Observational and Non-Interventional Study (ONIS)
New Data Collection Protocol

Document Number:	228892_977952_2.0
Boehringer Study Number:	1368-0122
Boehringer Investigational Product(s):	Spevigo®
Title:	A regulatory requirement non-interventional study to monitor the safety and effectiveness of Spesolimab in Korean patients with flares with generalized pustular psoriasis
Brief lay title:	Spesolimab post-marketing surveillance in Korean patients with flares with generalized pustular psoriasis
Protocol version identifier:	2.0
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PASS:	Yes
EU PAS register number:	EUPAS1000000278
Active substance:	Interleukin inhibitor (L04AC22) / Spesolimab
Medicinal product:	Spevigo injection
Product reference:	NA
Procedure number:	NA
Marketing authorisation holder(s):	[redacted]
Joint PASS:	No
Research question and objectives:	The primary and secondary outcomes are to observe respectively safety and effectiveness of Spesolimab in Korean patients with flares with generalized pustular psoriasis.

Country(-ies) of study:	[redacted]
Author:	[redacted] Email: [redacted]
Marketing authorisation holder(s):	[redacted]
MAH contact person:	
EU-QPPV:	Email: [redacted]
Signature of EU-QPPV:	The signature of the EU-QPPV is provided electronically.
Date:	21 January 2025

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
ALT	Alanine aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate aminotrasferase
ATC	Anatomical Therapeutic Chemical
CA	Competent Authority
CDA	Confidentiality Agreement
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
DMP	Data Management Plan
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practice
GPP	Generalized Pustular Psoriasis
GPPASI	Psoriasis Area and Severity Index for Generalized Pustular Psoriasis
GPPGA	Physician's Global Assessment for Generalized Pustular Psoriasis
GVP	Good Pharmacovigilance Practices
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
IV	Intravenous
KPAC	Korean Pharmaceutical Affairs Code
KPBMA	Korea Pharmaceutical and Bio-Pharma Manufacturers Association
KRPIA	Korean Research-based Pharma Industry Association
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
NCE	New Chemical Entity
ONIS	Observational and Non-Interventional Study
PASI	Psoriasis Area and Severity Index

PASS	Post-Authorisation Safety Study
PGA	Physician's Global Assessment
PMP	Project Management Plan
PMS	Post Marketing Surveillance
PPP	Palmo-Plantar Psoriasis
PRO	Patient-Reported Outcome
PSS	Psoriasis Symptom Scale
QV	Qualification Visit
RMP	Risk Management Plan
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFQ	Site Feasibility Questionnaire
SOP	Standard Operating Procedure
VAS	Visual Analogue Scale

3. RESPONSIBLE PARTIES

An ONIS lead who is appointed by [redacted] is responsible for coordinating all required activities, in order to:

- manage the study in accordance with applicable regulations and internal standard operating procedures (SOPs),
- direct the study team in the preparation, conduct, and reporting of the study,
- order the materials as needed for the study,
- ensure appropriate training and information of a Contract Research Organization (CRO) and site staff.

[redacted] delegate study tasks such as monitoring activities, data management, statistical analysis, etc. to a CRO and the delegated tasks are performed in accordance with the applicable SOPs of CRO or Boehringer Ingelheim as described in a project management plan (PMP).

Participating study sites are general hospitals or clinics. Contact details and the list of all investigators are kept in a stand-alone document.

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spevigo®			
Name of active ingredient: Interleukin inhibitor (L04AC22) / Spesolimab			
Protocol date: 08 October 2024	**Study number:** 1368-0122	**Version/Revision:** 2.0	**Version/Revision date:** 21 January 2025
Title of study:	A regulatory requirement non-interventional study to monitor the safety and effectiveness of Spesolimab in Korean patients with flares with generalized pustular psoriasis		
Rationale and background:	This Post Marketing Surveillance (PMS) is a local Post Authorized Safety Study (PASS) stipulated in the local PMS regulation: A surveillance that the Marketing Authorization Holder (MAH) conducts during the re-examination period (4-6 years) in order to collect, review, confirm, or verify the information regarding the safety and effectiveness of commercially licensed new drugs requiring the re-exmination. This real world data is submitted to the Ministry of Food and Drug Safety (MFDS) and the surveillance results are reflected in the approved information.		

	A 6-year PMS for Spesolimab IV was granted for treatment of generalized pustular psoriasis (GPP) flares, and safety data from 21 patients should be collected in a real world environment. Because patients with more diverse conditions are enrolled in routine settings than in clinical trials, this PMS will provide additional real-world data on Spesolimab in Korean patients with GPP.
Research question and objectives:	The primary and secondary objectives are to respectively monitor the safety and effectiveness of Spesolimab IV in Korean patients with flares with GPP in a routine medical practice.
Study design:	Single-arm, open-label, multi-centre, observational and non-interventional study based on newly collected data
Population:	Inclusion criteria: • Patients starting Spesolimab IV for the first time in accordance with the approved label in Korea (complete enumeration for the first 2 years after product launch) • Patients with GPP flare • Age ≧19 years at enrolment • Patients who have signed the data release consent form Exclusion criteria: • Patients with severe or life-threatening hypersensitivity to Spesolimab or to any of the excipients • Patients with clinically important active infections (e.g. active tuberculosis)
Variables:	Outcomes of safety: All reported adverse event (AE)s in patients who take at least one dose of Spesolimab IV Outcomes of effectiveness: Changes in the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation sub-score (mandatory), GPPGA score (mandatory), Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI) (if collected), pain Visual Analog Scale (VAS) (if collected) and Psoriasis Symptom Scale (PSS) (if collected) from baseline after 1 week and/or 4 weeks
Data sources:	Patients' medical records
Study size:	21 patients
Data analysis:	All statistical analyses will be explorative in nature. Patient characteristics will be reported using measures of central tendency (e.g., mean, median) and variance (standard deviation, quartiles) for continuous variables and using frequencies and percentages for count data. Frequency of safety events will be reported using frequencies and incidence with 95% confidence interval (CI). The changes of the effectiveness outcomes from baseline will be compared in an exploratory sense via paired t-test.
Milestones:	Start of data collection: March 2025 End of data collection: August 2029 Final study report: November 2029

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	20 January 2025	9.1 Study design	· Added “complete enumeration for the first 2 years after product launch”.	Specifies that this is a complete enumeration.
2	20 January 2025	9.2.2.2 Inclusion criteria	· Added “complete enumeration for the first 2 years after product launch”.	Specifies that this is a complete enumeration.
3	20 January 2025	9.5 Study size	· Added “Complete enumeration”.	Specifies that this is a complete enumeration.
4	20 January 2025	9.7.1.2 Number of cases to safety assessment	· Added clarification that cases enrolled during the complete enumeration period are included in the safety set.	Clarifies which cases are included in the safety set.

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	FEB 2025
Start of data collection	MAR 2025
End of data collection	JUN 2029
Interim report 1-1	APR 2024
Interim report 1-2	OCT 2024
Interim report 2-1	APR 2025
Interim report 2-2	OCT 2025
Interim report 3	OCT 2026
Interim report 4	OCT 2027
Interim report 5	OCT 2028
Registration in the EU PAS register	JUL 2024
Final report of study results:	NOV 2029

* The interim reporting schedule is determined from the date of market approval in accordance with Korean regulations.

