (BAY 3547926)

5.1 BAY 3547926 Packaging

^{225}Ac-GPC3 ACC is transported to the study sites in a temperature-controlled overpack containing a Type A shipping box with radioactivity hazard labels, according to international transportation guidelines for radioactive materials.

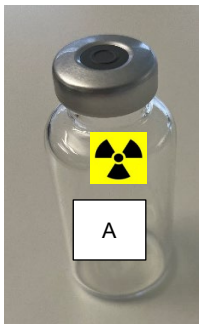
Example of shipment packaging:

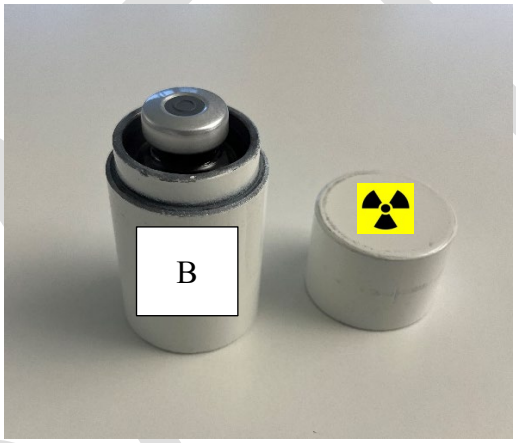
The secondary packaging material will be a lead lined pot with 1 vial containing the ^{225}Ac-GPC3 ACC solution for injection. ^{225}Ac-GPC3 ACC will be shipped in quarantine to the study site, and the pot will be secured by a padlock to prevent access to the study drug until after release of the product is confirmed.

For study sites in Canada and US, the code for unlocking will be provided by quality assurance of the contract manufacturer, who releases the material and prepares the relevant certificates once testing is completed, and results meet the product specification (see ***example Dispatch order form for ^{225}Ac-GPC3 ACC*** (Appendix 5)).

For study sites in EU, the code for unlocking will be provided by an EU Qualified Person (QP) of the contract manufacturer or Bayer AS, depending on where the contract manufacturer is located. The EU QP releases the material and prepares the relevant certificate once testing is completed and results meet the product specification. However, for study sites in **Belgium and UK**, an additional QP verification step is required, here the code for unlocking will be provided by the countries authorized personnel after review and approval of relevant certificates and temperature logger provided with the shipment from clinical site.

A 20mL capacity vial will be sent. The vial will contain approximately 14mL of ^{225}Ac-GPC3 ACC solution for injection comprising a 2.1 mg/mL antibody concentration and an actinium-225 concentration that is adjusted in accordance with each dose level.





Label A. Affixed to vial

Label B. Affixed to lead pot

The consignment will also contain the following:

- One additional lead pot label or copy of labels on master batch record
- Dispatch Order Form
- Delivery note or equivalent
- Temperature logger

The Certificate of Analysis including padlock code will be provided to the study site separate of the consignment by e-mail.

5.2 Ordering of ^{225}Ac-GPC3 ACC

A ***Study Drug Order Form for ^{225}Ac-GPC3 ACC*** (Appendix 3) must be completed and submitted at least **13 calendar days prior to the planned date of dose** for each administration (Cycle).

If the **assigned ^{225}Ac-GPC3 ACC radioactivity dose level is unknown for Cycle 1** the study site must still complete a Study Drug Order Form (as above) omitting the dose level. Once the dose level is determined, Bayer will inform the study site and the drug supply team of the dose level by updating the Study Drug Order Form and returning to the study site and to the drug supply team**.**

If there is a dose reduction, the new dose level should be ticked and "Dose reduction" box ticked on the Study Drug Order Form.

Note: The release of ^{225}Ac-GPC3 ACC to a study site will not be granted by the Sponsor until all required regulatory, radiation, ethics and local approvals and essential documents are in place as per Good Clinical Practice. Please contact your CRA for the status of your study site.

5.2.1 Delay/cancellation/reordering of study drug administration

In case of delay/cancellation of the study drug administration date, site staff must inform the respective contacts for study drug ordering (listed on the Study Drug Order Form) as soon as possible. When possible, at least 10 calendar days' notice should be given before the planned date of dosing, so the manufacturing and/or shipment of study drug to the study site can be stopped.

The email regarding delay/cancellation should contain the **study site name, study site number, participant number, initial planned dosing date and an explanation for the delay/cancellation**. This email should be filed in the ISF together with the delayed/cancelled drug order form.

