Boehringer Ingelheim

Non-Interventional Study (NIS) Protocol

Document Number:	c36738888-04
BI Study Number:	1368.93
BI Investigational Product:	Spesolimab
Title:	Post-marketing Surveillance of Spesolimab I.V. Infusion in improvement of Generalized Pustular Psoriasis (GPP) with acute symptoms in Japan
Brief lay title:	PMS of Spesolimab I.V. in GPP patients with acute symptoms
Protocol version identifier:	Version 4.0
Date of last version of protocol:	1 Apr 2024
PASS:	Yes
EU PAS register number:	EUPAS49953
Active substance:	Spesolimab
Medicinal product:	Spesolimab I.V. Infusion
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder:	[redacted]
Joint PASS:	No
Research question and objectives:	The primary outcome is the incidence of investigator/BI-defined drug reactions (including safety concerns: Serious infections, Serious hypersensitivity).
Country of study:	Japan
Author:	[redacted]

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

Marketing authorisation holder:	[redacted]
MAH contact person:	[redacted]
EU-QPPV:	[redacted]
Signature of EU-QPPV:	e-signature is on BIRDS.
Date:	1 APR 2024

Page 1 of 30

Proprietary confidential information
© 2024 Boehringer Ingelheim Group of companies. All rights reserved.
This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

1. TABLE OF CONTENTS

TITLE PAGE 1
1. TABLE OF CONTENTS 3
2. LIST OF ABBREVIATIONS 5
3. RESPONSIBLE PARTIES 6
4. ABSTRACT 7
5. AMENDMENTS AND UPDATES 9
6. MILESTONES 9
7. RATIONALE AND BACKGROUND 9
8. RESEARCH QUESTION AND OBJECTIVES 10
9. RESEARCH METHODS 10
9.1 STUDY DESIGN 10
9.2 SETTING 10
9.2.1 Study sites 10
9.2.2 Study population 11
9.2.2.1 Inclusion/ exclusion criteria 11
9.2.2.2 Registration period 11
9.2.2.3 Patient registration method 11
9.2.3 Study visits 11
9.2.4 Study discontinuation 12
9.3 VARIABLES 12
9.3.1 Exposures 12
9.3.2 Outcomes 12
9.3.2.1 Primary outcomes 12
9.3.2.2 Secondary outcomes 12
[redacted]
9.3.3 Covariates 13
9.4 DATA SOURCES 13
9.5 STUDY SIZE 14
9.6 DATA MANAGEMENT 14
9.7 DATA ANALYSIS 14
9.7.1 Main analysis 15
[redacted]

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

9.8 QUALITY CONTROL 15
9.9 LIMITATIONS OF THE RESEARCH METHODS 15
9.10 OTHER ASPECTS 16
9.10.1 Data quality assurance 16
9.10.2 Study records 16
9.10.2.1 Source documents 16
9.10.3 Completion of study 16
9.10.4 Protocol deviations 16
10. PROTECTION OF HUMAN SUBJECTS 16
10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT 17
10.2 STATEMENT OF CONFIDENTIALITY 17
11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 17
11.1 DEFINITIONS OF ADVERSE EVENTS 17
11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING 18
11.3 REPORTING TO HEALTH AUTHORITIES 20
12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS 20
13. REFERENCES 21
13.1 PUBLISHED REFERENCES 21
13.2 UNPUBLISHED REFERENCES 21
ANNEX 1. LIST OF STAND-ALONE DOCUMENTS 22
ANNEX 2. FLOW CHART OF VARRIABLES 23
ANNEX 3. JDA GPP SEVERITY SCORE 24
ANNEX 4. ENCEPP CHECKLIST FOR STUDY PROTOCOL 25

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

2. LIST OF ABBREVIATIONS

AD	Atopic Dermatitis
ADR(s)	Adverse Drug Reaction(s)
AE(s)	Adverse Event(s)
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BI	Boehringer Ingelheim
CRF	Case Report Form
CRP	C-reactive protein
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GPP	Generalized Pustular Psoriasis
GPSP	Good Post-marketing Study Practice
IRB	Institutional Review Board
JDA	Japanese Dermatological Association
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Drug Regulatory Activities
MHLW	Ministry of Health Labour and Welfare
[redacted]	[redacted]
ONIS	Observational Non-Interventional Study
PASS	Post-Authorization Safety Study
PMD	Pharmaceutical and Medical Device
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance
RBC	Red Blood cell Count
RMP	Risk Management Plan
SAE	Serious Adverse Event