7. RATIONALE AND BACKGROUND

GPP is a severe skin disease characterized by the repeated occurrence of acute flares caused by systemic inflammation affecting the skin and internal organs [R15-1421, R16-0933]. Therapeutic intervention in GPP is a major challenge. To date, there are no approved therapies indicated for treatment of GPP flares, despite the morbidity and mortality associated with GPP flares. There is limited evidence on the efficacy and safety for the use of nontargeted immunomodulatory therapies (e.g. methotrexate, cyclosporine, retinoids, systemic corticosteroids) for the treatment of GPP flares. Most of these therapies used in clinical practice are associated with toxicities that make them inappropriate for continued use [R17-3600, R19-1562].

Spesolimab is an anti-IL36R antibody with a high clinical activity to block IL36R signaling as demonstrated in patients with GPP, a severe skin disease driven by uncontrolled IL36 activity [c15875404-04].

In the randomised and placebo-controlled phase II trial (1368-0013), Spesolimab showed an acceptable safety profile. The overall rates of adverse events were generally comparable between treatment groups during Week 1. Non-serious infections were reported with a higher rate in the Spesolimab group than in the placebo group, with no apparent pattern regarding pathogen and affected organs. There was no increase in the incidence rates of adverse events

after longer observation time (12 weeks) or higher exposure to Spesolimab (2 to 3 doses) [c31523813-01].
This PMS is a local PASS stipulated in the local PMS regulation: A surveillance that the MAH conducts during the re-examination period (4-6 years) in order to collect, review, confirm, or verify the information regarding the safety and effectiveness of commercially licensed new drugs requiring the re-exmination. This real world data is submitted to the MFDS and the surveillance results are reflected in the approved information.
A 6-year PMS for Spesolimab IV was granted for treatment of GPP flares, and safety data from 21 patients should be collected in a real world environment.
Because patients with more diverse conditions are enrolled in routine settings than in clinical trials, this PMS will provide additional real-world data on Spesolimab in Korean patients with GPP.

8. RESEARCH QUESTION AND OBJECTIVES

8.1 PRIMARY OBJECTIVE

The primary objective is to monitor the safety profile of Spesolimab IV in Korean patients with flares with GPP in routine medical practice.

8.2 SECONDARY OBJECTIVE

The secondary objective is to monitor the effectiveness of Spesolimab IV by evaluating changes in the GPPGA pustulation sub-score (mandatory), GPPGA score (mandatory), GPPASI (if collected), pain VAS (if collected) and PSS (if collected) from baseline after 1 week and/or 4 weeks.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a single-arm, open-label, multi-centre, observational and non-interventional study based on newly collected data.
This study will be carried out by enrolling patients in a consecutive manner into the study requiring completion of case report forms (CRFs) from the patient who is initially administered the drug following the study start date to the requested number of patients without omission (complete enumeration for the first 2 years after product launch). Prior to the initiation of the study, written contract shall be concluded, and this contract shall be concluded among [redacted] CRO (if applicable) and with the head of the site or the investigator with his/her consent.
Patients will be managed according to the local practice guidelines. The choice of treatment will be solely at the discretion of the investigator. Spesolimab IV will be administered according to the approved label in Korea. Hence there are no additional risks to patients by participating in this PMS.

9.2 SETTING

9.2.1 Study sites

[redacted] will do our best to encourage the sites that prescribe Spesolimab IV to participate in this study as much as possible. Investigators will be mainly dermatologists.

As provided in the 「Standards for Re-examination of New Drugs, Etc.」of MFDS Notification, [redacted] should select study site according to the following requirements:

- Equipment, facility, and manpower capable of fully achieving the goal of investigation should be held.
- The investigator should have specialized knowledge of the drug subject to investigation and the indication, have completed education/training necessary for performing the investigation, or have practical experience.
- Study site and the investigator should strictly keep confidential the record of subject's personal data.
- The investigator should be fully aware of the「Standards for Re-examination of New Drugs, Etc.」and study protocol.

9.2.1.1 Managing Site and Physician/Investigator Selection, Contracting and Training

See Annex 3.

9.2.2 Study population

9.2.2.1 Main diagnosis for study entry

Patients diagnosed with GPP in Korea

9.2.2.2 Inclusion criteria

① Patients starting Spesolimab IV for the first time in accordance with the approved label in Korea (complete enumeration for the first 2 years after product launch)
② Patients with GPP flare
③ Age ≧ 19 years at enrolment
④ Patients who have signed the data release consent form

9.2.2.3 Exclusion criteria

① Patients with Severe or life-threatening hypersensitivity to Spesolimab or to any of the excipients
② Patients with clinically important active infections (e.g. active tuberculosis)

9.2.2.4 Investigation for patients of special interest

The patient who has signed on the data release consent form, patients of special interest (pediatric, geriatric, pregnant women, renal impairment, hepatic impairment and other special population) among the patients who conducted investigation for safety assessment after the administration of Spesolimab IV can be further summarized into subgroups collected from this.

9.2.3 Study visits

9.2.3.1 Visit 1: Baseline

At Visit 1, the informed consent is obtained from the patient using the data release consent form. After obtaining written consent, the following data will be collected.

- Visit date
- Signed date of data release consent
- Information on diagnosis of GPP and flare: date of diagnosis of GPP and this flare, average number of flares per year and family history of psoriasis
- Information on inclusion / exclusion criteria
- Demographics: gender, age (year and month of birth), current pregnancy and brestfeeding status (female only), smoking status, alcohol intake status
- Medical history: within 6 months
- Past / concomitant medications or non-drug therapy: within 6 months
- Physical examination: blood pressure, pulse rate, weight, height, body temperature
- GPPGA pustulation sub-score
- GPPGA score
- GPPASI (if available)
- Pain VAS (if available)
- PSS (if available)
- IL-36RN mutation status (if available)
- C-reactive protein (CRP) level (if available)
- Other laboratory test results (if available)
- Spesolimab IV administration status: date of administration, total daily dose

At Visit 1, the patient will be requested to contact the investigator in the event of any AEs noted after initiating Spesolimab IV treatment.

9.2.3.2 Visit 2: 1 week from Visit 1

After 1 week from Visit 1, the patient returns for follow-up. The following data will be collected.

- Visit date
- Physical examination: blood pressure, pulse rate, body temperature
- Concomitant medications or non-drug therapy
- Any changes in the Spesolimab IV administration status
- Subsequent exposure to subcutaneous Spesolimab
- GPPGA pustulation sub-score
- GPPGA score
- GPPASI (if available)
- CRP level (if available)
- Other laboratory test results (if available)
- Safety assessment: any AEs noted
- Study completion status (if applicable)
- Investigator’s overall effectiveness assessment (if applicable)

9.2.3.3 Visit 3: 4 weeks from Visit 1

After 4 weeks from Visit 1, the patient returns for follow-up. The following data will be collected.

- Visit date
- Physical examination: blood pressure, pulse rate, body temperature
- Concomitant medications or non-drug therapy
- Any changes in the Spesolimab IV administration status
- Subsequent exposure to subcutaneous Spesolimab
- GPPGA pustulation sub-score
- GPPGA score
- GPPASI (if available)
- Pain VAS (if available)
- PSS (if available)
- CRP level (if available)
- Other laboratory test results (if available)
- Safety assessment: any AEs noted
- Study completion status (if applicable)
- Investigator's overall effectiveness assessment (if applicable)

9.2.3.4 Visit 4: 24 weeks from Visit 1

After 24 weeks from Visit 1, the patient returns for a final follow-up. The following data will be collected.