If the date of study drug administration is rescheduled, the Study Drug Order Form should be updated with the rescheduled administration date, re-signed by the requester, and sent to the email addresses listed on the form. This process should also be followed if study sites need to re-order ^{225}Ac-GPC3 ACC study drug due to a temperature excursion.

When rescheduling dosing dates, it is critical that all applicable functions are consulted, including Bayer clinical drug supply, to ensure that study drug can be manufactured and delivered to a study site on the new planned dosing date. In some instances, a resupply of actinium-225 to the manufacturing facility itself might be needed, therefore it is important that dose delays/requests for resupplies are communicated to Bayer clinical drug supply and your CRA as soon as possible.

Any ^{225}Ac-GPC3 ACC study drug that is received at a study site but is unused must be stored for decay, as described in Section 6.

5.3 Receipt of study drug ^{225}Ac-GPC3 ACC at study site

A ***Dispatch Order Form for ^{225}Ac-GPC3 ACC*** (example Appendix 5) and a temperature logger will be included with the temperature-controlled (15-25 °C) shipment of ^{225}Ac-GPC3 ACC. The recipient is responsible for following the instructions on the Dispatch Order Form and returning a signed copy together with the temperature log report to the Bayer recipients as stated on the form to confirm that the delivery has arrived in good condition.

Detailed instructions on how to stop and interpret the temperature logger can be found on the Dispatch Order form within the shipment. The recipient at the study site is responsible for following the instructions provided with each shipment, to stop and to read the data logger immediately after receipt:

✓ symbol ensures that there was no temperature excursion during transport and study drug can be used

✖ (alarm symbol) forbids use of the study drug. The dispatch order form should be completed indicating a temperature excursion and returned as described on the Dispatch order form immediately. Please also inform your CRA immediately of the temperature excursion. Study drug should be destroyed per details in Section 8 - Destruction of Study Drug. Please see Section 5.2 for re-ordering study drug.

The temperature loggers and padlocks contained in the shipment are disposable and can be discarded only after the actions specified above are completed.

All certificates will need to be filed with the shipment documentation.

Site staff are to complete the ***Study Drug Accountability & Destruction Log for ^{225}Ac-GPC3 ACC*** (Appendix 8) for all vials received.

Please see the following sections for region/country specific import requirements and receipt of study drug at study sites;

- **5.3.3 for EU**
- **5.3.4 for UK**
- **5.3.5 for Belgium**

5.3.1 Receipt of study drug at study sites in Canada

The manufacturer will perform batch certification and import to Canada by providing the certificate and the code to unlock the padlock to access the dose. See Dispatch Order form for further details and see Table 3 below.

5.3.2 Receipt of study drug at study sites in USA

The manufacturer will perform batch certification and import to USA (if product provided by EU manufacturer) by providing the certificate and the code to unlock the padlock to access the dose. See Dispatch Order form for further details and see Table 3 below.

5.3.3 Receipt of study drug at EU study sites

For study drug doses manufactured in EU to be used in EU, the batch release certificate/CoA and the code to the padlock will be provided by email directly from the EU manufacturer.
For study drug doses manufactured in US to be used in EU, Bayer QPs will perform batch certification and import to EU by providing by email the batch release certificate/CoA and the code to unlock the padlock to access the dose. See Dispatch Order form for further details.

5.3.4 Receipt of study drug at UK study sites

Import of clinical doses to the UK requires an import confirmation, named IMP Oversight for Listed Country, by a QP situated in and approved by UK authorities, MHRA.
Eramol is a contracted company who will perform import verification by UK QPs as a release activity before dose can be administered. Eramol QPs require the transport temperature data, and it is therefore important that the data logger report is sent as soon as possible after receipt to avoid delay in the certification process by Eramol.

Import from USA – Eramol will confirm import to UK by providing the certificate along with a CoA, an EU import certificate and the code to unlock the padlock to access the dose.
Import from Germany – Eramol will confirm import to UK by providing the certificate along with a CoA and the code to unlock the padlock to access the dose.

5.3.5 Receipt of study drug at Belgian study sites

A Bayer QP or manufacturer QP will perform batch certification and import to EU (if applicable) by providing the certificate and the code to unlock the padlock to access the dose to the site's radio-pharmacist (Site QPs). The Site QPs are responsible for the release in the country. After country release and after the local site staff has verified the transport temperature data and has documented this on the Dispatch Order Form, the vial can be used for administration. See Table 3 below.