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

SEAP	Statistical and Epidemiological Analysis Plan
SOP	Standard Operating Procedure
WBC	White Blood cell Count

3. RESPONSIBLE PARTIES

[redacted]

Contact details and the list of all investigators will be kept in a stand-alone document. This document will be managed in the Post Marketing Surveillance (PMS) tracking system which manages the contracts with site and investigators name.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spesolimab I.V. Infusion			
Name of active ingredient: Spesolimab			
Protocol date: 27 Jul 2022	**Study number:** 1368.93	**Version/Revision:** Version 4.0	**Version/Revision date:** 1 Apr 2024
Title of study:	Post-marketing Surveillance of Spesolimab I.V. Infusion in improvement of Generalized Pustular Psoriasis (GPP) with acute symptoms in Japan		
Rationale and background:	This PMS plan is proposed as additional pharmacovigilance plan of the Japanese RMP. In Japan, post-approval execution of PMS is requested by the Japanese Pharmaceuticals and Medical Devices Act (J-PMD Act) due to accumulate safety and effectiveness data for re-examination. Re-examination period is defined by J-PMD Act. Eight years after approval for new indication of new compound, results of PMS need to be submitted as a part of re-examination dossier to the Japanese regulatory authority, the Ministry of Health, Labour and Welfare (MHLW). Collected data from PMS will be included in the Japanese periodic safety reports and submitted to PMDA on designated dates until the end of re-examination period. The Effisayil™ 1 (1368.13) was Multi-center, double-blind, randomized, placebo-controlled, Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose of Spesolimab in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity. As the number of Japanese patients treated with Spesolimab in Effisayil™ 1 study was only 2 (total: 51), confirmation of the safety profile of Spesolimab treatment for acute phase GPP patients in the real world clinical setting is required.		
Research question and objectives:	To evaluate the incidence of adverse drug reactions (including safety concerns: Serious infections, Serious hypersensitivity) of Spesolimab I.V. Infusion and to understand GPP disease activities in the real world setting in GPP patients with acute symptoms.		
Study design:	Non-interventional cohort study with new data collection (NISnd) Patients newly initiated Spesolimab I.V. Infusion will be enrolled and followed up to 28 weeks after the first dose of Spesolimab I.V. Infusion unless there is an inevitable incident (death, move to other hospital etc.,). The patients who are retreated with Spesolimab up to 28 weeks after the first dose of this drug will be followed by the investigators up to 8 weeks after the retreatment. The max observation period will be 36 weeks after the first dose of this drug.		

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spesolimab I.V. Infusion			
Name of active ingredient: Spesolimab			
Protocol date: 27 Jul 2022	**Study number:** 1368.93	**Version/Revision:** Version 4.0	**Version/Revision date:** 1 Apr 2024
Population:	Inclusion criteria - GPP patients with acute symptoms who are administered Spesolimab I.V. Infusion in Japan Patients who have never been treated with Spesolimab before enrolment		
Variables:	Outcomes: Primary outcome: Incidence of adverse drug reactions (ADRs) Secondary outcome: None [redacted] Others: characteristics associated with ADRs Demographics, baseline characteristics, labs and vitals as baseline, previous/concomitant medications etc.		
Data sources:	Patients' data will be collected by electronic Case Report Form on Electronic Data Capture system		
Study size:	38 (for safety set)		
Data analysis:	Analyses are descriptive in nature, incidence rates and corresponding confidence intervals will be given for all ADRs in terms of Spesolimab I.V. Infusion for GPP patients with acute symptoms.		
Milestones:	Planned start of data collection: 1 MAR 2023 Planned end of data collection: 31 DEC 2025 Study Report planned to be archived in 4Q 2026		

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
2.0	14 September, 2022	Study visits	Amendment	Added study visits by local agencies' requirement
3.0	22 September, 2023	ANNEX 4	Amendment (non-substantial)	Attached ENCePP Checklist due to CAPA corrective action. This amendment is non-substantial and categorized as unnecessary to submit to PMDA.
4.0	1 April, 2024	9.6 DATA MANAGEMENT	Amendment (non-substantial)	Contract 2 of 9.6 DATA MANAGEMENT was changed. This amendment is non-substantial and categorized as unnecessary to submit to PMDA.