- Visit date
- Any changes in the Spesolimab IV administration status
- Subsequent exposure to subcutaneous Spesolimab
- Safety assessment: any AEs noted
- Concomitant medications or non-drug therapy
- Study completion status

This visit can be conducted by phone.

9.2.3.5 Flow chart

Data points	**Baseline**	**Follow-up 1**	**Follow-up 2**	**Follow-up 3**
Visit Number	1	2	3	4
Week/s	0	1	4	24
Data release consent	X			
Diagnosis of GPP and flare[1)]	X			
Review of Inclusion / exclusion criteria	X			
Demographics[2)]	X			
Medical history[3)]	X			
Physical examination[4)]	X	X	X	X
Past / concomitant medicatons or non-drug therapy[5)]	X	X	X	X
Spesolimab IV administration status	X	X*	X**	X**
Supsequent exposure to subcutaneous spesolimab		X	X	X
GPPGA pustulation sub-score	X	X	X	

Data points	**Baseline**	**Follow-up 1**	**Follow-up 2**	**Follow-up 3**
Visit Number	1	2	3	4
Week/s	0	1	4	24
GPPGA score	X	X	X	
GPPASI	X[A]	X[A]	X[A]	
Pain VAS	X[A]		X[A]	
PSS	X[A]		X[A]	
CRP level	X[A]	X[A]	X[A]	
IL-36RN mutation status	X[A]			
Laboratory tests	X[A]	X[A]	X[A]	X[A]
AEs		X	X	X
Investigator's overall effectiveness assessment		X[B]	X	
Study completion		X[B]	X[B]	X

* If flare symptoms persist, an additional 900mg dose may be administered 1 week after the initial dose.
** Any changes to the Spesolimab IV administration status are collected.
[A] If collected
[B] If applicable
[1)] Date of diagnosis of GPP and this flare, average number of flares per year and family history of psoriasis
[2)] Gender, age (year and month of birth), current pregnancy and brestfeeding status (female only), smoking status, alcohol intake status
[3)] Within 6 months
[4)] Blood pressure, pulse rate, weight (at V1 only), height (at V1 only), body temperature
[5)] Within 6 months

9.2.4 Study discontinuation

Boehringer Ingelheim 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 Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by a study site, investigator or research collaborator, disturbing the appropriate conduct of the study

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

9.3 VARIABLES

9.3.1 Exposures

Exposure to Spesolimab IV will be estimated as number of doses and time from the first intake date to the last intake date of the patient during the study period.

The recommended dose of Spesolimab IV is a single dose of 900 mg (2 x 450 mg/7.5 ml vials) administered as an intravenous infusion.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The primary outcomes are the safety outcomes until study completion, calculated as the incidence of:

- Adverse events (AEs)
- Adverse drug reactions (ADRs)
- Serious adverse events (SAEs)
- Serious adverse drug reactions (SADRs)
- Unexpected adverse drug reactions
- Adverse events of special interest (AESIs)
- Adverse events leading to temporary or permanent discontinuation
- Adverse events leading to death

Assessment of safety:

- AE (event name / symptom / sign)
- Onset date and end date
- Intensity (mild / moderate / severe)
- Seriousness (serious / non-serious)
- Outcome of the event (recovered / not yet recovered / sequela / fatal / unknown)
- Causality (certain / probable·likely / possible / unlikely / conditional·unclassified / unassessable·unclassifiable)
- Action taken with study drug due to AE (dose not changed / dose reduced / dose increased / drug withdrawn / not applicable)
- AESIs (systemic hypersensitivity reactions including infusion reactions and anaphylactic reaction / severe infections / opportunistic and mycobacterium tuberculosis infections)

9.3.2.2 Secondary outcomes

The secondary outcomes are the effectiveness outcomes as follows:

- A GPPGA pustulation sub-score of 0 indicating no visible pustules at Week 1
- A GPPGA pustulation sub-score of 0 indicating no visible pustules at Week 4
- A GPPGA score of 0 or 1 at Week 1
- A GPPGA score of 0 or 1 at Week 4

The GPPGA is provided in Annex 4. It is a modified the Physician's Global Assessment (PGA), a physician's assessment of psoriatic lesions, which was adapted to the evaluation of GPP patients [R15-5200]. The investigator scores the erythema, pustules, and scaling of all GPP lesions from 0 to 4. Each component is graded separately, the average is calculated, and the final GPPA is determined from this composite score. A lower score indicates a lesser severity, with 0 being clear and 1 being almost clear.

9.3.2.3 Further outcomes

The further outcomes are as follows:

- A GPPASI 75 at Week 4 (if collected)
- A GPPASI 50 at Week 1 (if collected)
- A GPPASI 50 at Week 4 (if collected)
- The percent reduction in GPPASI from baseline at Week 1 (if collected)
- The percent reduction in GPPASI from baseline at Week 4 (if collected)
- Change from baseline in pain VAS score at Week 4 (if collected)
- Change from baseline in PSS score at Week 4 (if collected)
- Investigator's overall effectiveness assessment at Week 1 and/or Week 4

The GPPASI is provided in Annex 5. It is an adaptation for GPP patients of the Psoriasis Area and Severity Index (PASI), an established measure of severity and area of psoriatic lesions in patients with psoriasis [R96-3541]. Similar adaptions have been used for palmo-plantar psoriasis (PPP) [R16-3360]. In the GPPASI, the induration component was substituted with the pustules' component. It is a tool that provides a numeric scoring for a patient's overall GPP disease state, ranging from 0 to 72. It is a linear combination of percent of surface area of skin that is affected by erythema, pustules and scaling and the severity of erythema, pustules, and scaling (desquamation) over 4 body regions.

The pain VAS instrument is provided in Annex 6. The pain VAS is a unidimensional measure of pain intensity [R18-1989]. The respondent is asked to place a vertical (|) mark on the horizontal line to indicate the severity of the pain. Using a ruler, the score is determined by measuring the distance (mm) on the 10-cm line between the "no pain" anchor and the

patient's mark, providing a range of scores from 0–100. A higher score indicates greater pain intensity.

The PSS instrument is provided in Annex 7. The PSS is a 4-item patient-reported outcome (PRO) instrument that was developed to assess the severity of psoriasis symptoms in patients with moderate to severe psoriasis [R18-1990]. The symptoms included are pain, redness, itching, and burning. Current symptom severity is assessed using a 5-point scale ranging from 0 (none) to 4 (very severe). The symptom scores are added to an unweighted total score (range: 0 to 16).

The overall effectiveness assessment is performed at the investigator's discretion. The information includes:

- Improved: If determined as there is any effect of maintaining or improving symptoms.
- Unchanged: If symptoms have not been changed compared with before administration, and not determined as there is any effect of maintaining symptoms.
- Aggravated: If symptoms are worse than before administration.
- Unassessable: If it cannot be determined.