Table 3 Country Specifics

Clinical site	Temp. logger read out	Release certificate and padlock code will be received from:
Canada and USA	Check for alarm and fill out page 3 of Dispatch Order Form and return all pages and data logger report per instructions given on Form.	CoA/CoC is provided by manufacturer together with padlock code by email to the site
EU sites, except UK and Belgium	Check for alarm and fill out page 3 of Dispatch Order Form and return all pages and data logger report per instructions given on Form.	For EU manufacturing site: : CoA/CoC is provided by manufacturer together with padlock code by email to the site For US manufacturing site: CoA/CoC is provided by Bayer AS together with padlock code by email to the site

Clinical site	Temp. logger read out	Release certificate and padlock code will be received from:
Belgium,	Check for alarm and fill out page 3 of Dispatch Order Form and return all pages and data logger report per instructions given on Form.	Site QPs (see above)
UK	Check for alarm and immediately fill out page 3 of Dispatch Order Form and send all pages of Form together with data logger report per instructions on Dispatch Order Form After the certificate has been received from Eramol, fill out remaining activities on Dispatch Order Form prior to filing.	Eramol send certificate and padlock code by email after site has sent back temperature logger data to Eramol after receipt of dose.

5.4 Storage of ^{225}Ac-GPC3 ACC at Study Site

Upon receipt, ^{225}Ac-GPC3 ACC vials should be stored at 15-25°C as specified on the label in a temperature-controlled environment, designated for radioactive materials.

It is the study site's responsibility to monitor and record the temperature (manually on paper or electronic logger) while study materials are stored at the study site.

- If there is a temperature excursion while study materials are in storage at the study site, then a ***Temperature excursion at study site Report form (TESR)*** (Section 13, Appendix 11) must be completed and emailed along with any supporting temperature data to the Bayer recipients as instructed on the TESR.
- In case of a storage issue at the site, then a ***Storage issue at study site report*** (Section 13, Appendix 12) must be completed and emailed along with any supporting documentation to the Bayer recipients as instructed on the form.

The affected drug should be placed into quarantine and cannot be used until further assessment and approval for use from Bayer Quality Function QA has been received.

This area must have sufficient capacity to store all vials of ^{225}Ac-GPC3 ACC and allow for the segregation of incoming study drug from used, rejected, or expired vials.
Study site procedures should reflect this separation to ensure misadministration is avoided.

See Section 8 for details on study drug destruction and Section 11 on drug accountability.

5.5 ^{225}Ac-GPC3 ACC preparation

Sites will receive a ready-to-use vial of ^{225}Ac-GPC3-ACC with adequate actinium-225 to cover the radioactivity dose for each dose level throughout the entire shelf-life of the drug product. Based on the day of administration, site staff will prepare an aliquot containing the required radioactivity dose in an appropriately sized syringe.
The dose levels prescribed by the protocol are shown in the table below.

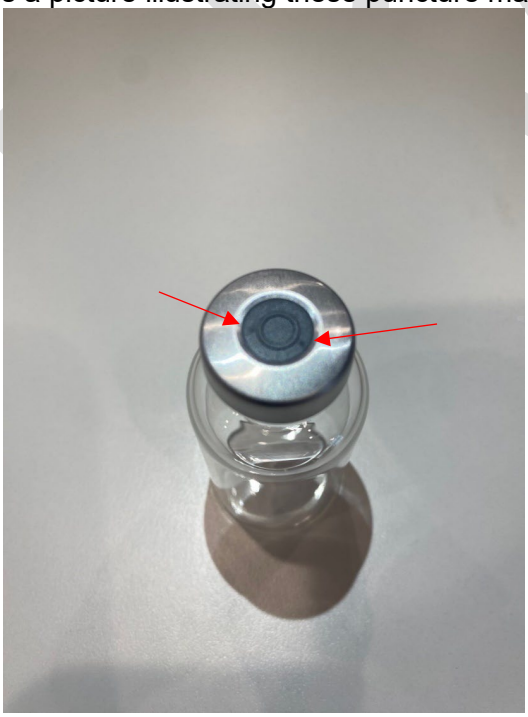
Table 4 Dose Levels

Dose level	Radioactivity Dose (MBq)
-1*	1.00
1	1.50
2	3.10
3	4.60
4	6.10
5	8.00
6	9.60

*Dose level "-1" to be used for de-escalation if needed

Prior to preparation, site Radiopharmacy / nuclear medicine staff should verify that the ^{225}Ac-GPC3 ACC was shipped and stored at 15-25°C and the Certificate of Analysis is available for the delivered vial as described in Section 5.3.

