Boehringer Ingelheim

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The purpose of this document is to provide a supplement to the clinical trial protocol and investigator´s brochure, including details of interest to the pharmacist and other site personnel directly involved in the handling of investigational product.

1. DESCRIPTION OF TRIAL MEDICATION

Trial medication will be provided by Boehringer Ingelheim, packaged in accordance with the principles of Good Manufacturing Practice and labelled in accordance with regulatory requirements:

- BI 765423 concentrate for solution for infusion, [redacted] glass vial ([redacted] nominal fill volume).
- Placebo for BI 765423 concentrate for solution for infusion [redacted], glass vial ([redacted] nominal fill volume).

Each vial will be covered with a yellow wrap-around foil for blinding purposes.

[redacted] vials of BI 765423 or placebo will be placed in one box. Each vial will be labelled with a wrap-around booklet label. Each box will be labelled with a booklet label and will also contain a tear-off sticker that can be used in patient documentation.

Storage conditions:
Store in a refrigerator at 2-8°C (36-46°F). Do not freeze. Keep the vials in the outer carton in order to protect them from light. Do not shake.

Prior to each administration of trial medication, the site personnel will access the interactive response technology (IRT) system used in this trial and enter the necessary information. The IRT system will assign unique medication numbers for the patient's visit. Instructions for this process can be found in the IRT reference document.

All vials are intended for single use only. Trial medication assigned to an individual patient must not be used for another patient. Residual volumes in vials and/ or in syringes must be discarded according to the requirements once preparation is completed. Used vials should be discarded according to local requirements.

2. GENERAL REMARKS

The pharmacist, his/ her deputy or other appropriately licensed and authorized drug-preparation personnel will prepare the trial medication as requested by the investigator. Handling and preparation of the trial medication should be performed according to routine site procedures using aseptic techniques.

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Prior and during the preparation and prior to the intravenous administration, the solution should be checked for any changes (e.g., color) and for the absence of particles. [redacted]

If you have any concerns regarding the appearance of the solution, please do not use the solution. Please retain the solution and contact your Clinical Research Associate (CRA) or the Clinical Trial Manager (CTM) who may require you to complete a complaints form.

In case any anomaly in either the vial before preparation or the intravenous administration after preparation are detected (to either the product itself or the packaging), submit a Product/Device Complaint Form (available in the ISF) to the BD&C Team [redacted]. The medication should be put in quarantine and a new medication should be assigned in IRT system.

Do not use pneumatic tubing for medication transport.

3. CONSUMABLES

The materials suitable for the preparation and administration of BI 765423/ placebo are listed in Table 1.

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Table 1 Suitable materials for preparation and administration of BI 765423/ placebo

Material	Dimension	Qualitative composition
Sterile blunt fill filter needles or sterile blunt fill needles without filter	18G x 1 ½"	Stainless steel
Optional: Vial adapter	N/A	Acrylonitrile-butadiene-styrene-copolymer (ABS) + Styrene-acrylonitrile-copolymer (SAN)
Sterile syringe with luer lock connection	[redacted]	Polypropylene (PP)
Optional: Syringe closure	N/A	Polyethylene (PE)
Optional: Three-way stopcock	N/A	Polyamide (PA)
Optional: Needle-free valve	N/A	Silicone, polycarbonate (PC)
Infusion line (tubing intended for syringe pump use)	Up to 300 cm	Polyethylene (PE)
	Up to 200 cm	Polybutadiene (PB)
0.2 µm inline-filter	Filter area ≤ 10 cm²	Polyethersulfone (PES) uncharged Polysulfone (PSU)
i.v. catheter	Up to 24G	Fluoroethylene-propylene (FEP) Polyurethane (PUR)

Materials suitable for preparation and administration of the trial medication listed in Table 1 as well as the syringe pump will be provided to sites by a central vendor. Please refrain from using your own (locally sourced) materials to avoid non-compliances which may impact patient safety.

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4. INSTRUCTIONS FOR PREPARATION OF BI 765423/ PLACEBO

4.1 CONDITIONING STEPS BEFORE DRUG PREPARATION

Prior to starting the preparation steps mentioned below in section 4.2, equilibrate the vials containing BI 765423/ placebo at room temperature over [redacted]. After conditioning, homogenize the vial content by gentle manual horizontal swirling. Do not invert the vial.

4.2 PREPARATION OF THE INFUSION SOLUTION

BI 765423 concentrate for solution for infusion (drug product) or placebo will be used undiluted.

A summary of the required volumes of drug product/ placebo (referred to as DP/placebo) as well as the required number of drug product/ placebo vials is provided in Table 2.

Table 2 Required volumes and number of vials for the preparation of infusion solution.

Target dose [mg]	Number of DP/placebo vials	DP/placebo volume [mL]	Target concentration [mg/mL]	Infusion volume [mL]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The prepared volume of infusion solution should be sufficient to account for the infusion volume and the dead volume of the infusion set (expected to be max. [redacted]).

For preparation of the infusion solution, collect the DP/placebo volume defined in Table 2 in a sterile [redacted] polypropylene syringe (using a needle or a vial adapter).

4.3 BLINDING AND LABELING

The possibility to differentiate between BI 765423 and placebo based on color and viscosity of solution cannot be ruled out. Therefore, additional blinding measures must be implemented. Specifically, a blinding label must be applied to the infusion syringe and a blinding cover must be applied to the infusion line to prevent inadvertent unblinding of the investigators/ site personnel or patients. Blinding materials will be provided to sites by a central vendor.

The pharmacist or the unblinded site personnel should create a label containing the trial number, the subject ID, the visit number and date, the medication numbers

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assigned by the IRT system and attach the label to the infusion syringe accordingly. Label text containing “BI 765423”, or “Placebo” must be avoided.

5. IN-USE STABILITY

Chemical and physical in-use stability and compatibility was demonstrated for BI 765423 diluted in [redacted] – [redacted] ≤[redacted] in clinical sets as described. Do not freeze.

*Note: The maximum total storage time must not exceed 24 hours (including storage at 2–8°C and ≤30°C).

From a microbiological point of view, the infusion solution should be used immediately. The infusion solution is not intended to be stored unless preparation has taken place under controlled and validated aseptic conditions. If not used immediately after preparation, in-use storage times and conditions are the responsibility of the user.

6. INSTRUCTIONS FOR ADMINISTRATION

In order to avoid an infusion reaction caused by the administration of low temperature solution the infusion container must be brought to room temperature before infusion.

Assemble the infusion set (i.e., infusion syringe, infusion line, inline filter, and optional components, see Table 1). Fill the infusion set with the prepared infusion solution to remove any air.

Administer the infusion over 1 h as described in section 4.1.1. and 4.1.4 of the clinical trial protocol using the administration volume provided in Table 2.
Please note that flushing is **NOT** required after completion of the infusion.

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7. VERSION HISTORY

Changes of the IPAP are listed in Table 3.

Table 3 Version history

Version	Effective Date	Description of changes	Author(s)
1.0	See signatures (electronically obtained)	Initial version	[redacted]
2.0	See signatures (electronically obtained)	PR #2394526: Adaption of in-use storage time in section 5 "In-use stability"	[redacted]

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Document Approvals

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