9.3.3 Covariates

1) Patient characteristics
    - Demographics: age, gender, current pregnancy status, current breastfeeding status, smoking status, alcohol intake status
    - Physical examinaton: height, weight, blood pressure, body temperature, pulse rate
    - Disease information: duration of disease, IL-36RN mutation status, medical history, past / concomitant medications or therapies, history and frequency of GPP flares, comorbidities (CV, hepatic or renal imparements, infection, skin diseases (i.e., plaque psoriasis)), family history
2) Spesolimab IV administration status: total duration of administration, total administered dose, average daily dose
3) Subsequent exposure to subcutaneous Spesolimab: total duration of administration, total administered dose
4) Patients of special investigation: pediatric population, geriatric population, pregnant women, lactating women, hepatic impairment, renal impairment
5) Laboratory test results
6) Others

9.4 DATA SOURCES

This study will be carried out in the manner of successive observation that the investigator will be asked to put clinical data in an electronic data capture (EDC) system from the patient who was initially administered the drug following the study start date to the requested number of patients without omission.

9.5 STUDY SIZE

The enrolment target is 21 patients for a total of 6 years, considering the prevalence of generalized pustular psoriasis with acute flares in Korea and the market conditons. [redacted] is committed to collecting data from all patients who receive Spesolimab IV within a 2-year period after the product's launch (complete enumeration).

9.6 DATA MANAGEMENT

Patients' data will be collected by EDC system. The data management procedures to ensure the quality of the data are described in detail in the data management plan (DMP). Data management and statistics will be outsourced to a qualified CRO. DMP will be developed following Boehringer Ingelheim and/or CRO relevant SOPs.

9.7 DATA ANALYSIS

The statistical analysis plan for the study is summarized below. Full details of the statistical analysis will be documented in the Statistical Analysis Plan (SAP), which will be finalized before the end of data collection.

9.7.1 Analysis sets

The safety analysis will comprise all patients who is administered Spesolimab IV and is completed at least one time of safety follow-up.

9.7.1.1 Number of cases to CRF collection

This number means the number of patients who signed the data release consent form to participate in the study, with a record of taking Spesolimab IV once at least.

9.7.1.2 Number of cases to safety assessment

These include those who signed the data release consent form to participate in this study, took Spesolimab IV once at least, and were followed up by the investigator once or more.

Based on the MFDS guideline, the cases below shall be excluded from safety analysis (defined below):

a. Patients who did not signed (signature missing), or patients who signed on the data release consent form prior to the contract date
b. Patients who took Spesolimab IV prior to the contract date
c. Patients who took Spesolimab IV prior to signing the data release consent form
d. Patients who have not taken Spesolimab IV
e. Patients who do not meet the inclusion/exclusion criteria
f. Follow-up failure: Patients whose safety information cannot be obtained due to lost-to-follow-up
g. Patients who were prescribed Spesolimab IV for indications outside the local label

However, cases enrolled during the complete enumeration period within 2 years of product launch will be included in the safety set even if the patients who took Spesolimab IV prior to the contract date or prior to signing the data release consent form.

9.7.1.3 Number of cases to effectiveness assessment

These cases include those who signed the data release consent form to participate in this study, visited as per the study schedule, took Spesolimab IV, and were evaluated for the effectiveness.

Based on the MFDS guideline, the cases below shall be excluded from effectiveness analysis (defined below):

a. Patients excluded from the safety analysis set listed in section 9.7.1.3.
b. Patients missing information of effectiveness assessment listed in section 9.3.2.2.

9.7.2 Safety analysis

Safety analyses will be performed on the safety set.

Frequency of safety events will be reported using numbers of patients with AEs, frequencies, incidence with 95% CIs. AEs will be tabulated by system organ class and preferred term for overall and for subgroup based on demographics and baseline characteristics.

Categorical variables will be reported using numbers of patients with AEs, frequencies, incidence with 95% CIs. Incidence will be analyzed using Pearson's chi-square or Fisher's exact test to determine if there are statistically significant differences.

Continuous variables will be reported using number of patients. Incidence will be reported using odds ratios and 95% CIs by simple logistic regression.
As a result of simple logistic regression, statistically significant variables will be reported using odds ratios and 95% CIs by multiple logistic regression.

AEs will be coded with the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Past / concomitant therapies will be coded according to the current version of the Anatomical Therapeutic Chemical (ATC) classification system.

Safety analyses will be based on all patients treated, i.e. all patients who received at least one dose of Spesolimab IV. However, if data for patients who have been treated with Spesolimab IV beyond the scope of approved label are collected, these will be listed separately.

9.7.3 Effectiveness analysis

Effectiveness analysis will be performed on the effectiveness set.

Effectiveness analyses will be performed by subgroup based on demographics and baseline characteristics.

The standard descriptive statistical parameters (number of patients, mean, standard deviation, median, minimum, maximum, etc.) will be summarized.

The changes of the effectiveness outcomes from baseline will be compared in an exploratory sense via paired t-test.

For investigator's overall effectiveness evaluation, the number and percentage of patients will be presented. If the result of overall evaluation is 'improved', it will be classified as 'effective'. If the result of overall evaluation is 'unchanged' or 'aggravated', it will be classified as 'ineffective'.

'Effective' and 'ineffective' will be reported using numbers of patients, percentages with 95% CIs.

Categorical variable will be reported using numbers of patients, numbers of patients assessed as 'effective', effective rates and 95% CIs. Effectiveness will be analyzed by Pearson's chi-squire test or Fisher's exact test to determine if there are statistically significant differences.

Continuous variable will be reported using numbers of patients. Odds ratio and 95% CIs by simple logistic regression will be summarized.
To estimate any factors that are thought to influence an effective rate, logistic regression analysis and/or poisson regression will be conducted, and for statistically significant covariates the meaning will be described.

9.7.4 Interim analysis

There will be interim analyses according to Korean regulations.

9.7.5 Handling of missing data

Maximum attempt will be made to ensure the completeness of data collection. All available data will be used in the data analysis. Missing or incomplete dates of AEs are imputed according to Boehringer Ingelheim standard.

9.8 QUALITY CONTROL

The quality control, review, and monitoring plan are summarized below. Greater details are documented in the DMP and PMP.

All entries in the Electronic Case Report Forms (eCRFs) and the existing coding will be stored in a database. The structure of the database is based on the division into sections and entry fields defined in the eCRFs. To improve and ensure data quality, data checks will be performed automatically in the eCRFs directly on electronic entry at the study site.
Plausible value ranges for numerical data entries and logical data and list entries will be filed in the eCRFs. The tests for consistency and completeness based on this will be performed during entry in the eCRFs. The validity of the recorded data will therefore be ensured by the validations incorporated in the documentation system, which highlight incorrect or implausible entries to the data entry clerk / doctor.

All changes after initial data entry will be documented in an audit trail.
An additional inspection/quality assurance check of the data collected within this ONIS can be performed in case of any deviation.

9.9 LIMITATIONS OF THE RESEARCH METHODS

9.9.1 Lost to follow up

All efforts will be made to minimize loss to follow up, particularly in the tracking of lost patients. To the extent possible, occurrence of adverse event, at minimum, for patients lost to follow up will be obtained via patient visit / telephone / letter / email etc. This allows assessment of the impact of informative censoring due to treatment discontinuation.