Please be aware of the condition of the vial septum prior to drug preparation. It should be noted that some manufacturers use a closed system fill method during the manufacturing process. Therefore, site staff should not be alarmed by the presence of puncture marks on the septum of a vial received from the manufacturer. To avoid possible coring of the septum, please do not pierce the vial near these puncture marks when withdrawing the ^{225}Ac-GPC3 ACC.
Below is a picture illustrating these puncture marks:



When preparing the ^{225}Ac-GPC3 ACC, please complete the ***Drug Preparation Form for ^{225}Ac-GPC3 ACC (BAY 3547926)*** (Section 13, Appendix 6a) and ***Drug Accountability Log for ^{225}Ac-GPC3 ACC (BAY 3547926)*** (Section 13, Appendix 8a) to document the vials used.

Prepare the dose of ^{225}Ac-GPC3 ACC as follows:

a) Remove the vial with its shielding container from the dedicated storage area.

b) Following local procedures, disinfect the vial and shielding container and place them in an ISO Class 5/Grade A laminar flow workstation (LAFW).

c) Use the table below to determine the necessary volume to withdraw from the vial.

Table 5 Volume to withdraw

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 5.5 (end of shelf-life)
Volume (mL)	6.3	6.8	7.3	7.8	8.4	8.7*
Mass of ACC (mg)	13.3	14.3	15.3	16.4	17.6	18.3

*This volume should be used on day 6 after manufacturing up to the time of expiration.

d) Assign a 12 hour beyond use date (BUD).

e) After swabbing the septum of the vial with sterile 70% isopropyl alcohol, use aseptic technique to withdraw the volume described in the table above into a shielded syringe.

f) Because the syringe markings do not allow for accurate measurement of volume in 0.1mL increments, please use your best estimation of the volume. The radioactivity measure in the next step will confirm the proper dose.

g) Using an approved dose calibrator (see Section 3), assay the syringe to confirm the radioactivity dose is within 10% of the radioactivity dose to which the participant is assigned.

h) If the measurement is outside the acceptable range, make the necessary adjustments to the volume to ensure the dose at the planned injection time is within 10% of the required radioactivity dose. If the initial measurement shows 15% or greater in difference to the expected radioactivity dose, please contact the CRA before making any adjustments or using the drug product.

i) Record the activity contained in the syringe as measured (no rounding) along with the date and time of preparation on the ***Drug Preparation Form for the ^{225}Ac-GPC3 ACC (BAY 3547926).***

j) Create 2 copies of the syringe label. One copy should be affixed to the syringe, and the other copy should accompany the dose to the administration suite for use by the administration staff.
The label should state (at minimum):

- *Protocol number (e.g., BAY 3547926 / 22262)*
- *Participant number*
- *Dose (MBq) at time of preparation*
- *Date & time of Assay*
- *Expiry date & time (BUD)*
- *Study drug name*
- *Volume (mL)*
- *Additional information may be added per local requirements.*

k) Ensure the ***Drug Preparation Form for ^{225}Ac-GPC3 ACC (BAY 3547926)*** (see Section 13, Appendix 6a) is completed for each dose prepared, even if the syringe is prepared but not administered. The extra label or batch record provided in the shipment should also be affixed to the ***Drug Preparation Form for ^{225}Ac-GPC3 ACC (BAY 3547926)*** (see Section 13, Appendix 6a).

5.6 Transfer of syringe to administering personnel

On the day of the ^{225}Ac-GPC3 ACC administration, the person performing the administration will receive the following from the person preparing each syringe:

- Labelled syringe containing the ^{225}Ac-GPC3 ACC
  - The syringe containing the ^{225}Ac-GPC3 ACC should be transported to the location where the participant will be dosed according to the local guidelines on transporting radioactive material.
- A copy of each syringe label for all syringes prepared, to affix to ***Drug Administration Forms*** (see Section 13, Appendix 7a and 7b).

The person who collected the syringe should sign the ***Drug Preparation Form for ^{225}Ac-GPC3 ACC (BAY 3547926)*** (see Section 13, Appendix 6a and 6b) as a confirmation of receipt of the syringes.

6. ADMINISTRATION OF THE COLD GPC3 ACC AND ^{225}Ac-GPC3 ACC

The cold GPC3 ACC will be administered to the participant first. To avoid infusion related reactions, site staff must use a syringe pump with a fixed rate of 0.25mL/min for the administration of both study interventions.
The ^{225}Ac-GPC3 ACC will be administered approximately 10 minutes after the end of the cold GPC3 ACC infusion, with a window of -10 minutes / + 20 minutes.