6. MILESTONES

Milestone	Planned Date
Start of data collection	1 March 2023
End of data collection	31 December 2025
Registration in the EU PAS register	4Q 2022
Final report of study results:	4Q 2026

7. RATIONALE AND BACKGROUND

Spesolimab is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signaling. Binding of Spesolimab to IL36R is anticipated to prevent the subsequent activation of IL36R by cognate ligands (IL36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways with the aim to reduce epithelial cell/ fibroblast/

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

immune cell-mediated inflammation and interrupt the inflammatory response that drives pathogenic cytokine production in inflammatory diseases including generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP), Atopic Dermatitis (AD), hidradenitis suppurativa (HS), and inflammatory bowel disease (IBD).
The 1368.0013 trial was a randomised and placebo controlled Phase II trial that evaluated the efficacy and safety of Spesolimab in patients with acute phase GPP. And the 1368.0013 is included into the CTD.

The number of Japanese patients treated with Spesolimab in 1368.0013 trial was two patients (1 patient: OL Spesolimab at Day 8 and 1 patient: Spesolimab from the baseline)
(2 Japanese patients, total of Spesolimab treatment: 51). (c31523813-01) The humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signaling for GPP will be the first-in-class in Japan. Therefore, we propose to conduct PMS to capture the safety information of Spesolimab treatment for GPP patients with acute symptoms in the real-world clinical setting from the time of J-NDA.

In Japan, a decision will be made Sep 2022 (Plan). This PMS plan is proposed as additional pharmacovigilance plan of the Japanese RMP.
In Japan, post-approval execution of PMS is requested by the Japanese Pharmaceuticals and Medical Devices Act (J-PMD Act) due to accumulate safety and effectiveness data for re-examination.

Re-examination period is defined by J-PMD Act. Eight years after approval for new indication on new compound, results of PMS need to be submitted as a part of re-examination dossier to the Japanese regulatory authority, the Ministry of Health, Labour and Welfare (MHLW).

Collected data from PMS will be included in the Japanese periodic safety reports and submitted to PMDA on designated dates until the end of re-examination period.

8. RESEARCH QUESTION AND OBJECTIVES

The primary objective is to evaluate the incidence of adverse drug reactions of Spesolimab I.V. Infusion and to understand GPP disease activities in the real world setting in GPP patients with acute symptoms.

9. RESEARCH METHODS

9.1 STUDY DESIGN

Non-interventional cohort study with new data collection (NISnd) (Observational)

9.2 SETTING

9.2.1 Study sites

Sites (mainly hospitals) at which Spesolimab I.V. Infusion are available for prescription throughout entire country will be selected according the number of GPP patients with acute symptoms.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

Planned number of sites: Approximately 70 Sites

A medical representative of Sales Division (GPSP Operating function) will explain the objectives and design of this study to the investigators at study sites and exchange a written contract with the head of the study site (e.g., hospital director).

9.2.2 Study population

As this is a non-interventional study, treatment with Spesolimab I.V. Infusion for GPP patients with acute symptoms at the contracted site is for participation. No limitations are set up on background factors and their concomitant drugs in use of actual medical practice.

9.2.2.1 Inclusion/ exclusion criteria

Inclusion criteria:
- GPP patients with acute symptoms who are administered Spesolimab I.V. Infusion in Japan
- Patients who have never been treated with Spesolimab I.V. Infusion before enrolment

Exclusion criteria:
None

9.2.2.2 Registration period

From 01 March 2023 to 28 February 2025

9.2.2.3 Patient registration method

The registration method will be a continuous investigation system. Patients who begin treatment with Spesolimab I.V. Infusion will be registered by entering necessary information in the Electronic Data Capture (EDC).

Patient registration will be stopped when the 38 target number of patients as safety set for the study is reached. After the end of the registration period, investigators use a signed form to confirm that patients have been registered continuously at the site. A log of all patients included in the study will be maintained at the site.

9.2.3 Study visits

The patients will be followed by the investigators up to 28 weeks after the first dose of Spesolimab I.V. Infusion (baseline, Week1, 4, 8, 16, 28) unless there is an inevitable incident (death, move to other hospital etc.,). The patients who are retreated with Spesolimab up to 28 weeks after the first dose of this drug will be followed by the investigators up to 8 weeks after the retreatment. In these cases, week 0, 1, 4, 8 after the retreatment will be added on the study visits and the max observation period will be 36 weeks after the first dose of this drug.

See ANNEX 2 for more details. The patients will be asked to come for follow up visits by investigators.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

9.2.4 Study discontinuation

[redacted] reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any effectiveness/safety information that could significantly affect continuation of the study or any other administrative reasons.
3. Violation of Good Post-marketing Study Practice (GPSP), the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

The investigator / the study site will be reimbursed for reasonable expenses incurred in case of study termination (except in case of the third reason).