9.9.2 Confounding

As in any observational study, confounding may affect the estimation of association between drug exposure and outcome of interest and statistical techniques. When the investigators assess the overall effectiveness, different assessment criteria among them may affect the study outcome. Also, information bias may occur and cause a distortion in the observed association due to a lack of accurate measurements of key study variables. If key study variables (exposure, health outcome, or confounders) are inaccurately measured or classified (which may happen in real-world clinical settings), bias in the risk ratio, rate ratio, or odds ratio can be produced.

9.10 OTHER ASPECTS

The protocol of this regulatory required ONIS will be submitted to MFDS for approval. Also, the protocol will be submitted to Institutional Review Board (IRBs) whenever required or requested by these study sites. This study will be conducted in accordance with the 「Standards for Re-examination of New Drugs, Etc.」 notified by MFDS, the Korean Pharmaceutical Affairs Code (KPAC), Enforcement Regulation of KPAC and other applicable local laws and industry code (including but not limited to the Regulations on Fair Competition in the Trade of Medicines of the Korea Pharmaceutical and Bio-Pharma Manufacturers Association (KPBMA) and the Korean Research-based Pharma Industry Association (KRPIA)).

[redacted]will submit periodic reports during re-examination period, and the study final report to MFDS upon study completion. The periodic report for the final year will be substituted with the final report. When required, the interim reports and the final report will be submitted to the IRBs as well.

9.10.1 Data quality assurance

A quality assurance audit / inspection of this study may be conducted by the sponsor or sponsor's designees or by IRBs / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.10.2 Study records

CRFs for individual patients will be provided by the sponsor, either on paper or via remote data capture, if applicable.

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 investigator's site.

Data entered in 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.

9.10.2.2 Direct access to source data and documents

The investigator / institution will permit study-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRFs / eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. US Food and Drug Administration (FDA)). Boehringer Ingelheim study staff and auditor may review all CRFs / eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.10.2.1.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, Guidelines for GPP, and the relevant Boehringer Ingelheim SOPs.

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

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This ONIS will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / IEC and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) per GPP and according to the regulatory and legal requirements of the participating country, if applicable.

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. Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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 AE 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 AE 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.

Serious Adverse event

A Serious Adverse Event (SAE) 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.

Adverse Event of Special Interest

The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

The following are considered as AESIs:

- Systemic hypersensitivity reactions including infusion reactions and anaphylactic reactions
- Severe infection
- Opportunistic and mycobacterium tuberculosis infections

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 adverse events

The study is a non-interventional study in real-world situation and will be conducted within the conditions of the approved marketing authorization. For this reason, the following AE collection and reporting requirements have been defined.

All serious adverse events, non-serious adverse events and AESIs occurring from the signing date on data release consent form to the end of the study need to be collected, documented and reported to the sponsor using the AE page of eCRF.

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

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 AE. An adverse reaction, in contrast to an AE, 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.

The causal relationship must be provided by the investigator for all potential study drugs, i.e. the Boehringer Ingelheim study drug and for all other study drugs. The reason for the decision on causal relationship needs to be provided in the eCRF and on the ONIS AE form (if applicable).

Related:

a. Certain: An event occurring in a plausible time relationship to drug administration and that cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

b. Probable/Likely: An event with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

c. Possible: An event with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

d. Conditional/Unclassified: Case of requiring more data or reviewing the additional data for the appropriate assessment

e. Unassessable/Unclassifiable: Case that it cannot be judged and complemented or confirmed due to the insufficient or contradictory information

Unrelated:

- Unlikely: An event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

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 ONIS. Once a patient has been enrolled in the study and has taken study medication, the investigator must report any drug exposure during pregnancy in a study participant within 7 days by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form (Part B).

The investigator site file (ISF) will contain the Pregnancy Monitoring Form (Part A and B). As pregnancy itself is not to be reported as an AE, in the absence of an accompanying AE, only the Pregnancy Monitoring Form and not the ONIS AE form is to be completed. If there is an AE associated with the pregnancy a ONIS AE form must be completed in addition.

Expedited Reporting of AEs and Drug Exposure during Pregnancy to Boehringer Ingelheim Patient Safety and Pharmacovigilance

The following must be reported by the investigator on the ONIS AE form (Annex 8) and / or Pregnancy Monitoring Form (Annex 9) from signing the informed consent onwards until the end of the study and provide Boehringer Ingelheim unique entry point:

Boehringer Ingelheim contact details
Local Patient Safety Lead (LPSL)

Tel: [redacted]
Fax:
Address:

Type of Report	Timeline
All **SAEs**	immediately within 24 hours
All **protocol specified AESIs**	Immediately within 24 hours
All **non-serious AEs**	7 calendar days
Drug exposure during pregnancy	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete the AE page of the eCRF and the ONIS AE form and report the ONIS AE form.

Information required

For each reportable AE, the investigator should provide the information requested on the appropriate (e)CRF page and the ONIS AE form.

The investigator should undertake all efforts to obtain and report the batch/lot number of the drug under study on the ONIS AE form.

11.3 REPORTING TO HEALTH AUTHORITIES

AE reporting to regulatory agencies will be done by MAH according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

According to the local regulations, periodic reports and the study final report will be submitted to MFDS.

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.

13. REFERENCES

13.1 PUBLISHED REFERENCES

R15-1421 Onoufriadis A, Simpson MA, Pink AE, Di Meglio P, Smith CH, Pullabhatla V, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. Am J Hum Genet. 2011;89(3):432-7.

R15-5200 Langley RG, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatolog Treat 2015;26(1):23-31.

R16-0933 Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. Int J Dermatol. 2014;53(6):676-84.

R16-3360 Brunasso AM, Salvini C, Massone C. Efalizumab for severe palmo-plantar psoriasis: an open-label pilot trial in five patients. J Eur Acad Dermatol Venereol 2009;23(4):415-419.

R17-3600 Robinson A, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Bebo BF, Jr., et al. Treatment of pustular psoriasis: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol. 2012;67(2):279-88.

R18-1989 Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) 2011;63 Suppl 11:S240-S252.

R18-1990 Rentz AM, Skalicky AM, Burslem K, et al. The content validity of the PSS in patients with plaque psoriasis. J Patient Rep Outcomes 2017;1(1):4.

R19-1562 Fujita H, Terui T, Hayama K, Akiyama M, Ikeda S, Mabuchi T, et al, The Japanese Dermatological Association Guidelines Development Committee for the Guidelines for the Management and Treatment of Generalized Pustular Psoriasis. Japanese guidelines for the management and treatment of generalized pustular psoriasis: the new pathogenesis and treatment of GPP. J Dermatol 2018 ; 45(11) ; 1235-1270.

R96-3541 Fredriksson T, Pettersson U. Severe psoriasis - oral therapy with a new retinoid. Dermatologica 1978;157(4):238-244.

13.2 UNPUBLISHED REFERENCES

c15875404-04 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. Clinical Trial Protocol 1365-0013 26 June 2020

c31523813-01 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. Clinical Trial Report 1365-0013 14 May 2021

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

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:
A regulatory requirement non-interventional study to monitor the safety and effectiveness of Spesolimab in Korean patients with flares with generalized pustular psoriasis

EU PAS Register® number: EUPAS1000000278
Study reference number (if applicable): N/A

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)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	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.

1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

1.1.3: According to the local regulation, periodic reports will be submitted to the regulatory authority.