The total mass dose administered is the sum of the Cold GPC3 ACC dose and the fixed antibody mass in the ^{225}Ac-GPC3 ACC.*

Materials and equipment: Only material tested by Bayer or equivalent material can be used for administration of the Cold GPC3 ACC and ^{225}Ac-GPC3 ACC (for materials refer to Section 13, Appendix 4). Because of the small volumes being administered, IV extension sets with minimal priming volume (i.e., microbore tubing) are required.
The site is responsible for providing all equipment and infusion supplies, including filter.

A separate (venous access) line should be used contralaterally to collect blood samples on day 1.

6.1 Guidelines for administration of Cold GPC3 ACC (BAY 3547922)

Please reference protocol section 6.6.2.6 for precautions (availability of emergency treatment and observation period).

The following guidelines apply to the administration of Cold GPC3 ACC:

1. Cold GPC3 ACC is to be administered as an infusion with an appropriate syringe pump/driver.

2. A 3-way stopcock should be used to allow flushing after the infusion. Because the syringe pump may interfere with the attachment of the stopcock to the syringe, a short extension (10-15cm) may be used before connecting the stopcock. Connect the remaining end of the stopcock to the IV administration / extension set and then attach the mandatory filter. Using the syringe containing the dose solution, prime the IV administration / extension set. This should include the short IV extension set, stopcock, longer IV extension set and filter. All IV set supplies require minimal priming volume (i.e., microbore). See materials in Section 13, Appendix 4. NOTE: priming may be completed in the pharmacy per site protocols.

3. Before connecting the Cold GPC3 ACC administration set to the participant's IV line, use a saline flush to confirm patency of the participant IV line.

4. After the flush, attach the infusion set primed with dose solution to the IV line.

5. Move the valve of the stopcock to the correct position to administer the Cold GPC3 ACC, start the pump, and allow complete infusion to occur.

6. Administer the Cold GPC3 ACC at a rate of infusion of 0.25mL/min (15mL/hr) until complete dose is given.

7. After the infusion of Cold GPC3 ACC is complete, use the syringe pump to deliver 1.5mL of saline solution through the infusion set. This flush must be delivered at the same rate as the previous infusion to prevent a large bolus of antibody from being delivered. NOTE: the stopcock must be positioned correctly for the saline to be delivered.

8. After the pump has delivered 1.5mL of saline flush, stop the pump (record this time as the infusion stop time) and remove the infusion set from the pump. Manually administer the remaining saline solution in the flush syringe as a bolus.

9. Disconnect the Cold GPC3 ACC infusion set (from filter through syringe) and discard. NOTE: leave the indwelling catheter in place for the infusion of ^{225}Ac-GPC3 ACC.

10. Complete the ***Drug Administration Form for Cold GPC3 ACC (BAY 3547922)*** (see Section 13, Appendix 3b) and affix a copy of the syringe label to the form. NOTE: a copy of the syringe label should be provided by the dose preparation staff.

Site-specific administration and filtering steps may be considered after obtaining Bayer written approval. A written description is to be provided by the site to Bayer and approval obtained prior to administration.

6.2 Guidelines for administration of ^{225}Ac-GPC3 ACC

The administration of ^{225}Ac-GPC3 ACC begins after the completion of Cold GPC3 ACC. The start of the ^{225}Ac-GPC3 ACC infusion should be 10 minutes after the completion of
The Cold GPC3 ACC infusion (window of -10 minutes, +20 minutes)
The following guidelines apply to the administration of ^{225}Ac-GPC3 ACC:

1. Administer a 10mL saline flush to ensure the patency of the patient's IV access.

2. Place an absorbent pad under the participant's arm to prevent contamination of the infusion chair prior to attaching the syringe containing the ^{225}Ac-GPC3 ACC to the IV line.

3. A 3-way stopcock should be used to allow flushing after the infusion. Because the syringe pump may interfere with the attachment of the stopcock to the syringe, a short extension (10-15cm) may be used before connecting the stopcock. Connect the remaining end of the stopcock to the IV administration / extension set. Using the syringe containing the dose solution, prime the IV administration / extension set. This should include the short IV extension set, stopcock, and longer IV extension set. All IV set supplies require minimal priming volume (i.e., microbore). See materials in Section 13, Appendix 4. NOTE: Priming may be completed in the radiopharmacy per site protocols.