9.3 VARIABLES

9.3.1 Exposures

Exposure to Spesolimab is estimated as time from the day the drug is initiated until the day the drug is last administrated on a patient-level (or the final contact with the patient during the regular observation period).

The patients will be followed by the investigators up to 28 weeks after the first dose of Spesolimab I.V. Infusion unless there is an inevitable incident (death, move to other hospital etc.,). The patients who retreat with Spesolimab up to 28 weeks after the first dose of this drug will be followed by the investigators up to 8 weeks after the retreatment. The max observation period will be 36 weeks after the first dose of this drug.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The primary outcome of this study is the incidence of adverse drug reactions (ADRs). ADRs definition and reporting is described in section 11.

9.3.2.2 Secondary outcomes

None

[redacted]

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

[redacted]

9.3.3 Covariates

- Demographics
  - Gender (Pregnancy status, only for female)
  - Age (Birth year)
  - Height (cm)
  - Weight (Kg)
  - Vital signs (blood pressure, pulse rate)
  - Smoking status
  - Reason for Spesolimab I.V. Infusion prescription (GPP with acute symptoms, other)
  - Hospitalisation caused by GPP (including the period)
- Date of diagnosis (GPP and this Flare)
- Treatment states of Spesolimab I.V. Infusion (start date, infusion volume and administration status)
- Medical history / Concomitant diagnosis
- Natural medical history for GPP (Average number of flares per year, Time with involved skin/involved skin with pustules over the last year, Trigger event for this flare, Duration of flare)
- Previous/Concomitant medications including GPP treatment
- Concomitant therapy
- Laboratory tests:
  Collect data which is needed for case.
  - Hematological (RBC, Hemoglobin, Hematocrit, Platelet count)
  - Liver function (AST[GOT], ALT[GPT], γ-GTP, ALP, Total Bilirubin)
  - Other biochemical (Creatinine, Na, K, CK)
  - Others
- Assessment of GPP disease activity:
  - JDA GPP Severity Score[1)]
  - Systemic symptoms (Fatigue, Malaise, Pain)

See ANNEX 2 for more details.
[1)] See ANNEX 3

9.4 DATA SOURCES

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via the EDC system.

In EDC system, one casebook will be set. And Book 1 includes baseline, Week 1, 4, 8, 16, 28. In the case that the patients are retreated with this drug up to 28 weeks after the first dose of this drug, week 0, 1, 4, 8 after the retreatment will be added on the study visits.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

The data are to be transmitted immediately after being entered into EDC at the end of observation period or at the study discontinuation.
For any adverse events, the data should be immediately entered into EDC and transmitted.

9.5 STUDY SIZE

In the 1368.0013 trial, safety specifications (Serious infections, Serious hypersensitivity) were not occurred in Japanese population.

The incidence rate of adverse events classified as Serious infections up to Week 1 after the start of the treatment was 2.9% (1 of 35 patients) in the Spesolimab group, and no such an event was not reported in the placebo group. Furthermore, 5.9% (3 of 51 cases) of Serious infections have been reported in 51 patients who received at least one dose of Spesolimab.

The incidence rate of adverse events classified as Serious hypersensitivity up to Week 1 after the start of the treatment was 5.7% (2 of 35 patients) in the Spesolimab group and 5.6% (1 of 18 patients) in the placebo group. Furthermore, 5.9% (3 of 51 cases) of serious hypersensitivity have been reported in 51 patients who received at least one dose of Spesolimab.

If the true proportion of patients with Serious infections, Serious hypersensitivity is assumed to be 3-fold (i.e., 17.7%), the sample size of 38 is required for rejecting the null hypothesis of incidence = 5.9% by using z test with a one-sided significance level of 0.05 and >=80% power.
Therefore, setting 38 patients as safety analysis set.

9.6 DATA MANAGEMENT

Patients' data will be gathered by EDC system provided by external vendor below.

	Contract 1	Contract 2
Company Name	[redacted]	
Outsourced work	EDC system setting Patient registration Clinical Data Management	Document management of contract with site.

9.7 DATA ANALYSIS

This is a non-interventional study to collect data on patients under routine medical practice on safety and appropriate use of Spesolimab treatment. Analyses are descriptive in nature, including confidence intervals. Subgroup analyses will be performed exploratorily.

Per local regulation, any patient who meets one of the following criteria is treated as ineligible for all analyses:

- No visit after registration.
- No required registration procedure was followed.
- No valid site contract was available.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

Full details of the statistical analysis will be documented in the SEAP, which will be finalized before the end of data collection.