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
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)	☒	☐	☐	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

2.1.4: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

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
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
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))	☐	☐	☒	
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:

3.3, 3.4: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.3.6
4.2.2 Age and sex	☒	☐	☐	9.2.2
4.2.3 Country of origin	☒	☐	☐	9.2.2
4.2.4 Disease/indication	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2.3.6
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)	☒	☐	☐	9.2.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

5.2, 5.3, 5.5, 5.6: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

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?	☒	☐	☐	9.3.2

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	
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)	☐	☐	☒	
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:

6.3, 6.4: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9.2
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.1, 9.2
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

7.3: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

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:

This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

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)	☐	☐	☒	

Section 9: Data sources	Yes	No	N/A	Section Number
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
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)	☒	☐	☐	9.2.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.2.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.2.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.7.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7.1
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.7.1
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

9.1.1, 9.4: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

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?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	
10.4 Are stratified analyses included?	☐	☐	☒	
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?	☒	☐	☐	9.7.4
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

10.2, 10.4, 10.5, 10.6, 10.8: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

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, 9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.10.1
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

11.3: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

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?	☒	☐	☐	9.1, 9.2
12.1.2 Information bias?	☒	☐	☐	9.9
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).	☒	☐	☐	9.9
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)	☐	☐	☒	

Comments:

12.2: This study is a regulatory PMS. This study is conducted using a use result surveillance method according to local guidelines.

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
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: 26/September/2024

Signature: [redacted]

ANNEX 3. MANAGE SITE AND PHYSICIAN / INVESTIGATOR SELECTION, CONTRACTING, AND TRAINING

Sites may be identified several ways:

- Suggestions from internal colleagues. For instance, obtaining suggestions from local affiliates is crucial.
- Suggestions from external stakeholders, such as vendor if study is outsourced or key external experts
- Existing data such as externally accessed prescriber data, participating physician databases, commercial listings and / or EMR, national registries, marketing information or other secondary data sources.

A comprehensive site list, including contact information for the sites, should be developed well ahead of protocol finalization and the site selection strategy should be clearly outlined in the protocol and operational documents.

Conduct site feasibility questionnaire, if applicable

To ensure that the most appropriate sites will participate in the study, a Site Feasibility Questionnaire (SFQ) can be useful in order to ask sites about their interest and ability to conduct the study. This is especially the case if many sites need to be identified.

Sites may find it helpful to have the study summary so they have a background regarding the study. Depending on local requirements, some countries may require a phone call prior to any study documents being sent.

Obtain signed confidentiality agreement (CDA) first

Before sharing information with a site, a confidentiality agreement (CDA) with the site should be signed. Signatures may take time, so, this should considered in the study timelines.

Considerations when selecting a site:

Below are some criteria for selecting a site:

- **Ability to conduct the study**: Most importantly, the site should be able to conduct the study as outlined in the study summary or protocol.
- **Representativeness**: Sites should not only be restricted to only those with previous research experience but optimized to ensure broad representation of the sites that typically diagnosis and / or treat the indication of interest in a given country. This is to ensure the study provides a representative picture of the real-world practice setting. Thus, the team should evaluate criteria such as the representativeness of practice type, practice size, and professional qualifications. Local input is often crucial.
- **Enrolment rate:** It is important to ask the site how many patients they can enrol. The team should evaluate if this aligns with the requirements of the study summary or protocol. When considering number of patients per site, it is advisable to consider if site enrollment caps are needed to be instituted to avoid the potential for center effects which drive results.
- **Resources:** It is important to confirm that the site has the needed resources (staff, computer equipment, etc) to conduct the study. Moreover, sites may have a heavy

workload or may prioritize other studies, especially if they are conducting clinical trials at the same time.

- **Compliance:** A due-diligence review should be conducted to ensure there are no compliance issues with investigators.

Number of sites:

- The number of sites depends on several factors. Based on sample size needed, it is important to determine the how many patients can be enrolled per site within the timeline of the study. Having several sites will help avoid individual sites dominating the results and potentially compromising the representativeness. Moreover, the team should consider identifying more sites than needed, including "back-up sites" in case site(s) drop out or more sites are needed in case, enrolment rates are lower than expected.

Verification from stakeholders and OPU's

- The study team should review the results of the SFQ, if done, to determine which sites may be selected for site qualification visits (QV) or phone calls (or "pre-study contact").
- The list should be verified with each OPU in terms of the target physician specialties and site types that reflect standard of care for the indication under study (e.g. If patients are followed most often by cardiologists in a tertiary care / academic setting, this should be built into the final site breakdown for an OPU). Clear communication pathways should be discussed and agreed upon to ensure that sites are receiving consistent information not only during start-up, but throughout the study.
- The site list should also be reviewed by the local teams to determine if there are existing relationships with the site staff, or if similar studies in the same indication have been previously managed by the team.

Conduct qualification call:

- During the qualification call, the study staff should discuss the protocol (or study summary), patient population of interest, and reconfirm the site's ability to conduct the study.
- Sites should be informed of the budget expectations, and relevant Boehringer Ingelheim or vendor specific business processes that may impact the site
- The results of the site qualification calls / visits are reported to the study team, after that the final selection of the sites for the study can take place.

ANNEX 4. PHYSICIAN'S GLOBAL ASSESSMENT FOR GENERALIZED PUSTULAR PSORIASIS (GPPGA)

Erythema

☐ 0 = Clear: Normal or postinflammatory hyperpigmentation

☐ 1 = Almost Clear: Faint, diffuse pink or slight red

☐ 2 = Mild: Light red

☐ 3 = Moderate: Bright red

☐ 4 = Severe: Deep fiery red

Pustules

☐ 0 = Clear: No visible pustules

☐ 1 = Almost Clear: Low density occasional small discrete (non coalescent) pustules

☐ 2 = Mild: Moderate density grouped discrete small pustules (non coalescent)

☐ 3 = Moderate: High density pustules with some coalescence

☐ 4 = Severe: Very high density pustules with pustular lakes

Scaling/crusting

☐ 0 = Clear: No scaling and no crusting

☐ 1 = Almost Clear: Superficial focal scaling or crusting restricted to periphery of lesions

☐ 2 = Mild: Predominantly fine scaling or crusting

☐ 3 = Moderate: Moderate scaling or crusting covering most or all of lesions

☐ 4 = Severe: Severe scaling or crusting covering most or all lesions

PGA Score for GPP

0 = If mean=0 for all three components

1 = If 0 < mean < 1.5

2 = If (1.5 <= mean < 2.5)

3 = If 2.5 <= mean < 3.5

4 = If mean >= 3.5

ANNEX 5. PSORIASIS AREA AND SEVERITY INDEX FOR GENERALIZED PUSTULAR PSORIASIS (GPPASI)