4. Use the same indwelling catheter for the ^{225}Ac-GPC3 ACC infusion as the one used to administer the Cold GPC3 ACC. **No filter** is to be used for the ^{225}Ac-GPC3 ACC (ensure the filter used for the Cold GPC3 ACC infusion has been removed).

5. Start the administration of the ^{225}Ac-GPC3 ACC approximately 10 minutes after the administration of Cold GPC3 ACC (acceptable window: –10 minutes, +20 minutes).

6. Record the start time of the infusion.

7. ^{225}Ac-GPC3 ACC should also be infused using a syringe pump at a rate of 0.25mL/min.

8. After the infusion of ^{225}Ac-GPC3 ACC is complete, use the syringe pump to deliver 1.5mL of saline solution through the infusion set. This portion of the flush must be delivered at the same rate as the infusion to prevent a large bolus of antibody from being delivered. NOTE: the stopcock must be positioned correctly for the saline to be delivered.

9. After the pump has delivered 1.5mL of saline flush, stop the pump (record this time as the infusion stop time) and remove the infusion set from the pump. Manually administer the remaining saline solution in the flush syringe as a bolus.

10. Complete the ***Drug Administration Form for ^{225}Ac-GPC3 ACC (BAY 3547926)*** (see Section 13, Appendix 7a) and affix a copy of the syringe label to the form. NOTE: a copy of the syringe label should be provided by the dose preparation staff.

6.3 Post administration

After administration of the ^{225}Ac-GPC3 ACC, the following post administration steps must be followed:

1. Observe participants as a routine precaution during the time required for post-dose vital signs and sample collection (see Protocol, SOA, Tables 1-1 Part 1).

2. Observation should be done by a medically qualified person in an area with resuscitation equipment and emergency agents.
3. Using an approved dose calibrator (see Section 3), measure the residual radioactivity in the syringe, tubing, and stopcock used to administer the ^{225}Ac-GPC3 ACC
   NOTE: if any material is spilled during the administration, the absorbent pad should be collected and measured for residual activity.

4. Record both the residual radioactivity and the time of measurement on the ***Drug Preparation Form for ^{225}Ac-GPC3 ACC (BAY 3547926)*** (Section 13, Appendix 6a). There is no further requirement for the syringe, and site staff are not required to store the syringe or tubing for drug accountability verification.

After administration, all potentially radioactive and non-radioactive waste (e.g. syringe, tubing etc.) should be disposed of according to local guidelines.

7. EXTRAVASCULAR ADMINISTRATION OF ^{225}Ac-GPC3 ACC or COLD GPC3 ACC

The risk of extravascular administration of the cold GPC3 ACC and of the ^{225}Ac-GPC3 ACC can be minimized by using careful injection technique. After properly placing the cannula, the infusion line should be flushed with saline solution to ensure patency. Flushes should be administered before and after administration of the Cold GPC3 ACC and ^{225}Ac-GPC3 ACC ('sandwich technique'). As described above, a 3-way stopcock should be used to facilitate flushes.

If extravasal administration is suspected the following actions may increase the rate of resorption:

- Flush with approx. 10 to 20 mL of isotonic saline solution.
- Elevate the arm and apply local heat (approx. 37 °C; body temperature)

Local management guidance should be followed.

Please record any cases of extravascular administration in the source documents and drug administration forms. Where clinically significant, please capture the extravasation in the source documents and eCRF as an adverse event.

An estimate of the approximate volume administered to the participant prior to extravasation and the remaining volume (and radioactivity of the ^{225}Ac-GPC3 ACC) in the syringe should be reported on the appropriate drug administration form.

8. DESTRUCTION OF STUDY DRUG

See Section 4 (BAY 3547922) and Section 5 (BAY 3547926) for storage of used study drug.

Local regulations for storage and disposal of investigational medicinal product must be followed when destroying Cold GPC3 ACC vials and syringes.

^{225}Ac-GPC3 ACC vials (used and unused) must be stored within appropriate shielding and in a secured area dedicated for storage of radioactive materials. This area must have sufficient capacity to store all vials of ^{225}Ac-GPC3 ACC and allow for the segregation of incoming study drug from used, rejected or expired vials. Study site procedures should reflect this separation to ensure misadministration is avoided.