9.7.1 Main analysis

In general, safety analyses will be descriptive in nature, and will be based on [redacted] standards, and will focus on any ADRs, serious AEs, AEs leading to death, AEs leading to treatment discontinuation. Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'in-treatment period'; the residual effect period (REP) is defined as 16 weeks after the last dose of Spesolimab. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'in treatment period'. Note that for patients who are observed beyond the REP, AE up to the end date of observation will be available for display in this study.

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). For this protocol, an AE is considered to be an ADR if either the physician who has reported the AE or the sponsor assesses its causal relationship as 'related'.

The frequency and incidence of AEs/ADRs will be tabulated by system organ class and preferred term for overall and for subgroups based on the important baseline characteristics (see section 9.3.3).

No imputation is planned for missing AE data except for missing onset dates which will be handled according to [redacted] standard.

[redacted]

9.8 QUALITY CONTROL

All processes are conducted according to GPSP Standard Operating Procedures (SOP) [redacted]. Appropriate records and documents are stored based on the GPSP SOPs and these processes are checked by internal self-check.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The general scientific objective of this non-interventional study is to obtain an incidence of adverse drug reactions in the population under study.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

Due to the design which uses a single cohort in this observational safety study, an important limitation is the absence of an internal comparator group to help indicate whether observed rates are higher than those expected.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

This PMS study is conducted in accordance with both the in-house SOP and working instructions which are compliant with GPSP.

9.10.2 Study records

The eCRFs for individual patients will be provided by the sponsor via remote data capture.

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the study site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

For eCRFs all data must be derived from source documents.

9.10.3 Completion of study

When the study is completed, the investigator should inform the head of the study site of the completion in writing, and the head of the study site should promptly inform the IRB and sponsor of the completion in writing if needed.

9.10.4 Protocol deviations

The investigator or sub-investigator should record all study protocol deviations. The investigator should provide and submit the sponsor and the head of the study site the records of deviations infringing the Japanese GPSP or deviations to eliminate an immediate hazard to study subjects and for other medically inevitable reasons.

10. PROTECTION OF HUMAN SUBJECTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

There is no regulation or requirement for ensuring the well-being and rights of participants in a non-interventional observational study.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the patient's treating physician.

The review by IRB is not mandatory for conducting PMS in Japanese GPSP. The sponsor will enter into a contract with a representative (e.g., head of hospital) in accordance with GPSP. Written informed consent prior to patient participation in the trial is not a regulatory or legal requirement in accordance with GPSP.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Data generated as a result of the PMS needs to be available for inspection on request by the regulatory authorities.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions (see [redacted] for collection requirements) and of any new information that might influence the evaluation of the benefit-risk balance of the product while the study is being conducted.

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse drug reaction
An adverse drug reaction (ADR) is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

Serious adverse event

A serious adverse event is defined as any AE which

- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

An AE which possibly leads to disability will be reported as an SAE. Every new occurrence of cancer or an exacerbation of an existing cancer will be reported as a SAE regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs

The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the eCRF. When any adverse events occur, the data should be immediately entered into eCRF and transmitted.

- all adverse events (AEs) (serious and non-serious),
- all AEs with fatal outcome,

All ADRs including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

The following should also be recorded as an (S)AE in the eCRF:

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

Causal relationship of adverse event

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**
- A **plausible time to onset of the event** relative to the time of drug exposure
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Pregnancy:
In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken Spesoimab, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the ONIS AE form is to be completed and forwarded as well within the respective timelines.

Focused safety specification on J-RMP:
Serious infections, Serious hypersensitivity (important identified risks)

Information required
For each reportable adverse event, the investigator should provide the information requested on the appropriate eCRF pages.

Reporting of related Adverse Events associated with any other BI drug
The investigator is encouraged to report all adverse events related to any BI drug other than the Spesolimab according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the Marketing Authorization Holder (MAH) according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The progress reports and final reports will be submitted to PMDA in Japan Periodic safety report. And also the final report for this PMS is included in re-examination documents.
This study is planned for the publication based on the Study report.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

The rights of the physician and of the sponsor with regard to publication of the results of this PMS study are described in the contract. As a general rule, no PMS study results should be published prior to finalization of the Study Report.

In addition, further interim analysis might be performed for the scientific presentations and publications for the purposes of promoting appropriate use of Spesolimab I.V. Infusion.

13. REFERENCES

13.1 PUBLISHED REFERENCES

R18-1702 Review Report - Cosentyx. Pharmaceutical and Medical Devices Agency (PMDA) Nov. 12, 2015.

13.2 UNPUBLISHED REFERENCES

c31523813-01 [redacted] Effisayil™ 1: Multi-center, double-blind, randomized, placebocontrolled, Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose of BI 655130 in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity. 14 May 2021.

[redacted]

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
None	None		

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

ANNEX 2. FLOW CHART OF VARRIABLES

Items	Observation period Time point	
	Baseline (before treatment of Spesolimab)	Week 1, 4, 8, 16, 28 or at discontinuation (week 0, 1, 4, 8 after the retreatment in the case that the patients are retreated with this drug up to 28 weeks after the first dose of this drug*[4])
Demographics*[1]	X	-
Treatment states of Spesolimab	X	X
Medical history/Concomitant diagnosis	X	-
Previous/Concomitant medications	X	X
Laboratory test*[2]	X	X
Assessment of GPP disease activity	X	X*[4]
Pregnancy status	X	X
Adverse events, including laboratory tests (if corresponding AEs are reported) *[3]	X	X

*1: Demographics (see section 9.3.3) at baseline are recorded. Pregnancy status will be recorded if a patient has become pregnant.
*2: Laboratory tests (see section 9.3.3) are recorded. Collect only the points that is examined, if applicable.
*3: CRFs will be provided via the EDC system promptly when adverse event occurs.
*4: Assessment of GPP disease activity will be recorded at also week 0, 1, 4, 8 after the retreatment in the case that the patients are retreated with this drug up to 28 weeks after the first dose of this drug.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

ANNEX 3. JDA GPP SEVERITY SCORE

Severity assessment criteria score (JDA total score) specified by the Japanese Dermatological Association (R18-1702).

A Assessment of skin symptoms: erythema, pustules, edema (0-9)			
B Assessment of Systemic symptoms / assessment of laboratory test findings: fever, WBC count, serum CRP, serum albumin (0-8)			
Severity:	**Mild**	**Moderate**	**Severe**
(Total Score)	(0 – 6)	(7 – 10)	(11 – 17)

A Assessment of skin symptoms (0-9)

	Severe	**Moderate**	**Mild**	**None**
Erythema area (total)*	3	2	1	0
Erythema area with pustules **	3	2	1	0
Edema area **	3	2	1	0

*% vs. BSA (severe: ≥75%, moderate: ≥ 25% and <75%, mild: <25%
**% vs. BSA (severe: ≥50%, moderate: ≥10% and <50%, mild: <10%)

B Assessment systemic symptoms/assessment of test findings (0-8)

Score	2	1	0
Fever (°C)	≥38.5	≥37 and < 38.5	<37
WBC count (/µL)	≥15,000	≥10,000 and <15,000	<10,000
Serum CRP (mg/dL)	≥7.0	≥0.3 and <7.0	<0.3
Serum albumin (g/dL)	<3.0	≥3.0 and <3.8	≥3.8

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

ANNEX 4. ENCEPP CHECKLIST FOR STUDY PROTOCOL

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Post-marketing Surveillance of Spesolimab I.V. Infusion in improvement of Generalized Pustular Psoriasis (GPP) with acute symptoms in Japan

EU PAS Register® number: EUPAS49953
Study reference number (if applicable): 1368-0093

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	12
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

Comments:

Section 2: Research question		Yes	No	N/A	Section Number
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.5
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

Comments:

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.3.2
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.4
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.2
	4.2.2 Age and sex	☒	☐	☐	9.2.2
	4.2.3 Country of origin	☐	☐	☒	
	4.2.4 Disease/indication	☒	☐	☐	9.2.2

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2.5 Duration of follow-up	☒	☐	☐	9.2.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

ENCePP Checklist for Study Protocols (Revision 4) Page 3/6

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.7
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.10.2

ENCePP Checklist for Study Protocols (Revision 4) Page 4/6

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.7
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.10
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☐	☐	☒	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	7

Comments:

Proprietary confidential information © 2024 Boehringer Ingelheim International GmbH

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: [redacted]

Date: dd/Month/year 15/Sep/2023

Signature: [redacted]

APPROVAL / SIGNATURE PAGE

Document Number: c36738888 **Technical Version Number:4.0**

Document Name: 1368-0093-protocol

Title: Post-marketing Surveillance of Spesolimab I.V. Infusion in improvement of Generalized Pustular Psoriasis (GPP) with acute symptoms in Japan

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	04 Apr 2024 11:24 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**