Severity

Erythema

Head ☐ 0=Clear ☐ 1=Almost clear ☐ 2=Mild ☐ 3=Moderate ☐ 4=Severe

Trunk ☐ 0=Clear ☐ 1=Almost clear ☐ 2=Mild ☐ 3=Moderate ☐ 4=Severe

Upper Limb ☐ 0=Clear ☐ 1=Almost clear ☐ 2=Mild ☐ 3=Moderate ☐ 4=Severe

Lower Limb ☐ 0=Clear ☐ 1=Almost clear ☐ 2=Mild ☐ 3=Moderate ☐ 4=Severe

Pustules

Head ☐ 0=Clear ☐ 1=Almost clear ☐ 2=Mild ☐ 3=Moderate ☐ 4=Severe

Trunk ☐ 0=Clear ☐ 1=Almost clear ☐ 2=Mild ☐ 3=Moderate ☐ 4=Severe

Upper Limb ☐ 0=Clear ☐ 1=Almost clear ☐ 2=Mild ☐ 3=Moderate ☐ 4=Severe

Lower Limb ☐ 0=Clear ☐ 1=Almost clear ☐ 2=Mild ☐ 3=Moderate ☐ 4=Severe

Scaling

Head ☐ 0=Clear ☐ 1=Almost clear ☐ 2=Mild ☐ 3=Moderate ☐ 4=Severe

Trunk ☐ 0=Clear ☐ 1=Almost clear ☐ 2=Mild ☐ 3=Moderate ☐ 4=Severe

Upper Limb ☐ 0=Clear ☐ 1=Almost clear ☐ 2=Mild ☐ 3=Moderate ☐ 4=Severe

Lower Limb ☐ 0=Clear ☐ 1=Almost clear ☐ 2=Mild ☐ 3=Moderate ☐ 4=Severe

AREA OF INVOLVEMENT

Provide the percentage of involved area in each body region (=area affected by pustules scaling [not the area for each component separately])

Head ☐ 0=0% ☐ 1=1 to < 10% ☐ 2=10 to < 30% ☐ 3=30 to < 50%

☐ 4=50 to < 70% ☐ 5=70 to < 90% ☐ 6=90 to 100%

Trunk ☐ 0=0% ☐ 1=1 to < 10% ☐ 2=10 to < 30% ☐ 3=30 to < 50%

☐ 4=50 to < 70% ☐ 5=70 to < 90% ☐ 6=90 to 100%

Upper Limb ☐ 0=0% ☐ 1=1 to < 10% ☐ 2=10 to < 30% ☐ 3=30 to < 50%

☐ 4=50 to < 70% ☐ 5=70 to < 90% ☐ 6=90 to 100%

Lower Limb ☐ 0=0% ☐ 1=1 to < 10% ☐ 2=10 to < 30% ☐ 3=30 to < 50%

☐ 4=50 to < 70% ☐ 5=70 to < 90% ☐ 6=90 to 100%

ANNEX 6. PATIENT'S ASSESSMENT OF PAIN VISUAL ANALOG SCALE (VAS)

How much pain have you had because of your generalized pustular psoriasis (GPP) in the past week?
Place a vertical (|) mark on the line to indicate the severity of the pain.

No pain Severe pain

0 ——————————————————————————— 100

ANNEX 7. PSORIASIS SYMPTOM SCALE (PSS)

Listed below are a set of problems that people with psoriasis have said are important. For each question, click on the circle that best describes the severity of your symptoms during the past 24 hours. Please answer every question.

1. How severe was your pain from your psoriasis during the past 24 hours?
   - o None
   - o Mild
   - o Moderate
   - o Severe
   - o Very severe
2. How severe was the redness from your psoriasis during the past 24 hours?
   - o None
   - o Mild
   - o Moderate
   - o Severe
   - o Very severe
3. How severe was your itching from your psoriasis during the past 24 hours?
   - o None
   - o Mild
   - o Moderate
   - o Severe
   - o Very severe
4. How severe was your burning from your psoriasis during the past 24 hours?
   - o None
   - o Mild
   - o Moderate
   - o Severe
   - o Very severe

ANNEX 8. OBSERVATIONAL AND NON-INTERVENTIONAL STUDY (ONIS) ADVERSE EVENT FORM

Boehringer Ingelheim	**Observational and Non-Interventional Study (ONIS) Adverse Event Form**	BI Study No:	Country:
		Site No:	Subject No:

No. of pages, including this page:

To: Boehringer Ingelheim [*or CRO*] [Address] [Fax number]	From: [site stamp]

BY SIGNING THIS FORM, YOU ARE CONFIRMING THAT THE INFORMATION CONTAINED HEREIN IS ACCURATE.

Record all dates in ddmmmyyyy format (e.g. 01Jan2016)

Type of report	Date	Investigator's signature	Remarks
☐ Initial		_____	
☐ Follow-up		_____	
☐ Follow-up		_____	
☐ Follow-up		_____	
☐ Follow-up		_____	
☐ Follow-up		_____	
☐ Follow-up		_____	

SUBJECT DEMOGRAPHICS

Year of birth: Height _(cm) Weight __(kg)
If unknown, record 'UNK'

Sex: ☐ Male ☐ Female Pregnant: ☐ No ☐ Yes weeks
If pregnant, please submit completed Pregnancy Monitoring Form for Studies

Boehringer Ingelheim	**Observational and Non-Interventional Study (ONIS) Adverse Event Form**	BI Study No:	Country:
		Site No:	Subject No:

EVENT INFORMATION

Record all dates in ddmmmyyyy format (e.g. 01Jan2016). If ongoing, enter 'CONT.' Record all times in 24-hour (hh:mm) format. If time is unknown, record 'UNK.'

		Event No. [ ]	Event No. [ ]	Event No. [ ]	Event No. [ ]
Adverse Event term (If available, enter the diagnosis)					
Onset date					
Onset time					
End date					
End time					
Was the event serious?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If serious, please mark reason for seriousness	Results in death	☐	☐	☐	☐
	Immediately life-threatening	☐	☐	☐	☐
	Persistent or significant disability / incapacity	☐	☐	☐	☐
	Requires / prolongs hospitalisation	☐	☐	☐	☐
	Congenital anomaly/birth defect	☐	☐	☐	☐
	Other comparable medical criteria (*specify in Description of Event section*)	☐	☐	☐	☐
Was the event a protocol-specified Adverse Event of Special Interest (AESI)?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Is there a reasonable causal relationship between the Adverse Event and: (*provide description of rationale, other possible causes on page 3*)					
BI studied medication or BI product given for the disease in scope of ONIS		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Concomitant medications: Please refer to concomitant medication section to document causal relationship.					
Outcome of event (*check only one*)					
Recovered (report AE end date above)		☐	☐	☐	☐
Not yet recovered		☐	☐	☐	☐
Recovered with sequelae (report AE end date above)		☐	☐	☐	☐
Unknown		☐	☐	☐	☐
Fatal		☐	☐	☐	☐
If fatal, was this event the primary cause of death?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If subject died, record date of death:					
Was an autopsy performed?		☐ Yes	☐ No	☐ Unknown	
Was therapy for the event administered?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
If yes, specify therapy in Description of Event section.					
Was a dechallenge performed?		☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA
If yes, did the event disappear or significantly decrease in intensity after the BI product was stopped?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Was a rechallenge performed?		☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA	☐ Yes ☐ No ☐ NA
If yes, did the event reappear after reintroduction?		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

Boehringer Ingelheim	**Observational and Non-Interventional Study (ONIS) Adverse Event Form**	BI Study No:	Country:
		Site No:	Subject No:

RATIONALE FOR CAUSALITY ASSESSMENT

Please document the event(s) and provide your rationale for the causal assessment to BI product and include a rationale for any other causal relationships which are considered relevant. Rationale may include temporal relationships, confounding factors (i.e. disease/medication), positive dechallenge / rechallenge, interactions with other medications and/or pattern of reaction.