Both used and unused vials of ^{225}Ac-GPC3 ACC, and other contaminated materials used for preparation and administration, are to be treated as radioactive waste. The half-life of actinium-225 (9.92 days) allows for decay-in-storage, which typically ranges from 10 to 20 half-lives. However, some jurisdictions may require the use of a third-party waste broker for the disposal of vials and contaminated materials. Please refer to your local regulations for storage and disposal. See also Section 11.

It is possible that your CRA may need access to the unused Cold GPC3 ACC (BAY 3547922) lyophilizate vials (as permitted as per local guidelines). Destruction of the unused Cold GPC3 ACC vials should only be performed after drug accountability verification is confirmed by the CRA and the CRA has given permission for destruction.

Complete the ***Drug Accountability Log for ^{225}Ac-GPC3 ACC (BAY 3547926)*** (Section 13, Appendix 7a) and ***Drug Accountability Log for Cold GPC3 ACC (BAY 3547922)*** (Section 13, Appendix 7b) for the vials sent for destruction/decay. In addition, all vials can be added to the ***Destruction Certificate*** (see Section 13, Appendix 9a and 9b) ***for ^{225}Ac-GPC3 ACC (BAY 3547926)*** and ***Cold GPC3 ACC (BAY 3547922).***

9. RADIATION EXPOSURE PRECAUTIONS & PARTICIPANT MANAGEMENT

Due to the advantageous properties of α-particle emitting radiopharmaceuticals, the expected radiation doses related to drug handling and participant management are considerably lower as compared to common radiopharmaceuticals. β- and γ-emissions associated with the actinium-225 decay, however, may lead to - even though small external exposure.

Following best practice procedures (i.e. wearing protective clothes) and the ALARA principles (i.e. minimize the time of exposure, hold distance from radioactive sources, and apply suitable shielding) for the handling of radioactive materials ensures safety of the study site staff in handling ^{225}*Ac-GPC3 ACC*.

However, administration of radioactive drugs involves a potential risk for others due to radiation from the participant (external exposure) and possible contamination (accidental intake) from spillages of urine, faeces, blood etc. (internal exposure).

As a general precaution, contact with the participant's bodily fluids (including stools) should be avoided. This is of particular importance for pregnant woman and small children.

a) External exposure from the participant's body
Once injected, both α- and β-particles are stopped by the participant's body tissue. Attenuation is less pronounced for γ-emissions though γ-radiation from the participant's body is minimal. Pursuant to regulations based on dose rates from participants being treated with radionuclides, participants being treated with ^{225}Ac-GPC3 ACC are allowed to leave the study site after the injection unless study procedures/local regulations require hospitalization.

b) Internal exposure
During the study treatment and after the last administration of ^{225}Ac-GPC3 ACC, a certain amount of radioactivity is eliminated via faeces and urine. Within two weeks of administration radioactivity is predominantly eliminated via faeces. Therefore, the participant, as well as others (e.g., caregivers, members of the participant's household, relatives), are requested to strictly follow the provided recommendations for participants, or the equivalent local study site document(s) (Appendix 10). The participant is given a participant contact card with the names and phone numbers of contact persons at the study site in case of emergency.

c) Surgery / Post-mortems
Because radioactive actinium-225 may remain in the body for long periods of time, it is recommended that precautions are used if surgery or invasive post-mortem examinations are carried out within four months of the administration of ^{225}Ac-GPC3 ACC. Biological waste from surgery and autopsies should be regarded as radioactive biohazard waste and should be disposed of in accordance with local regulations. Surgical teams should be advised by the participant (or family member) of the last treatment date of ^{225}Ac-GPC3 ACC (the participant contact card provides contact information to address any radiation questions or concerns).

d) Catheterized participants
If a participant is catheterized, absorbent chucks are placed below the line and urine collection bag. Additionally, a plastic container should be placed under the bag to collect urine in the event of a collection bag leakage.

The participant or the caregiver should wear disposable gloves when handling the catheter and urine disposal bags. The urine should be disposed in the toilet and the toilet should then be flushed. The collection bags and used gloves should be placed in a sealed plastic bag and disposed of as ordinary waste products.

10. RADIOACTIVE CONTAMINATION MONITORING & DECONTAMINATION PROCEDURE

As actinium-225 and its progeny emit α-, β- and γ-radiation, a wide range of contamination monitors can be used to detect potential contamination from ^{225}Ac-GPC3 ACC. Use of conventional beta/gamma contamination probes are advantageous over alpha specific monitors for the routine daily check for potential contamination. Alpha detectors work best at distance of 2 cm and less.

10.1 Spillage of ^{225}Ac-GPC3 ACC

Following best practice procedures (i.e., wearing protective clothes) and the ALARA principles ensures safety of the study personnel site staff handling the ^{225}Ac-GPC3 ACC.

In the event of spillage from ^{225}Ac-GPC3-ACC, monitoring of working areas, radioactivity measurements and decontamination measures are to be carried out by trained staff according to the local radioprotection policy.

For ^{225}Ac-GPC3-ACC, the use of commercially available decontamination solutions like "Count-off" (Perkin Elmer) on paper tissues are recommended for the decontamination. Decontamination solutions may leave some dry debris. This can easily be wiped off with a tissue dampened with water. In case of contact with eyes, rinse immediately with plenty of water.

Record details of any spillages in the ***Drug Administration Form for ^{225}Ac-GPC3 ACC (BAY 3547926)*** (Section 13, Appendix 7a).

11. DRUG ACCOUNTABILITY

It is important that vials (including unused vials) are NOT disposed of until confirmation has been given by the CRA if this is permitted per local guidelines.

In order for the CRA to trace ^{225}Ac-GPC3 ACC and Cold GPC3 ACC from vial to participant, the CRA is required to access all study drug related documents during visits to the imaging site and/or the radiopharmacy/nuclear medicine department (as appropriate and depending on where the documentation of the used vials is stored).

The following key documents may be reviewed during drug accountability:

- Study Drug shipping documents:
  - Dispatch Order Forms / copy of the order for ^{225}Ac-GPC3 ACC and Cold GPC3 ACC
  - Temperature logger data
- Drug Preparation Forms
- Drug Administration Forms
- Drug Accountability Logs
- Destruction/decay documentation

Drug accountability will be done based on the documentation above, which covers study drug circulation from the shipment to the site until destruction. CRA should have access to the unused Cold GPC3 ACC if needed and if permitted per local guidelines.
Accountability of ^{225}Ac-GPC3 ACC vials will be completed via the above documentation which should be made available for review by the CRA.

12. COMPLETING STUDY DRUG HANDLING DOCUMENTS

The forms/logs listed in the Section 13 are important essential documents for clinical trials involving ^{225}Ac-GPC3 ACC. The Study Drug Accountability & Destruction Log, Study Drug Preparation Form, Study Drug Administration Form, and Destruction Certificate must be completed and filed for each vial/ administration/participant.

If you are unsure of how to complete a document, please contact your CRA for advice.

If you wish to use your own local drug accountability/destruction logs please contact your CRA (before implementation) who will review and verify if Bayer requirements are met.

13. LIST OF APPENDICES

	Documents
1	Handling & Radioprotection Information Package for Radioactive Materials License Towards Actinium
2	Approval Form for Dial Setting of Dose Calibrators
3a	Study Drug Order Form for ^{225}Ac-GPC3 ACC (BAY 3547926)
3b	Study Drug Order Form for Cold GPC3 ACC
4	Materials tested for compatibility (BAY 3547926 and BAY 3547922)
5a	Dispatch Order Form for ^{225}Ac-GPC3 ACC (BAY 3547926) (example)
5b	Dispatch Order Form for Cold GPC3 ACC (example)
6a	Study Drug Preparation form for ^{225}Ac-GPC3 ACC (BAY 3547926)
6b	Study Drug Preparation form for Cold GPC3 ACC
7a	Study Drug Administration form for ^{225}Ac-GPC3 ACC (BAY 3547926)
7b	Study Drug Administration form for Cold GPC3 ACC
8a	Study Drug Accountability & Destruction Log for ^{225}Ac-GPC3 ACC (BAY 3547926)
8b	Study Drug Accountability & Destruction Log for Cold GPC3 ACC
9a	Destruction Certificate for ^{225}Ac-GPC3 ACC (BAY 3547926)
9b	Destruction Certificate for Cold GPC3 ACC
10	Recommendations for Participants in Targeted Alpha Therapy Studies
11	Temperature Excursion at study site report (TESR) form
12	Storage issue at Site Report form

BAYER APPROVAL SIGNATURES		
Title/Role	**Printed name**	**Sign and date**
Study Manager	Ida Ratih	
Study Lead Monitor	Ed Brewster	
IMM	Thomas Hayto	
TDT Lead	Aasmund Larsen	
QA Specialist	Beate Brenna	
Clinical Supply Manager – Cold	Jessica Vorholz	
Clinical Supply Manager – Hot	Eva Haaland	
Senior TAT Expert	Eric Smith	
Radiation Safety Committee	Haavar Gausemel	