DESCRIPTION OF THE EVENT(S)

Please highlight any additional information (not otherwise provided on this form) which may contribute to the assessment of the case including but not limited to relevant diagnostic/lab test results (with reference ranges) and therapeutic measures given for event.

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Boehringer Ingelheim	**Observational and Non-Interventional Study (ONIS) Adverse Event Form**	BI Study No:	Country:
		Site No:	Subject No:

RELEVANT BASELINE CONDITIONS INCLUDING PAST MEDICAL HISTORY

Record all dates in ddmmmyyyy format (e.g. 01Jan 2015). If ongoing, enter 'CONT.'

☐ None ☐ Yes (*specify below*)	If concomitant, provide onset date	Past - Please check box only if ended prior to (S)AE onset
1.		☐
2.		☐
3.		☐
4.		☐
5.		☐
6.		☐

BOEHRINGER-INGELHEIM PRODUCT

Indication Lot Number

Name of BI studied medication or BI product given for the disease in scope of ONIS:		
Formulation		
Total daily dose at onset of event (*dose, unit*)		
Route		
Start date		
Start time		
Date of last administration prior to event		
End date		
End time		
Was the administration correct?	☐ Yes ☐ No	
If the administration was not correct, check all applicable boxes: overdose, abuse, misuse, medication error, other (i.e. occupational exposure, lack of effect, unexpected benefit)	☐ Misuse / Abuse ☐ Medication error ☐ Overdose ☐ Other:	
Action taken with BI studied medication or BI product administered for the disease in scope of ONIS as a result of the event (*check one*)	Dose not changed	☐
	Dose reduced	☐
	Dose increased	☐
	Drug withdrawn	☐
	Not applicable	☐

Boehringer Ingelheim	**Observational and Non-Interventional Study (ONIS) Adverse Event Form**	BI Study No:	Country:
		Site No:	Subject No:

RELEVANT PAST AND CONCOMITANT MEDICATIONS

Please preferably provide trade name. Do not include medications used solely to treat the adverse event(s).

☐ None ☐ Yes (*specify below*)	Indication	Past	Start/end dates *ddmmmyyyy or cont.*	Total daily dose at onset of event (*dose/ unit*)	Route	Is there a reasonable causal relationship between the event and the past or concomitant therapy? If Yes, record event number from page 2
1.		☐	Start:			☐ No ☐ Yes
			End:			Event #
2.		☐	Start:			☐ No ☐ Yes
			End:			Event #
3.		☐	Start:			☐ No ☐ Yes
			End:			Event #
4.		☐	Start:			☐ No ☐ Yes
			End:			Event #
5.		☐	Start:			☐ No ☐ Yes
			End:			Event #
6.		☐	Start:			☐ No ☐ Yes
			End:			Event #
7.		☐	Start:			☐ No ☐ Yes
			End:			Event #
8.		☐	Start:			☐ No ☐ Yes
			End:			Event #

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ANNEX 9. PREGNANCY MONITORING FORM FOR STUDIES

Boehringer Ingelheim	**Pregnancy Monitoring Form for Studies**	BI Trial No.:
		Subject No.:

No. of pages, including cover page: .....

To: Boehringer Ingelheim *[or CRO]*	**From:** *[site stamp]*	**Site No.:** .....
[Address] [redacted]		
[Fax No.] [redacted]		**Country:** [redacted]

Please use this cover page for each report

Date received at:

BI OPU or CRO Date (dd mon yyyy or date stamp)

Use current version of Medicine Regulation only! BI-VQD-12736_05-501_AD-17 (4.0)

Boehringer Ingelheim	**Pregnancy Monitoring Form for Studies** **Part A**	BI Trial No.:
		Subject No.:

- This form is to be completed by the **investigator** for reporting any drug exposure during pregnancy after exposure to study medication. The form must be signed, dated and forwarded immediately to the **sponsor/CRO** (preferably by fax).
- If in addition a Serious Adverse Event or Adverse Event of Special Interest is experienced, an SAE form must also be completed.

Pregnancy occurred in	☐ Female study subject ☐ Female partner of a male study subject

Demographic Information:

Year of Birth (yyyy):	Height (cm):	Weight (kg):
_____	_____	_____

** Please leave blank, if regulations within your country prohibit the collection of this information.*

Medications: Please list all treatments given during pregnancy to date, if available.
Continue on a separate sheet if necessary.

Drug name		Route	Daily Dose	Indication for Use	Start Date (dd mmm yyyy)	End Date (dd mmm yyyy)
Trial Drug(s)	1.					
	2.					
	3.					
Concomitant Medication(s)	4.					
	5.					
	6.					
	7.					

Relevant Maternal History: *Any maternal health problems, underlying diseases and medications, smoking, drug and/or alcohol use during the pregnancy, previous infertility therapy, obstetric history including previous miscarriages and pertinent family history:*

_____
_____
_____

First day of last menstrual period:	Date (dd mmm yyyy): _____
Estimated date of delivery:	Date (dd mmm yyyy): _____
Enter gestation at time of initial exposure (if known):	No. of weeks: _____ If weeks not known: ☐ 1st trimester ☐2nd trimester ☐3rd trimester

Date (dd mmm yyyy): Investigator's signature:

Use current version of Medicine Regulation only! BI-VQD-12736_05-501_AD-17 (4.0)
This document is the property of Boehringer Ingelheim Group of Companies.

Boehringer Ingelheim	**Pregnancy Monitoring Form for Studies**	BI Trial No.:
		Subject No.:

No. of pages, including cover page: .....

To: Boehringer Ingelheim ***[or CRO]***	**From:** ***[site stamp]*** **Site No.:** .....
[Address] [redacted]	
[Fax No.] [redacted]	**Country:** [redacted]

Please use this cover page for each report

Date received at:

BI OPU or CRO Date (dd mon yyyy or date stamp)

Boehringer Ingelheim	**Pregnancy Monitoring Form for Studies** Part B	BI Trial No.: Subject No.:

- This form is to be completed by the **investigator** after delivery/termination of pregnancy. The form must be signed, dated and forwarded immediately to the **sponsor/CRO** (preferably by fax).
- If in addition a Serious Adverse Event or Adverse Event of Special Interest is experienced, an SAE form must also be completed.

Pregnancy occurred in	☐ Female study subject ☐ Female partner of a male study subject

Demographic Information:

Year of Birth (yyyy):	Height (cm):	Weight (kg):
_____	_____	_____

** Please leave blank, if regulations within your country prohibit the collection of this information.*

Pregnancy Information:

Birth Outcome (tick the appropriate box)		
Unknown	☐	
Induced Abortion	☐	Please complete SAE form
Live Birth		
Normal Newborn	☐	
Congenital Malformation/Anomaly	☐	Please complete SAE form
Spontaneous Abortion/Miscarriage	☐	Please complete SAE form
Still Birth	☐	Please complete SAE form

Multiple Pregnancy	no ☐	yes ☐	Enter gestational age at birth (weeks): _____

**If yes, please complete an additional page / additional pages for each additional newborn*

Year of Birth (yyyy):	Birth weight (grams):	Birth Height (cm)	APGAR Score (1-10):	Gender:
_____	_____	_____	_____	male ☐ female ☐

Date (dd mmm yyyy): Investigator's signature: