Clinical Trial Protocol

Document Number:		**c38465777-03**
EU Trial No.	2022-501104-10-00	
BI Trial No.	1368-0104	
UTN	U1111-1289-6825	
BI Investigational Medicinal Product	Spesolimab, BI 655130	
Title	Evasayil™ : A placebo-controlled trial to evaluate the efficacy and safety of spesolimab in the treatment of patients with Netherton syndrome	
Lay Title	A study to test whether spesolimab helps people with skin disease called Netherton syndrome	
Clinical Phase	II/III	
Clinical Trial Leader	[redacted] Phone: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted]	
Current Version and Date	Version: 3.0, 24 Sep 2024	
Original Protocol Date	22 Nov 2022	**Page 1 of 131**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	22 Nov 2022
Revision date	24 Sep 2024
BI trial number	1368-0104
EU Trial No.	2022-501104-10-00
UTN	U1111-1289-6825
Title of trial	Evasayil™ : A placebo-controlled trial to evaluate the efficacy and safety of spesolimab in the treatment of patients with Netherton syndrome
Coordinating Investigator	[redacted] Phone: [redacted]
Trial site(s)	Multi-center trial conducted globally
Clinical phase	II/III
Trial rationale	IL-36 is an upstream driver of barrier dysfunction and activator of pathogenic responses in NS. As for GPP, dysregulated IL-36 signaling causes a chronic inflammatory loop and pustule formation and treatment with spesolimab showed efficacy in patients with GPP. Netherton syndrome and GPP have overlaps with respect to the pathobiology involving IL-36R pathway and associated neutrophil mediated skin disease by promoting a feed forward loop of pro-inflammatory mediators.
Trial objective(s)	The primary objective is to evaluate the treatment response of spesolimab (determined by 50% improvement at Week 16 in IASI score). The secondary objectives are to evaluate reduction in other skin severity assessments, improvement in quality-of-life assessments, improvement in sleep, itch and scalp hair assessments and describe safety descriptively, with incidence of AEs.
Trial endpoints	<u>Primary endpoint:</u> The primary endpoint is IASI response, defined as a decrease of at least 50% absolute change in IASI score from baseline at Week 16 (Yes/No). <u>Key secondary endpoint:</u> The key secondary endpoint is IGA response, defined as a decrease of at least 1-grade absolute change in IGA score from baseline at Week 16 (Yes/No).

	Efficacy o IGA score of 0 or 1 at Weeks 4, 8, 12, and 16 (Yes/No) o IASI response, defined as a decrease of at least 50% absolute change in IASI score from baseline at Weeks 4, 8, and 12 (Yes/No) o IASI-E subscore response, defined as a decrease of at least 50% absolute change in IASI-E subscore at Weeks 4, 8, 12, and 16 (Yes/No) o IASI-S subscore response, defined as a decrease of at least 50% absolute change in IASI-S subscore from baseline at Weeks 4, 8, 12, and 16 (Yes/No) o Percent change from baseline in IASI score at Weeks 4, 8, 12 and 16 o Absolute change from baseline in NRS pain at Weeks 4, 8, 12 and 16 o Absolute change from baseline in NRS itch at Weeks 4, 8, 12 and 16 o Absolute change from baseline in DLQI score at Weeks 8 and 16 o Absolute change from baseline in CDLQI score at Weeks 8 and 16 Safety o The occurrence of treatment emergent adverse events including serious and/or opportunistic infections
Trial design	Multi-center, randomised, double blind, placebo-controlled Phase II/III to evaluate the efficacy and safety of spesolimab compared with placebo in the treatment of patients with Netherton syndrome
Total number of patients randomised	Approximately 39 Including at least 6 adolescent patients, randomisation ratio 2:1 (active: placebo)
Number of patients per treatment group	Approximately 26 patients in the active group Approximately 13 patients in placebo group
Diagnosis	Adolescents ≥12 years old and adult patients with Netherton syndrome
Main inclusion and exclusion criteria	**Inclusion criteria** • Male or female patients, aged 12 years and older (weight minimum is 35 kg) • Confirmed diagnosis of NS (*SPINK5* causative mutations) at baseline • At least moderate severity of erythema at baseline (IASI score ≥16 and IASI-E score ≥8) and ≥3 on IGA score • Signed and dated written informed consent and assent in accordance with ICH-GCP and local legislation prior to admission in the trial

	• Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the CTP as well as in the patient, parent(s) (or patient's legal guardian) information. [1]A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is not a method of permanent sterilization. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. **Exclusion criteria** • Patients who have used topical corticosteroids (medium to high, US class I-V), topical retinoids, topical calcineurin inhibitors or keratolytics within 1 week prior to randomisation • Patients who have used emollient on the area to be biopsied in the previous 24 h • Patients who have used systemic retinoids, other systemic immunosuppressants, systemic corticosteroids or phototherapy within 4 weeks prior to randomisation • Patients who have used systemic antibiotics within 2 weeks prior to randomisation • Patients who have received live vaccines within 4 weeks prior to randomisation • Patients who have received investigational products, biologics or immunoglobulins within 4 weeks or 5 half-lives (whichever is longer) prior to randomisation • Relevant chronic or acute infections including active tuberculosis, human immunodeficiency virus (HIV) infection or viral hepatitis at the time of randomisation. A patient can be re-screened if the patient was treated and is cured from the acute infection.
Test product(s)	BI 655130 (spesolimab)
Dose	[redacted] doses at Week 0 (Day1) followed by [redacted]
Mode of administration	[redacted]
Comparator product(s)	Placebo

Dose	Matching placebo [redacted] placebo at Week 0 (Day 1) followed by every [redacted] placebo [redacted]
Mode of administration	[redacted]
Duration of treatment	[redacted]
Statistical methods	Suissa-Shuster Z-pooled test will be used to test if spesolimab is different from placebo regarding the primary binary endpoint variable (the proportions of IASI response at Week 16).

FLOW CHART 1 (WHOLE TRIAL)

	Screening	**Randomised Treatment Period**					**CO** *	**Open Label Treatment period**								**Extended Treatment Period From [redacted] up to [redacted] ****	**FUP**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	**16 to 40**	**41/EoT[2]**	**EoS[3]**
Visit location[19]- C: visits at clinic; C/R: Clinic or Remote visits	C	C	C	C	2C	C	C	C	C	C	C	C	C	C	C	C/R	C	C
Week	[redacted]																	
Day																		
Visit Window (days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+/-14	+/-14	+7
Informed consent	X																	
Confirmation NS diagnosis[4]	X																	
Infection testing[5]	X														X	Visit 29		X
Demographics	X																	
Medical History	X																	
Vital signs[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [19]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[20]	X														X		X	
Weight	X	X				X				X					X		X	
Pregnancy tests[7]	X[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every [redacted] weeks	X	X
Safety laboratory tests[8]	X	X	X	X	X	X	X	X		X			X		X	Every [redacted] weeks	X	X
12 lead-ECG [9]	X	X	X			X	X			X			X		X	Every [redacted] weeks		X
Review of in/-exclusion criteria	X	X																
IASI (E & S)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every [redacted] weeks	X	X

FLOW CHART 1 (WHOLE TRIAL) cont'd

	Screening	**Randomised Treatment Period**					**CO** *	**Open Label Treatment period**								**Extended Treatment Period From [redacted] up to [redacted] ****	**FUP**
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	**16 to 40**	**41/EoT[2]**	**EoS[3]**
Visit location[19]- C: visits at clinic; C/R: Clinic or Remote visits	C	C	C	C	2C	C	C	C	C	C	C	C	C	C	C	C/R	C	C
Week	[redacted]																	
Day																		
Visit Window (days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+/-14	+/-14	+7
IGA		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every [redacted] weeks	X	X
NASA		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every [redacted] weeks	X	X
[redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Itch, Pain NRS		X	X	X	X	X	X	X	X	X		X			X	Every [redacted] weeks	X	X
DLQI/CDLQI		X		X		X		X		X					X	Every [redacted] weeks	X	X
5-D Itch scale		X		X		X				X					X			X
HADS		X		X		X				X					X			X
[redacted]		X		X		X				X					X			X
[redacted]		X		X		X				X					X			X
Itchy Qol		X		X		X				X					X			X
PGIS-E		X	X	X	X	X				X		X			X			X
PGIS-S		X	X	X	X	X				X		X			X			X
PGIC			X	X	X	X				X		X			X			X
In- trial interviews (sub study-optional)[21]						X												
Local tolerability [10]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

FLOW CHART 1 (WHOLE TRIAL) cont'd

	Screening	Randomised Treatment Period					CO *	Open Label Treatment period								Extended Treatment Period From W56 up to W156**		FUP
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	**16 to 40**	**41/EoT[2]**	**EoS[3]**
Visit location[19]- C: visits at clinic; C/R: Clinic or Remote visits	C	C	C	C	2C	C	C	C	C	C	C	C	C	C	C	C/R	C	C
Week	[redacted]																	
Day																		
Visit Window (days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+/-14	+/-14	+7
ADA/Nab Sampling[11]		X	X	X	X	X	X	X	X	X			X		X	Every [redacted] weeks		X
PK sampling[11]		X	X	X	X	X	X	X	X	X			X		X	Every [redacted] weeks		X
Photographs of skin lesions[12]	X	X	X	X	X	X		X		X			X		X			X
Skin Biopsies -Lesional (L) and non lesional (NL)[13]		X (L; NL)				X(L)												
Microbiome sample - Lesional (L) and non lesional (NL)[14]		X (L; NL)	X (L)			X(L)												
Soluble serum biomarkers		X	X		X	X		X		X					X			
Blood sample (gene expression analysis)		X	X		X	X		X		X					X			
Sampling for biobanking[15]		X																
Randomisation		X																
Administration trial drug[17]		[redacted]														[redacted] Every [redacted] weeks	[redacted]	
Issue patient diary[18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Every [redacted] weeks		

FLOW CHART 1 (WHOLE TRIAL) cont'd

	Screening	Randomised Treatment Period					CO *	Open Label Treatment period								Extended Treatment Period From W56 up to W156**		FUP
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	**16 to 40**	**41/EoT[2]**	**EoS[3]**
Visit location[19]- C: visits at clinic; C/R: Clinic or Remote visits	C	C	C	C	2C	C	C	C	C	C	C	C	C	C	C	C/R	C	C
Week	[redacted]																	[redacted] after last dose
Day																		
Visit Window (days)			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+/-14	+/-14	+7
Review patient diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Every [redacted] weeks	X	
All AEs/SAEs/ AESIs[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Completion of patient participation																		X

* CO: Crossover, **: For detailed overview of assessments per individual visit for the extended treatment period, please see "Flow Chart 2".
S: serum

Footnotes to Flow Chart 1:

[1] Day of Randomisation / Day of first intake of randomised medication

[2] After Visit 15 (Week [redacted]), each individual patient may continue receiving the trial drug up to Week [redacted] (approximately additional [redacted] years). EoT will be at Week [redacted]. All patients who stop treatment prior to Week [redacted] will be considered early discontinued. Timepoint of early EoT will be considered the visit when the last dose of IMP was administered. In case of early discontinuation from trial treatment, every effort should be made to keep the patient in the trial and complete all of the remaining visits up to Week [redacted] (without IMP administration in that case). At a minimum, patients should come to an End-of-study Visit (EoS), [redacted] weeks after the last dose to cover full REP.

[3] End of Study (EoS), synonym for End of Trial. Regularly, EoS is [redacted] weeks after last dose of trial medication. If a patient discontinues early from trial treatment and continues with original visit schedule (without receiving treatment), EoS could also take place beyond [redacted] weeks after last treatment dose. EoS visit would be performed as the last patient visit in that case.

[4] *SPINK5* causative mutations to be confirmed by the investigator.

[5] Infection testing at screening includes tuberculosis (QuantiFERON® or T-Spot®), hepatitis B, hepatitis C, and HIV assessments. See Section 5.2.3 for complete list of testing required. For patients who sign the informed consent ≥4 weeks prior to V2, infection testing must be repeated 2 to 4 weeks prior to V2. For patients who continue in the extended treatment period, tuberculosis test is to be repeated at Week [redacted], Week [redacted] and at EOS.

[6] Measurements of vital signs should precede blood sampling. In addition, at dosing visits, vital signs will be assessed pre dose, prior to blood sampling, approximately 10 minutes after the end of trial drug administration [redacted] and approximately 60 minutes after the end of the trial drug administration [redacted] (see Section 5.2.2)

[7] Pregnancy test: Only applicable for women of childbearing potential. Serum pregnancy test (performed at screening). Urine pregnancy tests will be performed at all other visits indicated, and every 4 weeks in the extended treatment period. Urine pregnancy testing should be done prior to trial drug administration. Trial drug should only be administered in case of a negative test result. In case of a positive urine pregnancy test, a serum pregnancy test will be done (via central laboratory) and trial drug administration will be postponed until negative result of serum pregnancy test is available.

[8] Safety lab test: Laboratory tests will be performed at a central laboratory. Patient is not required to be fasting prior to blood collection. Please refer to Section 5.2.3 for further details.

[9] ECG measurements should always precede blood sampling and drug administration.

[10] Local tolerability at the administration site of spesolimab or placebo will be assessed during the trial drug administration on site or by questioning retrospectively since the last visit, if local tolerability related to AEs was observed. Any observed local tolerability reaction, e.g. swelling induration, heat, redness, pain, and other findings should be reported as an AE.

[11] PK/ADA/Nab samples will be obtained predose at all indicated visits. In addition, post-dose PK samples will be collected right after the [redacted] at Visit [redacted] and Visit [redacted]

[12] Photographs of skin lesions are to precede skin biopsies and trial drug administration. In addition to photographs of skin lesions, biopsy site photographs will also be taken at Visit 2 and Visit 6.

[13] Skin biopsy is mandatory. [redacted]) prior to trial dug administration. Each skin biopsy should be collected prior to trial drug infusion. After approval of protocol amendment v2.0, skin biopsies will be obtained only from adult patients.

[14] [redacted] samples must be taken before biopsies are taken and before trial drug administration. Patients should be instructed to not bathe, shower, or apply any topical product to the area that will be tested 24 h before Visit 2, Visit 3, and Visit 6.

[15] DNA biobanking requires only one blood sample, preferably at Visit 2 or later during the trial, if not obtained at Visit 2.

[16] After the EoS visit (individual patient's end of the trial) the investigator should report only any cancers of new histology and exacerbations of existing cancer, trial drug related SAEs and trial drug related AESIs, of which the investigator may become aware of and only via the BI SAE form, please see Section 5.2.6.2.1.

[17] At Week [redacted] (Visit 6) each patient will receive [redacted] spesolimab [redacted] mg)/placebo plus [redacted] spesolimab [redacted] mg)/placebo.

[18] A patient diary will be given to the patient to collect daily information about NRS Pain score and NRS Itch score during the past 7 days prior to the scheduled visit. Changes in the use of concomitant therapies for NS (e.g. emollients, corticosteroids, antibiotics and analgesics use to manage pain) should be documented in the diary and eCRF throughout the trial. The diary should be given to the patient every [redacted] weeks until Visit [redacted] and every [redacted] weeks starting Visit [redacted]. The diary should be reviewed by the trial staff during the visit.

[19] During extension treatment phase, visits with reduced number of assessments (i.e every second visit starting Visit 16 and up to Visit 40) could be either performed at the investigational site or remotely by a trained Health Care Professional (HCP) at the patient's home During remote visits, an abbreviated body system assessment

will be conducted by the trained HCP instead of a physical exam. This abbreviated body system assessment will include evaluation of organ systems associated with AE(s) symptoms and is only observational and conversational with patient.

[20] At Visit 15, and at EOT visit, height will be measured only for adolescent patients.

[21] Interviews should occur within 4 weeks after the Week [redacted] visit. They can also be at early termination visit if this visit occurs between Week [redacted] and Week [redacted]. Interviews will be conducted by [redacted]. Consent to participate in the in-trial interviews can be collected at any visit up to Week [redacted] visit included.

FLOW CHART 2 (EXTENDED TREATMENT PERIOD, ASSESSMENTS PER INDIVIDUAL VISITS)

	From [redacted] up to [redacted]																										FUP
Visit	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**EoT[1]**	**EoS[2]**
Visit location[12] (C: visits at clinic; C/R: Clinic or Remote visits)	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C
Week	[redacted]																										[redacted] wks after last dose
Day																											
Visit Window (days)	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±7
Infection testing[3]														X													X
Vital signs[4], Physical examination[12]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[13]																										X	
Weight																										X	
Pregnancy tests[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests[6]		X		X		X		X		X		X		X		X		X		X		X		X		X	X
12 lead-ECG[7]				X				X				X				X				X				X			X
IASI (E & S), IGA, NASA		X		X		X		X		X		X		X		X		X		X		X		X		X	X
ISS																											X
Itch, Pain NRS			X			X			X			X			X			X			X			X			X

FLOW CHART 2 (EXTENDED TREATMENT PERIOD, ASSESSMENTS PER INDIVIDUAL VISITS) cont'd

	From [redacted] up to [redacted]																										FUP
Visit	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**EoT[1]**	**EoS[2]**
Visit location[12] (C: visits at clinic; C/R: Clinic or Remote visits)	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C
Week	[redacted]																										[redacted] wks after last dose
Day																											
DLQI/CDLQI						X						X						X						X		X	X
5-D Itch scale, HADS, MOS Sleep, HADS, Itch QoL, PGIS-E, PGIS-S, PGIC, Scalp Hair Assessment																											X
Local tolerability[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK/ADA/Nab Sampling[9]						X						X						X						X			X
Photographs of skin lesions																											X
Administration trial drug	[redacted]																										
Issue patient diary[11]		X			X			X			X			X			X			X			X		X		
Review patient diary			X			X			X			X			X			X			X			X		X	
All AEs, SAEs, AESIs[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

FLOW CHART 2 (EXTENDED TREATMENT PERIOD, ASSESSMENTS PER INDIVIDUAL VISITS) cont'd

	From [redacted] up to [redacted]																										FUP
Visit	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**	**EoT[1]**	**EoS[2]**
Visit location[12] (C: visits at clinic; C/R: Clinic or Remote visits)	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C/R	C	C
Week	[redacted]																										[redacted] wks after last dose
Completion of patient participation																											X

Footnotes to Flow Chart 2:

[1] After Visit 15 ([redacted]), each individual patient may continue receiving the trial drug up to Week [redacted] (approximately additional [redacted]). EoT will be at Week [redacted]. All patients who stop treatment prior to Week [redacted] will be considered early discontinued. Timepoint of early EoT will be considered the visit when the last dose of IMP was administered. In case of early discontinuation from trial treatment, every effort should be made to keep the patient in the trial and complete all of the remaining visits up to Week [redacted] (without IMP administration in that case). At a minimum, patients should come to an End-of-study Visit (EoS), [redacted] weeks after the last dose to cover full REP.

[2] End of Study (EoS), synonym for End of Trial. Regularly, EoS is [redacted] weeks after last dose of trial medication. If a patient discontinues early from trial treatment and continues with original visit schedule (without receiving treatment), EoS could also take place beyond [redacted] weeks after last treatment dose. EoS visit would be performed as the last patient visit in that case.

[3] Tuberculosis test has to be repeated at Week [redacted] (Visit 29) and EoS. See Section 5.2.3 for complete list of testing required.

[4] Measurements of vital signs should precede blood sampling. At dosing visits, vital signs will be assessed pre dose, prior to blood sampling and approximately 10 min after the end of trial drug administration (see Section 5.2.2)

[5] Pregnancy test: Only applicable for women of childbearing potential. Urine pregnancy tests will be performed every [redacted] weeks in the extended treatment period. Urine pregnancy testing should be done prior to trial drug administration. Trial drug should only be administered in case of a negative test result. In case of a positive urine pregnancy test, a serum pregnancy test will be done (via central laboratory) and trial drug administration will be postponed until negative result of serum pregnancy test is available.

[6] Safety lab test: Laboratory tests will be performed at a central laboratory. Patient is not required to be fasting prior to blood collection. Please refer to Section 5.2.3 for further details.

[7] ECG measurements should always precede blood sampling and drug administration.

[8] Local tolerability at the administration site of spesolimab or placebo will be assessed during the trial drug administration on site or by questioning retrospectively since the last visit, if local tolerability related to AEs was observed. Any observed local tolerability reaction, e.g. swelling induration, heat, redness, pain, and other findings should be reported as an AE.
[9] PK/ADA/Nab samples will be obtained predose at all indicated visits.
[10] After the EoS visit (individual patient's end of the trial) the investigator should report only any cancers of new histology and exacerbations of existing cancer, trial drug related SAEs and trial drug related AESIs, of which the investigator may become aware of and only via the BI SAE form, please see Section 5.2.6.2.1.
[11] A patient diary will be given to the patient to collect daily information about NRS Pain score and NRS Itch score during the past 7 days prior to the scheduled visit. Changes in the use of concomitant therapies for NS (e.g. emollients, corticosteroids, antibiotics and analgesics use to manage pain) should be documented in the diary and eCRF throughout the trial. During extended treatment phase, the diary should be given to the patient every [redacted] weeks. The diary should be reviewed by the trial staff during the visit.
[12] During extension treatment phase, visits with reduced number of assessments (i.e. every second visit starting Visit 16 and up to Visit 40) could be either performed at the investigational site or remotely by a trained Health Care Professional (HCP) at the patient's home. During remote visits, an abbreviated body system assessment will be conducted by the trained HCP instead of a physical exam. This abbreviated body system assessment will include evaluation of organ systems associated with AE(s) symptoms and is only observational and conversational with patient.
[13] At EoT visit, height will be measured only for adolescent patients.

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[redacted]

[redacted]

ABBREVIATIONS AND DEFINITIONS

ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
CA	Competent Authority
CD	Crohn's disease
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence Interval
Cmax	Maximum Plasma Concentration
CO	Cross over
Cmin	Minimum Plasma Concentration
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as "eCRF")
CRO	Contract Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
DBL	Database Lock
DILI	Drug Induced Liver Injury
DLQI	Dermatology Life Quality Index
[redacted]	[redacted]
EC	Ethics Committee
ECG	Electrocardiogram
(e)COA	(electronic) Clinical Outcome Assessment
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EoS	End of Study (corresponds with End of Trial)

ADA	Anti-Drug Antibodies
EoT	End of Treatment
FC	Flow Chart
FUP	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPP	Generalized pustular psoriasis
IGA	Investigator Global Assessment
HA	Health Authority
HADS	Hospital Anxiety and Depression Scale
HCP	Health Care Professional
HS	Hidradenitis suppurativa
IASI	Ichthyosis Area Severity Index
[redacted]	[redacted]
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
INN	International Non-Proprietary Name
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LPLT	Last patient last treatment
LPLV	Last patient last visit
MedDRA	Medical Dictionary for Drug Regulatory Activities
nAb	Neutralizing Anti-Drug Antibodies
NASA	Netherton Area Severity Assessment Score
NS	Netherton syndrome
OPU	Operative Unit
PBO	Placebo
PGI	Patient Global Impression

ADA	Anti-Drug Antibodies
PK	Pharmacokinetics
[redacted]	[redacted]
PPP	Palmoplantar pustulosis
PV	Pharmacovigilance
RA	Regulatory Authority
QoL	Quality of life
REP	Residual effect period
[redacted]	[redacted]
SAE	Serious Adverse Event
SD	Standard deviation
SC	Steering Committee
SMC	Safety Monitoring Committee
SoC	Standard of care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
t1/2	Half-life time
tmax	Timepoint of maximum plasma concentration
TEAE	Treatment-emergent adverse event
TMF	Trial Master File
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
UTN	Universal Trial Number
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Netherton syndrome (NS) is an ultra-rare and severe autosomal recessive ichthyosis syndrome, which manifests at birth or shortly thereafter. There is marked variability in disease expression from patient to patient and over time. The severity of the skin condition may lessen somewhat as patients grow into adulthood; however, it remains a serious and debilitating condition. Patients with NS are characterized by 3 main signs: ichthyosis linearis circumflexa or congenital ichthyosis, trichorrhexis invaginata ("bamboo hair"), and atopic predisposition. The pathogenesis of NS lay in the mutations in the *SPINK5* gene, which result in a deficiency or lack of lympho-epithelial Kazal-type-related inhibitor (LEKTI) and lead to unregulated desquamation resulting in a profound skin barrier defect and triggers the activation of inflammatory pathways.

Spesolimab is a humanized antagonistic monoclonal IgG1 antibody blocking IL36α-, IL36β- and IL36γ-induced IL36R activation. The IL-36 pathway has been associated with the pathogenesis of several inflammatory diseases, including pustular psoriasis (generalized pustular psoriasis [GPP] and palmoplantar pustulosis [PPP]), hidradenitis suppurativa (HS), and inflammatory bowel disease (IBD and Crohn`s disease [CD]).

In NS, IL-36γ isoform, which is normally not expressed in healthy skin, is significantly increased in skin biopsies from lesional and non-lesional skin [R22-0746]. Immunostaining of IL-36R was also upregulated in the skin sections from NS patients [R22-0856].

Transcriptomic analysis performed in lesional and non-lesional skin biopsy samples obtained from NS patients and healthy donors showed that genes involved in IL-36 pathway (S100A7/8/9, IL-36α, IL-36β, IL-36γ and CCL20) were among the highest expressed in lesional as well as non-lesional skin biopsies from NS patients [R22-0856; R22-0746]. Highly significant Pearson correlation was found between the clinical erythema/inflammation severity scores (IASI-E) and IL36γ gene expression on the skin from patients with NS [R22-1085].

[redacted]

1.2 DRUG PROFILE

Mode of action

BI 655130 (INN: spesolimab) is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signalling. Binding of spesolimab to IL36R is anticipated to prevent the subsequent activation of IL36R by cognate ligands (IL36α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways in inflammatory skin and bowel diseases such as generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP), atopic dermatitis (AD), hidradenitis suppurativa (HS), and inflammatory bowel disease (IBD). Thus,

spesolimab may be unique in directly suppressing not only pro-inflammatory but also profibrotic mechanisms in these diseases.

Data from non-clinical studies

Preclinical Studies
BI 655130 binds to human IL36R with a binding avidity of less than 1 pM. BI 655130 inhibits IL36 ligand-stimulated NF-κB activation in HT29 and transformed epithelial cells and in primary human dermal fibroblasts or intestinal myofibroblasts with IC90 values in a consistent range of 0.7 to 3.7 nM. BI 655130 also inhibits IL8 release in primary human intestinal myofibroblasts and IFNγ secretion in human PBMC stimulated with IL36α, IL36β, or IL36γ combined with IL12. Mutations of two key residues (L234 and L235) to alanine were made to BI 655130 to abrogate FcR binding activity and function. Direct assessment of the impact of the mutations in the IgG1 FcR binding sites on both antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) effector functions revealed that the mutations abrogate both ADCC and CDC effector functions and indicate that BI 655130 will be a non-depleting therapy *in vivo*.

Toxicology studies
BI 655130 does not bind to IL-36R from common toxicology species. Therefore, meaningful toxicity studies of the molecule cannot be performed in any animal species with BI 655130. However, hazard identification studies of the mode-of-action (MoA) of IL-36R inhibition were performed in mice using a mouse specific anti-IL-36R monoclonal antibody (BI 674304), which is a mouse IgG2a monoclonal antibody with rat variable regions. In a 13-week intravenous toxicity study of BI 674304 in mice, no adverse effects of IL-36R antagonism was seen at a dose (50 mg/kg, twice weekly) that was 5-fold higher than the dose that was protective in an experimental mouse colonic inflammation model. In the 26-Week toxicity study, male and female mice (20- 30/sex/group at 0, 10 and 50 mg/kg/day) were administered BI 674304 twice Weekly for 26 weeks by intravenous injection via the caudal vein. There were no BI 674304-related changes in clinical observations, body weights, food consumption, ophthalmology, clinical pathology parameters (hematology, clinical chemistry), organ weights, macroscopic or microscopic examinations. The no-observed-adverse-effect level (NOAEL) was considered to be 50 mg/kg/day. The *in vitro* cytokine release and tissue

cross-reactivity assays demonstrate that the risk of transient cytokine release in humans is low and that, as expected, BI 655130 stains epithelium in a variety of tissues. There were no signs of local irritation after single, 1 mL injections of the subcutaneous formulation in rabbits. These preclinical toxicology data support chronic BI 655130 dosing in humans.

Data from clinical studies

For a more detailed description of the BI 655130 profile, please refer to the current Investigator's Brochure (c03320877).

In the First-in-Human (FIH) study, BI 655130 or placebo (PBO) was administered to 78 healthy volunteers with 58 subjects assigned to single ascending i.v. doses from 0.001 mg/kg to 10 mg/kg body weight and 20 subjects assigned to placebo. Safety and tolerability of all tested i.v. doses were good. There were no SAEs. AEs categorized as related to treatment were observed in 3/20 (15.0%) subjects in the placebo group and in 8/58 (13.8%) subjects treated with BI 655130. The most frequent treatment-emergent AEs were nasopharyngitis (BI 655130: 20.7%; PBO: 15.0%), headache (BI 655130: 8.6%; PBO: 15.0%), influenza like illness (BI 655130: 6.9%; PBO: 10.0%), and diarrhea (BI 655130: 3.4%; PBO: 10.0%). There were two AEs of moderate intensity (injection site haematoma, headache), all remaining AEs were of mild intensity. There were no serious AEs, no AEs that led to discontinuation of trial drug, no protocol-specified AEs of special interest and no other significant AEs.

No relevant changes were observed in safety laboratory tests, vital signs, and electrocardiograms (ECGs). Importantly, there were no relevant differences in frequencies of subjects with treatment emergent AEs between the treatment groups, and no dosedependency was observed.

PK analysis showed that exposure (AUC0-tz and Cmax) to BI 655130 increased with increasing dose in an approximately dose-proportional manner from 0.3 to 10 mg/kg. The effective half-life of BI 655130 is approximately 4 weeks in the linear dose range. PK data suggests target-mediated drug disposition (TMDD) kinetics for BI 655130 below 0.3 mg/kg dose. Anti-drug antibodies (ADA) were detected in 9 subjects (8 subjects on BI 655130 and 1 subject on placebo), 3 of those had pre-existing levels. [redacted]

In a multiple rising dose trial, BI 655130 or placebo have been administered to healthy volunteers at multiple ascending i.v. doses of 3, 6,10 and 20 mg/kg given Weekly for 4 weeks (i.e. 4 administrations) or a single dose of 20 mg/kg (8 subjects each, 3:1 on active or PBO). Overall, multiple i.v. doses of 3 mg/kg, 6 mg/kg, and 10 mg/kg, as well as single and multiple doses of 20 mg/kg BI 655130 were found to be safe and well tolerated by the healthy male subjects in this trial. The incidence and intensity of drug related AEs appeared to be higher in the 20 mg/kg multiple dose BI 655130 treatment group than in the other treatment groups, mainly driven by headache. No dose-dependent AEs or other clinically relevant changes in safety laboratory tests, vital signs, or ECG were observed. For further details refer to the current Investigator`s Brochure.

Study 1368.3 explored pharmacokinetics as well as safety and tolerability of a subcutaneous formulation of BI 655130 at two different dose strengths of 150 mg (1 mL) and 300 mg (2 mL) using an open-label, single dose, parallel group, matched pair design to determine the relative bioavailability of the 300 mg s.c. compared with one single 300 mg i.v. dose of BI 655130. In this study, 36 healthy male and female subjects have been treated with BI 655130, with 12 subjects per dose group. 35 subjects completed the study per protocol, one subject discontinued for logistical reasons (work-related issues).

No important protocol violations occurred. Pharmacokinetic data from 34 subjects (94.4%) were analysed for the primary and secondary endpoints. The minimum number of 11 subjects per treatment group was considered sufficient for the exploratory assessment of the primary objective. The precision and accuracy of the analytic methods used for the determination of PK parameters were adequate to achieve the trial aims. Matching was only performed for the 300 mg BI 655130 IV and 300 mg BI 655130 SC groups; however, the demographics were comparable across all treatment groups.

In a double-blind, randomised, and placebo-controlled trial in patient with GPP (study 1368.13), patients were randomised in a 2:1 ratio to receive a single dose of spesolimab 900 mg i.v. (35 patients) or placebo (18 patients) on Day 1. All randomised patients were treated. Patients could qualify to receive an open-label treatment with spesolimab on Day 8 (27 patients overall) and/or rescue treatment with spesolimab after Day 8 (6 patients overall; of those, 3 patients received both an open-label and a rescue dose).

The proportion of patients achieving a GPPGA pustulation subscore of 0 at Week 1 was higher in the spesolimab group (54.3%) than in the placebo group (5.6%). The risk difference between spesolimab and placebo of 48.7% was statistically significant ($p = 0.0004$). Similarly, the proportion of patients achieving a GPPGA total score of 0 or 1 at Week 1 was higher in the spesolimab group (42.9%) than in the placebo group (11.1%). The risk difference between spesolimab and placebo of 31.7% was statistically significant ($p = 0.0118$).

The effect of spesolimab on clearing pustules and achieving clear or almost clear skin for all skin manifestations seen in the primary analysis was consistent across prespecified sensitivity analyses and the prespecified subgroups, thereby demonstrating the robustness of the efficacy of spesolimab over placebo for treating a GPP flare.

A GPPASI 75 at Week 4 was achieved by a higher proportion of patients in the spesolimab group (45.7%) than in the placebo group (11.1%), with a risk difference of 34.6% in favour of spesolimab ($p = 0.0081$). The results of the sensitivity and subgroup analyses were generally consistent with the primary analyses for the GPPASI 75, and treatment effects seen at Week 4 were maintained until Week 12.

Pharmacokinetics
Statistical analysis of relative bioavailability showed that on average, the value of the AUCs of the 300 mg BI 655130 SC dose group was two-thirds of the value of the AUCs of the 300 mg BI 655130 IV dose group. The Cmax of 300 mg BI 655130 SC dose group was one-third of the value of 300 mg BI 655130 IV dose group. The inter-individual variability of exposure parameters ranged from 23.7 to 26.6%. Exposures following the 300 mg BI 655130 IV dose were comparable with those observed in the SRD study 1368.1. At least for a 300 mg 655130 SC dose, exposure following this dose is expected to result in a sustained >90% MIP-1 β inhibition.

The relative bioavailability of the 300 mg BI 655130 SC dose group was more than double the bioavailability of the 150 mg BI 655130 SC dose group. For all parameters, the value of the 300 mg BI 655130 SC dose group was 2.7 times higher (on average) than the value of the 150 mg BI 655130 SC dose group. The 90% CI was above the expected value of 200%. The inter-individual variability of exposure parameters ranged from 34.8 to 38.7%.

The assessment of dose normalised PK parameters of 300 mg BI 655130 IV compared with 150 mg BI 655130 SC is consistent with the other two assessments: the gMean ratios of Cmax, norm (21%) and AUCnorm (50%) were even smaller than the comparison of 300 mg BI 655130 SC vs. 300 mg BI 655130 IV.

The geometric mean terminal elimination half-life for BI 655130 after IV administration of 300 mg was 27.1 d. After SC administration of 150 mg and 300 mg, the geometric mean terminal elimination half-life for BI 655130 was 20.6 d and 25.6 d, respectively.

Safety
In study 1368.3, single doses of BI 655130 given as SC injection or IV infusion were safe and well tolerated by the healthy subjects included in this trial. no AEs of severe intensity, protocol-specified AESIs, deaths, or other serious AEs were reported. One subject discontinued trial medication due to an AE (panic attack) beginning shortly after the start of the infusion, which was considered possibly related to trial drug administration. The overall incidence of AEs was higher in the 300 mg dose groups (both IV and SC) than the 150 mg SC group (300 mg BI IV: 11 subjects, 91.7%; 300 mg BI SC: 11 subjects, 91.7%; 150 mg BI SC: 8 subjects, 66.7%). This difference was mainly driven by the AE dermatitis acneiform. Since AUC and Cmax were substantially lower for 300 mg BI SC than for 300 mg BI IV, there was no clear exposure /AE relationship. The incidence of AEs assessed as possibly drug-related by the investigator was higher in the SC groups than in the IV group (150 mg BI SC: 5 subjects, 41.7%; 300 mg BI SC: 5 subjects, 41.7%; 300 mg BI IV: 3 subjects, 25.0%).

Safety laboratory tests and the evaluation of vital signs, oral body temperature, local tolerability, and electrocardiogram recordings revealed no clinically relevant findings.

In study 1368.13, The proportions and incidence rates of patients with any AE, as well as severe, serious, and investigator-defined drug-related AEs were comparable between the placebo and the spesolimab treatment group during Week 1 (i.e. following 1 dose of trial medication). Around two-thirds of patients reported any AE and a third of patients were reported with investigator-defined drug-related AEs. Serious adverse events were reported for 3 patients in the placebo group (16.7%) and 5 patients in the spesolimab group (14.3%). no AEs leading to death occurred in this study.

Regarding safety laboratory values, the number of patients who were within normal range at baseline and then shifted to either below or above limits of normal was generally low. With the exception of parameters such as CRP which may be related to the GPP flare, no marked increases or decreases of mean values from baseline to end-of-treatment were observed for any parameter. For none of the vital signs, marked increases or decreases of mean values were observed over time. The overall frequency of patients with local tolerability symptoms at the infusion site was lower in the placebo group than in the spesolimab group. No clear pattern of symptoms was observed.

Overall, spesolimab showed an acceptable safety profile. The overall rates of adverse events were generally comparable between treatment groups during Week 1. 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).

Overall conclusions:
The relative bioavailability comparison showed that the 300 mg BI 655130 SC formulation obtained approximately two-thirds of the 300 mg IV total exposure (AUC0-tz and AUC0-∞) and approximately one-third of the peak exposure (Cmax). Single IV and SC doses of BI 655130 were safe and well tolerated by the healthy subjects in this trial.

In 1368.9 trial, 32 healthy Japanese male subjects were enrolled in 4 dose groups comprising 8 subjects per group. The study consisted of three dose groups receiving single rising intravenous doses of BI 655130 (300 mg, 600 mg, and 1200 mg) and one dose group receiving single subcutaneous doses of BI 655130 (300 mg). In each dose group, 6 subjects received BI 655130 and 2 subjects, placebo.

Treatments were administered in a double-blind fashion within dose groups. In total, 24 subjects received BI 655130 and 8 subjects, placebo. Three subjects in the 600 mg i.v. group (1 of them allocate to placebo) and 1 subject in the 1200 mg i.v. group discontinued the trial prematurely due to personal reasons.

A total of 3 out of 18 subjects (16.7%) on intravenous doses of BI 655130 (1 subject per i.v. dose level) were reported with an AE compared with 2 out of 8 subjects (25%) on placebo. No subject was reported with an AE following subcutaneous administration of BI 655130. Adverse events by preferred term reported on placebo were vomiting, chest discomfort, and allergic rhinitis, while AEs reported on BI 655130 were upper respiratory infection (300 mg i.v.), contusion (600 mg i.v.), gastroenteritis (1200 mg i.v.), and temporomandibular joint syndrome (1200 mg i.v.). None of the observed AEs were judged by the investigator as related to the trial medication.

The open-label, single group Phase I study (1368.11) was conducted to investigate the safety, tolerability, pharmacokinetics, pharmacogenomics, and efficacy of a single intravenous dose of BI 655130 (10 mg/kg) in 7 patients with acute flare of generalized pustular psoriasis. Based on the PK results in GPP patients, the elimination half-life of BI 655130 was approximately 3 weeks in GPP patients. The proof-of-concept (PoC) for IL36R inhibition in GPP was achieved in these patients who showed rapid clinical responses to single administrations of BI 655130. Five of these 7 patients became clear or almost clear of GPP 1 week after the infusion, and all of them reached this status by 4 weeks after treatment.

Within 48 h of treatment, pustules were completely cleared in 3 patients; pustules were cleared by Week 1 in 5 patients, and by Week 2 in 6 patients. The early response in the skin was also accompanied by an early response in systemic components (C-Reactive Protein [CRP] approaching normalization within 4 weeks). A major improvement in GPPASI was observed in all patients very early with a mean (SD) percent change from baseline of 73.2% (16.2) at Week 2; by Week 4, this was further reduced to 79.8% (15.6), and was maintained to Week 20 (83.6%). Additional improvements (mean [SD]) from baseline to Week 2 were observed in FACIT-F, 12.3 (10.1); Pain-VAS, –45.9 (32.3); and PSS, –5.14 (3.18), all of which were also sustained through Week 4. For further details and most recent results refer to the current IB and published letter in the New England Journal of Medicine [P19-01888].

A placebo-controlled Phase II study (1368-0015) has also been conducted in 59 patients with palmoplantar pustulosis (PPP), 38 of whom received infusions of BI 655130 at doses up to 900 mg every 4 weeks (0, 4, 8 and 12 weeks) and were followed-up through Week 32. Two

Serious AEs (SAEs) were reported (one patient each in the 300 mg BI 655130 and placebo arm). While the majority of AEs were mild or moderate and expected for the population, a severe AE was reported in 2 patients for each of the three study arms (300 mg BI 655130, 900 mg BI 655130 and placebo). Four AEs (10.5%) in patients treated with BI 655130 and three AEs (14.3%) in patients treated with placebo led to discontinuation of trial medication. Three patients in the 900 mg BI 655130 arm and two in the placebo arm experienced a significant AE. no AEs of special interest (AESI) were reported. No clinically relevant abnormalities with respect to safety laboratory and vital signs were observed.

While the proportion of patients who achieved ppPASI50 at Week 16 in the total population was similar in all treatment groups (6 of 19 in 900 mg BI 655130 arm, 6 of 19 in 300 mg BI 655130 arm, and 5 of 21 in placebo arm) the baseline disease severity within the trial population was lower than expected, with half of the patients having a baseline ppPASI total score ≤16.70. In the overall population, the proportion of patients achieving ppPASI50 at Week 16 was not statistically different between the BI 655130 groups (900 mg and 300 mg: each 31.6% [95% CI 15.4%, 54.0%]) and the placebo group (23.8% [95% CI 10.6%, 45.1%]). Thus, the primary endpoint was not met. In patients with baseline disease scores >16.7, post hoc subgroup analyses indicated efficacy for both doses of BI 655130 relative to placebo. The mean percent reduction from baseline in ppPASI total score was 40%, 24% and 8%, at Week 16 for BI 655130 900 mg, BI 655130 300 mg, and placebo respectively in this subgroup. The mean percent reduction from baseline in pustular severity was 57%, 30% and 5% for the 900 mg BI 655130, 300 mg BI 655130 and placebo groups respectively at Week 16 of this subgroup, indicating a pronounced reduction in pustule severity.

Summary
BI 655130 is an anti-IL36R antibody with a high clinical activity to block IL36R signaling as demonstrated in patients with Generalized Pustular Psoriasis, a severe inflammatory skin disease driven by uncontrolled IL36 activity. BI 655130 has been tested in healthy volunteers who received multiple doses every week for 4 weeks. These Weekly doses of up to 20 mg/kg i.v. were all found to be safe in the subjects treated. In addition, IL36R inhibition shows a favorable nonclinical safety profile. BI 655130 has also been tested in acute flare of GPP patients. In these patients, BI 655130 was well tolerated, with no serious adverse events or other clinically notable safety concerns. In a larger trial investigating patients with PPP no safety signals have been identified for BI 655130.

For further details and most recent results refer to the current IB (c03320877).

1.3 RATIONALE FOR PERFORMING THE TRIAL

It has been shown that IL-36 is an upstream driver of barrier dysfunction and activator of pathogenic responses in NS. As for GPP, dysregulated IL-36 signaling causes a chronic inflammatory loop and pustule formation and treatment with spesolimab showed efficacy in patients with GPP [P22-00345]. Altogether, NS and GPP have overlaps with respect to the pathobiology involving IL-36R pathway and associated neutrophil mediated skin disease by promoting a feed forward loop of pro-inflammatory mediators.

Currently, there are no established treatment guidelines for NS. Topical corticosteroids are the main treatment option for NS, but treatment is limited to a short duration and body area due to potential side effects associated with prolonged use of corticosteroids (e.g. Cushing

syndrome). Additionally, daily application of topicals can be time-consuming, impacting patient and caregiver QoL [R22-0760]. Thus, there is an unmet need for an effective therapy that targets the NS pathophysiology with a tolerable and long-term safety profile.

Based on the current knowledge about the mechanism of action, and disease similarity between adults and paediatric subjects, BI expects that similar exposure (i.e. plasma concentrations) will result in similar efficacy and safety in adults and paediatrics with NS. [redacted] The same pharmaceutical forms and formulations are planned to be used in adults and adolescents 12 to <18 years based on the similarity of disease pathophysiology between adolescents and adults in this genetic disorder.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Preclinical profiles of BI 655130 and clinical data from healthy volunteer trials suggest that BI 655130 is safe, tolerable and may address an unmet medical need in NS patients.

We hypothesize that in NS, due to the increase activation of different proteases, inactive IL-36 cytokines are cleaved and activated. These cytokines can target different types of cells, from keratinocytes to immune cells, promoting the production of pro-inflammatory cytokines, including IL-36, thus establishing an autocrine loop which further amplifies inflammation. IL-36 cytokines also have a strong ability to recruit neutrophils to the skin and, in turn, neutrophil-derived proteases process IL-36 cytokines, enhancing their biological activity. Altogether, data are supportive of a pivotal role of the IL-36 pathway in orchestrating the skin inflammatory cascades implicated in the pathogenesis of NS and define the therapeutic potential for IL-36 pathway inhibition in NS. Please refer to IB (c03320877). for additional details.

No relevant animal species is available for toxicology testing of the highly human specific antibody BI 655130. However, preclinical toxicology studies with a mouse surrogate antibody have demonstrated the safety of IL-36R inhibition in mice (c03320877). As of September 2023, an estimated 863 subjects have been exposed to spesolimab, out of a total of 966 subjects in the clinical development programme. For additional details please refer to IB (c03320877). [redacted]

1.4.2 Risks

There are no identified risks for BI 655130, based on the toxicology program or any clinical trials conducted for this product to date. No other IL-36 receptor antagonist is currently approved, providing information on identified risks in molecules of this class.

There are 4 important potential risks identified for BI 655130, as shown in the table below. The first 3, including hypersensitivity reaction, infections, and malignancies are generally hypothetical in nature; these are derived from general safety considerations of immunomodulatory drugs. T[he] 4th, peripheral neuropathy, is based on clinical trial

experience, in which observed cases showed a heterogenous pattern. A causal association to spesolimab to any of the reported cases was assessed to be unlikely.

[redacted]

Blood volumes for safety analysis will be reduced for adolescent patients in this trial. In EU countries, the total blood volume collected will be in line with the EU recommendations for clinical trials on medicinal products conducted with minors across the study [R23-1267].

Table 1.4.2:1 Overview of trial related risks

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product		
Hypersensitivity reaction	After administration of any biologic agent or protein, there is a possibility of occurrence of immediate adverse immune reactions (such as anaphylaxis) or delayed (such as drug reaction with eosinophilia and systemic symptoms)	Patients with a history of allergy/hypersensibility to the systemically administered trial medication agent or its excipients are excluded from the trial
Infections	Inhibition of the immune response with an immune-modulating biologic may increase the risk of infections	Screening procedures for infections are defined for the trial. Patients with any relevant chronic or acute infections including human immunodeficiency virus (HIV), viral hepatitis or tuberculosis are excluded from the trial. Treatment of infections should be initiated promptly according to standards of care

Table 1.4.2:1 (cont'd) Overview of trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product		
Malignancies	Inhibition of the immune response with an immunomodulatory drug may potentially impair immune defences and thus theoretically decrease immune defense against malignancies	Patients with a recent history of malignancy within 5 years will be excluded from participation in this trial. In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or *in situ* carcinoma of uterine cervix, the investigator should discontinue treatment with spesolimab. Diagnostics and treatment have to be initiated according to the local standard of care. Malignancies represent always serious adverse events and are subject to close monitoring.
Peripheral Neuropathy	Three cases reported by the investigator as Guillain-Barré syndrome (GBS) were received in ongoing clinical trials with spesolimab. A panel of independent neurologists and experts in the study of neuropathies assessed the 3 cases. Only 1 met level 4 diagnostic certainty for the diagnosis of GBS (lowest level on Brighton scale of 1 to 4). In that case, there was a coincident infection with SARS-CoV-2. The other 2 cases were assessed as not GBS. Observed cases showed a heterogenous pattern. A causal association to spesolimab to any of the reported cases was assessed to be unlikely. As per assessment by the panel of external neurologists the nonspecific symptoms and findings in all three cases may best be referred to as peripheral neuropathy.	Timely detection, evaluation, and follow-up of suspected peripheral neuropathies to ensure patients´ safety. Use of dedicated questions to elicit neurologic history during screening and exclusion criteria to avoid selection of patients with acute demyelinating neuropathy. Targeted Follow up questions to gather detailed information in case of any event during trial to ensure proper decision making. Trial treatment continuation criteria as well as criteria for trial treatment restart are implemented for relevant cases.

Table 1.4.2:1 (cont'd) Overview of trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product		
Drug-induced liver injury	Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, DILI is considered as a standard risk in all BI development programs.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety. Trial treatment discontinuation criteria as well as criteria for trial treatment restart are implemented for relevant cases.
Blood sampling	As with all blood sampling, there is a risk of mild pain, local irritation, or bruising at the puncture site. Furthermore, there is a small risk of light-headness and/or fainting. In rare cases, the puncture site can also become infected, or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensations of touch and persistent pain	The risks will be addressed by careful safety monitoring for AEs, selection of experienced sites and staff and training.
Skin biopsy	Skin biopsy can cause local bruising, inflammation, nerve damage and pain	These risks will be addressed by careful monitoring and risk mitigation measures such as: close clinical monitoring for AEs, selection of sites with experienced staff, training

Based on the findings in the nonclinical studies conducted to date and in accordance with international regulatory guidelines, the inclusion of Women of Childbearing Potential (WOCBP) in this study is justified. To minimize the risk of unintentional exposure of an embryo or fetus to the investigational drug, WOCBP must agree to the requirements for the pregnancy testing and contraceptive methods described in the protocol.

Benefit-Risk Assessment in context of COVID-19 pandemic for patients participating in clinical trials investigating Spesolimab:

A thorough assessment based on the data available as of 31 May 2021 has been conducted to evaluate whether spesolimab may pose a higher risk associated with COVID-19 infection. Additionally, the general risk of COVID-19 infection in context of the trial population's

underlying disease and common co-morbidities was assessed. The key aspects of the assessment are summarized below.

Spesolimab is an immune-modulating humanized monoclonal antibody that blocks the human IL-36 receptor and thereby the pro-inflammatory IL-36 pathway. Available non-clinical and clinical data in [redacted] subjects (see c03320877) have not shown an increased risk of infections with spesolimab. However, as reflected in Table 1.4.2:1 above and the patient informed consent form, similar to other immune modulating biological treatments, spesolimab may hypothetically increase the risk of infections. Therefore, risk mitigation measures, such as exclusion of patients with increased risk of infections, close monitoring of adverse events, as well as guidance on treatment and handling of acute infections occurring during the trial have been included within this clinical trial protocol.

As any other acute infection, a suspected or diagnosed COVID-19 infection should be treated according to the standard of care and interruption of study medication should be considered.

Currently, information about the immune response in patients with COVID-19 is sparse and inconclusive. There are some reports suggesting high-levels of pro-inflammatory cytokines in the severe cases, with much of the morbidity associated with coronavirus infection, potentially related to immune activation and inflammation. To date, there is no reliable evidence suggesting a link between SARS-CoV-2 infections and the IL-36 pathway targeted by spesolimab. Considering the current knowledge of COVID-19 and the implemented risk mitigation measures addressing the potential risk of infections, patients studied in trials with spesolimab are not believed to be at higher risk of COVID-19 due to their background or concomitant diseases. Protocol-defined procedures do not impose undue risk to study participants.

The benefit-risk assessment of spesolimab remains favourable in the context of the COVID-19 pandemics. Patients participating in trials with spesolimab are expected to benefit from trial treatment and interruption of treatment may worsen their disease. Published guidance for the use of biologics during the COVID-19 pandemic recommends to continue treatment with biologics (e.g. NICE COVID-19 rapid guideline: severe asthma [R20-2257], American College of Allergy, Asthma&Immunology [R20-2258], and National Psoriasis Foundation [R20-2256]. In line with this guidance no systematic testing for SARS-CoV-2 is required to be performed on the trial. However, the investigator may choose to perform the testing as per his/her discretion if useful based on individual medical consideration and in the case of suspected COVID-19 infection. Patients may receive COVID-19 vaccination in line with local recommendations/guidance and approved labels. However, it is not known whether there is any negative impact of spesolimab on the protective effect of COVID-19 vaccines.

To address potential risks associated with operational aspects related to the participation in this clinical trial in context of COVID-19 pandemic, the following risk mitigation measures are to be considered based on local requirements and development of pandemic.

The investigators will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each patient's (continued) participation in the planned trials. BI as the sponsor, where

required, will support the investigator in their decision finding. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, wellbeing, and/or is in the best interest of the patient.

1.4.3 Discussion

In the context of the unmet medical need and anticipated benefit of spesolimab, the benefit risk evaluation of the compound, based upon the available preclinical and clinical information, is favourable.
Considering the medical need for the development of a better tolerated and more effective treatment for patients with NS, the expected benefit outweighs the potential risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

This trial will assess the efficacy, safety, PK and the tolerability of [redacted] followed by [redacted] of spesolimab compared with placebo in patients ≥12 years old with confirmed diagnosis of NS (*SPINK5* causative mutations). The primary objective is to evaluate the treatment response of spesolimab (determined by 50% improvement at Week 16 in IASI score). The secondary objectives are to evaluate reduction in other skin severity assessments, improvement in quality-of-life assessments, improvement in sleep, itch and scalp hair assessments and describe safety descriptively, with incidence of AEs.

2.1.2 Primary endpoint(s)

The primary endpoint of the trial is:

- IASI response, defined as a decrease of at least 50% absolute change in IASI score from baseline at Week 16 (Yes/No)

2.1.3 Key secondary endpoint(s)

The key secondary endpoint of this trial is:

- IGA response, defined as a decrease of at least 1-grade absolute change in IGA score from baseline at Week 16 (Yes/No)

2.1.4 Secondary endpoint(s)

Secondary endpoints of the trial are:

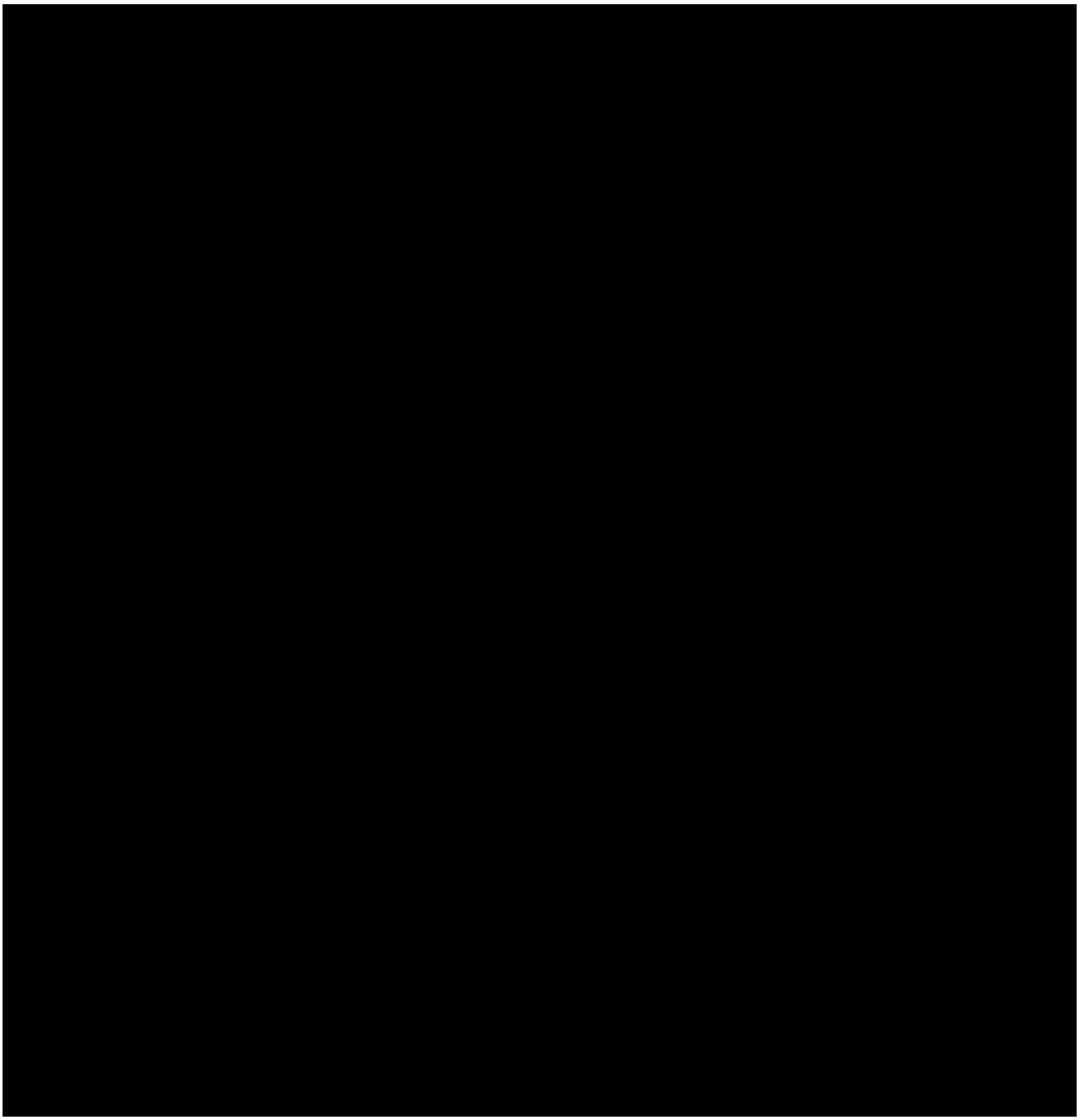
Efficacy:

- IGA score of 0 or 1 at Weeks 4, 8, 12 and 16 (Yes/No)
- IASI response, defined as a decrease of at least 50% absolute change in IASI score from baseline at Weeks 4, 8, and 12 (Yes/No)

- IASI-E subscore response, defined as a decrease of at least 50% absolute change in IASI-E subscore at Weeks 4, 8, 12, and 16 (Yes/No)
- IASI-S subscore response, defined as a decrease of at least 50% absolute change in IASI-S subscore from baseline at Weeks 4, 8, 12, and 16 (Yes/No)
- Percent change from baseline in IASI score at Weeks 4, 8, 12 and 16
- Absolute change from baseline in NRS pain at Weeks 4, 8, 12 and 16
- Absolute change from baseline in NRS itch at Weeks 4, 8, 12 and 16
- Absolute change from baseline in DLQI score at Weeks 8 and 16
- Absolute change from baseline in CDLQI score at Weeks 8 and 16

Safety

- The occurrence of treatment emergent adverse events including serious and/or opportunistic infections



[redacted]

- **Safety**
  - Intensity of adverse events will be assessed by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
  - Safety laboratory tests
  - Physical examination
  - Vital signs (blood pressure, pulse rate, body temperature, respiratory rate)
  - 12-lead Electrocardiogram (ECG)
  - Local tolerability
  - Immunogenicity (ADA/Nab)

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a multicentre, randomised double blind, placebo-controlled Phase II/III trial comprising a spesolimab treatment group compared with placebo in 2:1 ratio in patients with moderate to severe NS.

Randomised period
After providing informed consent, patients will enter the screening period for up to [redacted] days. Eligible patients will be randomised either in the active treatment arm to receive spesolimab [redacted] at Week 0 plus spesolimab [redacted] every [redacted] weeks starting from Week [redacted] or in the placebo arm to receive placebo [redacted]

Crossover period
There will be a crossover period when patients reach Week [redacted] where patients initially in placebo arm will receive spesolimab [redacted] and patients initially in spesolimab arm will receive [redacted] at Week [redacted] and continue receiving spesolimab [redacted].

To maintain the blinding during the crossover, each patient will receive [redacted] at Week [redacted] in addition to the [redacted] Therefore, neither the patient nor the investigator (or the trial staff) will know if the patient had received spesolimab or placebo in the double-blind portion.

Patients will be evaluated for the primary endpoint defined as 50% improvement in IASI score at Week 16.

The primary analysis of this trial is planned to be performed once all randomised patients have completed the 16 weeks or early discontinued from the trial, to support an early submission; a database lock for the primary analysis will then be performed.

Final analysis is planned to be performed at the end of the trial once all patients have completed the trial (including any follow-up period if applicable).

Open label period
At Week [redacted], all patients will enter the open label period to receive spesolimab [redacted]. At Week [redacted], patients will be evaluated for response to treatment.

Patients who have responded (responders), defined as having more than or equal to [redacted] at Week [redacted] compared with baseline will receive a [redacted] dose of spesolimab, [redacted] every [redacted] weeks. Patients who have not responded (non- responders), defined as having less than [redacted] in IASI score at Week [redacted] compared with baseline will continue receiving [redacted] of spesolimab every 4 weeks until Week [redacted].

For patients who were responders at Week [redacted] and were [redacted] can be conducted if the patients, based on the investigator's judgement, experience [redacted] of less than [redacted] response. The dose escalation should be applicable only once.

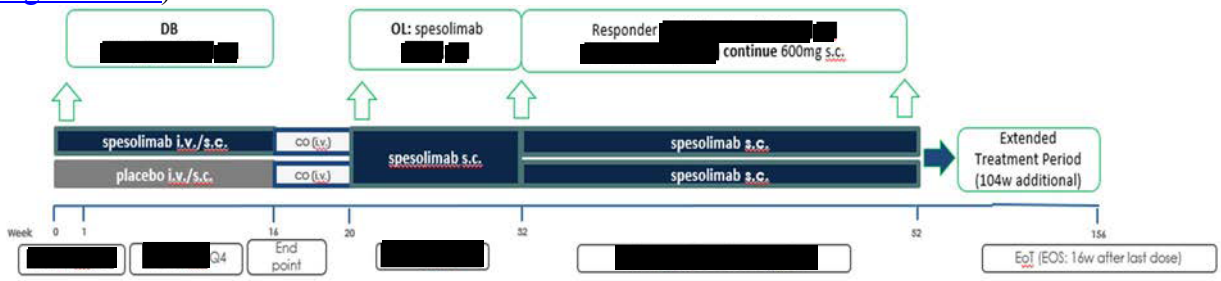
[redacted] **Period (from Week [redacted] to Week [redacted])**
After completing the first [redacted] weeks of treatment, the patients are offered to continue receiving their assigned treatment at Visit 16 (i.e. Spesolimab [redacted]) in the extended treatment period up to additional [redacted] weeks.
Starting Week 56:

- Patients receiving [redacted] of spesolimab and experiencing a reduction of less than [redacted] on IASI compared with Visit 2 for two consecutive visits should be discontinued from the trial treatment. These two consecutive visits should be at least 4 weeks apart. [redacted] from [redacted] will not be permitted during the extended treatment period.
- Patients who are receiving spesolimab [redacted] and experience a [redacted] on IASI should not be discontinued, but [redacted] first. Only if the patient still

shows reduction of less than 50% on IASI on [redacted] for two consecutive visits, patient should be discontinued.

Patients will then enter the [redacted] follow up period for ongoing safety data collection. The patient's trial participation is complete when they have completed the last planned visit (EoS) [redacted] weeks after the EoT visit.

Patients who prematurely discontinue from the trial drug will be encouraged to continue with the original visit schedule up to Week [redacted] (without IMP administration in that case). EoS (End of Study) visit will be performed as the last patient visit in that case. At a minimum, patients should come to an EoS Visit [redacted] weeks after the last dose to cover full REP (see Figure 3.1:1).



DB: double blind
OL: open label
CO: Cross over ([redacted]):

- Placebo patients receive spesolimab [redacted]
- Spesolimab patients receive placebo

Figure 3.1:1 Trial design

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

The placebo control is required to control for investigator bias and/or beneficial effects of being in a clinical trial. The 2:1 randomisation (active: placebo) is warranted in order to maximize the number of patients receiving active treatment and is being controlled for a statistical standpoint. The rationale for switching placebo patients to active treatment at Week [redacted] is to allow patients who have not received active treatment at baseline and during the double-blind portion of the trial to have the opportunity to receive active treatment during open label portion of the trial. In addition, the extended treatment period after Week [redacted] is included to provide trial patients with continued treatment and assessments, and to collect further efficacy and safety evaluations.

As part of the trial, patients may participate to the Qualitative Interview sub-study to understand their experience with the received treatment during the clinical trial. Participation in the interview is optional and details will be described in an optional informed consent form/Assent. The interview will be conducted after a separate patient interview informed consent has been given in accordance with local ethical and regulatory requirements. Further details will be provided in a separate In-trial interview Manual.

This trial will also include an option for adult participants to complete anonymized questionnaires to provide feedback on their clinical trial experience. Providing this feedback is not required for trial participation, and information collected from these questionnaires will not be analysed as part of the clinical data for the trial (see Appendix 10.2).

3.3 SELECTION OF TRIAL POPULATION

The trial will be conducted worldwide in approximately 20-25 countries, at sites experienced in the management of dermatologic diseases, including rare dermatological conditions like GPP and NS.
The regions and clinical sites will be selected based on availability of patients with NS and experience in the conduct of clinical trials and use of the clinical assessments.

A total of approximately 39 patients with NS including at least [redacted] adolescent patients will be randomised. It is planned to enrol at least 1-2 patients per site due to the rareness of the disease. A sufficient number of patients will be screened to meet the randomised goal.

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial. Patients already in screening at this time will be allowed to continue to randomisation if eligible.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.

If retrospectively it is found that a patient has been in error (=did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment a decision will be made whether continued trial participation is possible or not.

3.3.1 Main diagnosis for trial entry

This trial will assess treatment of patients with history of NS.
The patient eligibility will be based on a confirmed causative *SPINK5* mutations, and at least moderate severity of erythema defined as (IASI score ≥16 and IASI-E score ≥8) at baseline (Visit 2) and ≥3 on IGA score.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Male or female patients, aged 12 years and older (weight minimum is 35 kg)
2. Confirmed diagnosis of NS (causative *SPINK5* mutations) at baseline (Visit 2)

3. At least moderate severity of erythema at baseline (Visit 2) (IASI score ≥16 and IASI-E score ≥8) and ≥3 on IGA score.
4. Signed and dated written informed consent and assent in accordance with ICH-GCP and local legislation prior to admission in the trial.
5. Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the CTP as well as in the patient, parent(s) (or patient's legal guardian) information.

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is not a method of permanent sterilization. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

3.3.3 Exclusion criteria

1. Patients who have used topical corticosteroids (medium to high, US class I-V), topical retinoids, topical calcineurin inhibitors or keratolytics within 1 week prior to randomisation
2. Patients who have used emollient on the area to be biopsied in the previous 24 h
3. Patients who have used systemic retinoids, other systemic immunosuppressants, systemic corticosteroids or phototherapy within 4 weeks prior to randomisation
4. Patients who have used systemic antibiotics within 2 weeks prior to randomisation
5. Patients who have received live vaccines within 4 weeks prior to randomisation
6. Patients who have received investigational products, biologics or immunoglobulins within 4 weeks or 5 half-lives (whichever is longer) prior to randomisation
7. Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold Upper Limit of Normal (ULN) elevation in AST or ALT or alkaline phosphatase, or >2x ULN elevation in total bilirubin
8. Patients who have any prior exposure to BI 655130 or another IL-36R inhibitor biologics
9. Increased risk of infectious complications (e.g. recent pyogenic infection, any congenital or acquired immunodeficiency (e.g. HIV), past organ or stem cell transplantation), as assessed by the investigator
10. Relevant chronic or acute infections including active tuberculosis, human immunodeficiency virus (HIV) infection or viral hepatitis at the time of randomisation. A patient can be re-screened if the patient was treated and is cured from the acute infection
11. Active or Latent TB:
    - Patients with active tuberculosis should be excluded
    - Patients with a positive QuantiFERON® (or if applicable, T-Spot®) TB test during screening are excluded, unless the patient had previous diagnosis of active or latent TB and has completed appropriate treatment per the discretion of the local investigator within the last 3 years and at the latest at the time of screening

(i.e. 2 to 4 weeks before study drug administration); patients may be re-screened once to meet this criterion)

- Patients with suspected false positive or indeterminate QuantiFERON® (or if applicable, T-Spot®) TB result may be re-tested once
- If QuantiFERON® (or if applicable, T-Spot®) TB testing is not available or provides indeterminate results after repeat testing, a tuberculin skin test (TST) or any alternative test/procedure (as per local standards) to rule out TB can be performed: a TST reaction of ≥10 mm (≥5 mm if receiving ≥15 mg/d prednisone or its equivalent) is considered positive.

12. Active skin infection requiring the use of a systemic therapy within 2 weeks
13. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients
14. Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s) or receiving other investigational treatment(s)
15. Women who are pregnant, nursing, or who plan to become pregnant while in the trial. Women who stop nursing before the trial drug administration do not need to be excluded from participating; they should refrain from breastfeeding for [redacted] weeks after the last trial drug administration
16. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to receiving first dose of trial drug or planned during the trial, e.g. hip replacement, aneurysm removal, stomach ligation, as assessed by the investigator
17. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse or congestive heart disease or any condition) other than NS, surgical procedure, psychiatric or social problems, medical examination finding (including vital signs and electrocardiogram (ECG), or laboratory value at the screening outside the reference range that in the opinion of the investigator is clinically significant and would make the trial participant unreliable to adhere to the protocol, comply with all trial visits/procedures or to complete the trial, compromise the safety of the patient or compromise the quality of the data.
18. Any other condition that according to the investigator will impair the ability to evaluate treatment effect.
19. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or *in situ* carcinoma of uterine cervix.
20. Previous enrolment in this trial (re-screening is allowed).
21. Presence of acute demyelinating neuropathy.

3.3.4 Discontinuation of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

However, if the patients agree, they should stay in the trial. Even if continued trial treatment is not possible, they should attend further trial visits to ensure their safety and to collect important trial data.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.
The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see Section 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment. The patient will be asked to explain the reasons but has the right to refuse to answer.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of the investigator, the safety of the patient cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the safety of the investigational medicinal product or other trial treatment
- The patient can no longer receive trial treatment for medical reasons as per physician's discretion (such as surgery, adverse events, other diseases, or pregnancy
- If a hepatic injury alert is detected without identification of an alternative cause in the work-up according to the "DILI checklist" (see Section 5.2.6.1.4), the patient should not receive subsequent doses of trial medication
- For individual stopping rules related to specific adverse events, please see
- Section 4.2.1 "Other treatments and emergency procedures."
- Worsening of clinical status or symptoms requiring treatment with restricted medication in the investigator's opinion
- In case of a temporary reason, trial treatment should be restarted if medically justified, please see Section 4.1.4.

In case the study drug administration is permanently discontinued before EoT visit, all effortsshould be made to keep the patient in observation for the remaining trial visits up to the regular EoT visit at Week [redacted], according to Flowchart. EoS visit will be performed as the last patient visit in that case. As a minimum, the patient should come back to an EoS Visit [redacted] weeks after the last dose ofthe study drug.

If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

Even if the trial treatment is discontinued, the patients remain in the trial and, given their agreement, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flowchart and Section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see Section 3.3.4.1.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.
4. Termination of development of compound in this indication

Further treatment and follow up of patients affected will occur as described in section 3.3.4.1.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1:1 Test product 1: BI 655130 (spesolimab)

Substance:	BI 655130 (spesolimab)
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	BI 655130 [redacted]
Posology:	Spesolimab arm: [redacted] at Week **0** Placebo arm: [redacted] spesolimab at Week [redacted]
Mode of administration:	[redacted]

Table 4.1.1:2 Test product 1: BI 655130 (spesolimab)

Substance:	BI 655130 (spesolimab)
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	BI 655130 [redacted]
Posology:	Spesolimab arm: [redacted] weeks [redacted] Placebo arm: [redacted] weeks
Mode of administration:	[redacted]

Table 4.1.1:3 Placebo comparator

Substance:	Placebo matching to spesolimab
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Placebo matching to spesolimab [redacted]
Posology:	Placebo arm: [redacted] Spesolimab arm: [redacted]
Mode of administration:	

Table 4.1.1:4 Placebo comparator

Substance:	Placebo matching to spesolimab
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Placebo matching to spesolimab [redacted]
Posology:	Placebo arm: Placebo [redacted]
Mode of administration:	

4.1.2 Selection of doses in the trial and dose modifications

As dose ranging is not feasible in this extremely rare disease, a high yet safe dosing regimen is proposed in the NS trial 1368-0104: [redacted] spesolimab [redacted] on Day 1 followed by [redacted] starting from Week [redacted]. In responders, the dose is reduced to [redacted] to explore the efficacy of a lower dose.

[redacted]

In the on-going GPP prevention trial 1368-0027, spesolimab s.c. up to 300 mg q4w is being evaluated. To account for potential difference in the dose-response relationship between NS and GPP, 600 mg s.c. q4w is proposed as maintenance dose for NS patients considering the chronic nature of the disease and the potential need for persistent inhibition of IL-36. A dose regimen of 600 mg q4w is expected to be safe (see below) and considered to provide an appropriate balance between efficacy and patient burden in the administration of required injections per visit (2 shots for 600 mg). The dose reduction (to 300 mg q4w) in responders at Week 32 provides opportunity to explore the dose-response in this rare disease population. Based on the similarity of disease pathophysiology between adolescents and adults as an underlying genetic disorder, the same dose is proposed for adolescents in trial 1368-0104. Adolescents have been included in GPP trial 1368-0027 up to 300 mg spesolimab s.c. q4w and no safety signals have been identified specific to this subpopulation. The proposed dosing regimen in adults and adolescents is expected to be safe.

Spesolimab has been generally well tolerated throughout the clinical development (c03320877), [redacted] As there is no PK data in NS population, typical parameters were used from a popPK model developed from other indications, [redacted] (c34990476).

[redacted]

Table 4.1.2:1 Observed exposures or exposures predicted from a Population PK model

Study	Population	Dose Regimen	Body weight (kg)	Cmax, overall (mcg/mL)	AUC over last 4 weeks (mcg/mL*day)
Predicted exposure metrics for NS					
[redacted]					
Predicted or observed exposure metrics from other populations					
1368.2	Healthy	20 mg/kg i.v., q1w, x4 doses, until Week 4	75.6 (8.2)*	826 (15.8%) [2]	13400 (9.3%) [2]
[redacted]					

[redacted]

2. Observed geometric mean exposures (gCV%) for 1368.2 (HV)

* Mean (SD)

4.1.3 Method of assigning patients to treatment groups

An Interactive Response Technology (IRT) will be used to screen eligible patients, perform drug assignment, manage initial/re-supply ordering of drug supplies and handle emergency un-blinding. The investigator will receive all necessary instructions to access the IRT from the Sponsor. Detailed IRT functions and procedures will be documented in the user requirement specifications mutually agreed to by the sponsor and the IRT vendor.

After the assessment of all in- and exclusion criteria, each eligible patient will be randomised to a treatment group according to a randomisation plan in a 2:1 ratio at Visit 2 via Interactive Response Technology (IRT). Note that the medication number is different from the patient

number (the latter is generated during screening via the IRT System). Each syringe and vial will have an individual medication number for dispensation.

4.1.4 Drug assignment and administration of doses for each patient

Prior to each administration of trial drug, a urine pregnancy test will be performed on site. If this test has positive result, the administration of trial drug should not proceed, and this urine test should be confirmed by a serum pregnancy test.

The trial drug will be prepared and handled according to the 'clinical supplies handling instruction' which will be filed in the ISF.

Upon randomisation, patients will receive a [redacted] or placebo [redacted]). Throughout the randomised portion of trial, patients will receive either speoslimab [redacted] or placebo [redacted]s at Week [redacted]. The administration of the trial medication [redacted] will be done under the supervision of the investigating physician or designee.

To maintain the treatment blind during the [redacted], all patients will receive [redacted] placebo at Week [redacted].

During the open label period starting at Week [redacted], all patients will receive spesolimab [redacted]. every [redacted] weeks. During the visits with reduced number of assessments e.g. Weeks [redacted], and extended treatment period, patients will be offered to receive spesolimab s.c. at home or closer to the patient's home, administered by a specialized vendor/HCP if applicable. However, if preferable for the patient and the investigational site, all s.c. injections will be performed at the trial site. Patient self-administration is not permitted.

Detailed instructions for administration of the s.c. injections are provided in the ISF.

The [redacted] will be administered over a period of [redacted] min. In case of safety concerns, e.g. due to systemic hypersensitivity including infusion reactions, it is at the discretion of the investigator or his/her designee to adapt the infusion scheme, including but not limited to slowing down the infusion rate, stopping the infusion, and provided no further safety concern exists, restarting at a slower rate. Regardless, the total duration of infusion should not exceed 180 min (3 h). Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 1 hour after the i.v. dose of trial drug administered at Visit 2 and Visit 6. Hypersensitivity reactions should be treated according to medical standards. Further based on his/her medical judgment the investigator will provide medications as needed.

[redacted] personnel should observe the injection site for signs of redness, swelling or hardness. They should also ask patients about itching, dizziness or shortness of breath. Patients should be advised that if they experience redness, swelling or other changes at the injection site, they should notify site personnel. They should further be advised that if

they experience itching all over or a feeling of being swollen, dizzy or short of breath, they should notify site personnel or their own healthcare provider immediately. Pre-medications for further injections might be considered upon discussion with the sponsor.
In exceptional cases of missed or delayed visits, if any of these visits has to be rescheduled, the date of subsequent visit should be calculated from Visit 2/Day 1.

During the COVID-19 pandemic, physical visits to the trial sites may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue the trial treatment and trial medication [redacted] may be administered at patient's home if acceptable according to local law and regulations.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The primary analysis of this trial is planned to be performed once all randomized patients have completed the [redacted] weeks or early discontinued from the trial, to support an early submission; a database lock for the primary analysis will then be performed and treatment will be unblinded to the sponsor.

Patients, investigators and central reviewers involved in trial conduct in this double-blind trial will remain blinded regarding the randomised treatment assignments until the database is declared ready for final analysis according to the sponsor's SOPs. Further details regarding the timepoint of unblinding the database for analysis is documented in the TSAP.

The access to the randomisation code will be kept restricted until its release for analysis.

The randomisation codes may be provided to bioanalytics before the last patient completed the trial for the PK and ADA analysis. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial has been officially un-blinded to the sponsor.

A fully external DMC will perform an unblinded safety and efficacy assessment at specified intervals in order to ensure that patients are protected from potential harm, please refer to Section 8.7 for further details.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the

code will only be given to authorised Pharmacovigilance representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.
In accordance with the Clinical Trial regulation (EU) No 536/2014 and the corresponding Annex VI, omitting of label content with the following justifications:

- the translation of country specific label text may differ from the Master Label Text based on specific local requirements. This could include the omission, addition or revision of some text per local regulation compliance.
- the Investigator name was omitted from the label due to IRT System.

For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the Clinical Research Associate CRA (as provided in the list of contacts) must be contacted immediately.
The trial medication will be prepared for infusion just prior to infusion, for further details please refer to preparation instructions in the ISF.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor or delegate when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site,
- Approval / notification of the regulatory authority, e.g. competent authority,
- Availability of the *curriculum vitae* of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator (if applicable),
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics.
The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry (‘use- by’) dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator’s possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

4.2.1.1 Other treatments

Overall, the choice of Standard of Care (SoC) treatment will be left at the discretion of the investigator.

All concomitant treatment(s) taken during the trial must be recorded in the source documents (e.g. patient files) and on the CRF.

Skin Care
Emollients will be used throughout the trial. The use is at least twice a day. Emollients must not include urea or salicylic acid, should not be keratolytics and
should not be medicinal products (i.e. no treatment indications).

The use of emollients will be documented in a patient diary and eCRF.

Supporting medications
Low potency topical corticosteroids (US class VI and VII) for treatment of NS are allowed according to investigator’s judgement. The use of topical corticosteroids will help retention of patients in the study. Patients who experience skin infection requiring antibiotics during the trial will not be discontinued from trial drug or withdrawn from the trial.

Supporting medications will be documented in a patient diary and eCRF.

Restricted medications and treatments for NS
If the patient experiences an intolerable worsening of NS during the course of the trial, the patient will be discontinued from trial treatment to receive alternative medication or the patient will receive treatment for NS (including restricted medications with the exception of biologics,immunoglobulins and investigational products, in which case the patientneeds to be discontinued from trial treatment) as deemed appropriate by the investigator.

In case of early discontinuation from trial treatment, the patient will be followed up as described in the Flowchart 1 (Footnote 2) for early EoT.

Supporting medications and alternative treatments will not be provided by BI.

4.2.1.2 Emergency procedures

Systemic hypersensitivity including infusion reaction and anaphylactic reaction
In case of systemic hypersensitivity including infusion reaction and anaphylactic reaction emerging during or after infusion(s) / injection(s) of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to:

- Immediately interrupt the infusion (i.v) or stop further injections (s.c.).
- Treat with systemic antihistamines, i.v. steroids, and in case of a severe allergic reaction (e.g. anaphylactic reaction) epinephrine.

Also draw a plasma sample for IgE and ADA as detailed in the Lab Manual in the ISF. Please initiate the evaluation of histamine, serum tryptase, and complement components.

In case of infusion reaction/systemic hypersensitivity, based on patient's clinical course and medical judgment, the infusion may be re-initiated in case of mild or moderate infusion reactions/systemic hypersensitivity (according to CTCAE grading) at lower speed with gradual increase to complete the infusion as detailed in the Instructions for Preparation and Handling of spesolimab/placebo in the Investigator Site File.
In any case, the [redacted].

In case of anaphylactic reaction based on the criteria discussed in the statement paper from Sampson HA (Appendix 10.1.12, R11-4890) suspected to be caused by the trial medication, the investigator should permanently discontinue treatment with spesolimab/placebo.

When a delayed hypersensitivity reaction is suspected, please draw a blood sample for laboratory assessment and evaluate for signs of extra-cutaneous organ involvement. The decision to discontinue treatment and/or restart treatment after resolution of the reaction should be based on reaction type and severity.

Severe infections (according to CTCAE Version 5.0), serious infections, opportunistic or mycobacterium tuberculosis infections.
Treatment of the infection should be initiated promptly according to local standard of care. No further trial medication should be administered until the active infection has resolved. Treatment with spesolimab may be restarted when the patient has recovered according to investigator's assessment.

Malignancies
In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or *in situ* carcinoma of uterine cervix, the investigator should discontinue treatment with BI 655130. Diagnostics and treatment must be initiated according to local standard of care.

Peripheral Neuropathy
If peripheral neuropathy is suspected, treatment with spesolimab should be temporarily discontinued until a full neurological investigation has been conducted. After completion of the neurological investigation, treatment can be restarted based on medical judgement of the investigator.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The medications (or classes of medications) listed in Table 4.2.2.1:1 must not be taken for the time periods as specified.

Table 4.2.2.1:1 Restricted medications and treatments

Medication or class of medications or treatment	**Restriction duration**
Topical retinoids, Topical calcineurin inhibitors, keratolytics (including urea)	1 week prior to Visit 2 and until EoT visit
Medium and high potency topical corticosteroids (US class I-V)[1]	1 week prior to Visit 2 and until EoT visit
Systemic immunosuppressants (e.g. cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, JAK inhibitors), Systemic retinoids (e.g. acitretin, alitretinoin, isotretinoin, etretinate), Systemic corticosteroids[2] or phototherapy	4 weeks prior to Visit 2 and until EoT visit
Systemic antibiotics[3]	2 weeks prior to Visit 2 and until EoT visit
Live vaccines	4 weeks prior to Visit 2 and until EoS visit
Investigational products, biologics (e.g. secukinumab), immunoglobins	4 weeks or 5 half-lives (whichever is longer) prior to Visit 2 and until EoS visit

[1] No restriction on inhaled corticosteroids to treat asthma, intranasal corticosteroids to treat allergic rhinitis, or corticosteroid drops administered in the eye or ear.
[2] To treat non−NS-related conditions such as asthma or allergy/anaphylaxis allowed according to Investigator's judgment.
[3] Allowed in case of skin infection of NS, emergency or other indication than NS.

4.2.2.2 Restrictions on diet and lifestyle

No specific restrictions on diet or lifestyle of the patients are required

4.2.2.3 Contraception requirements

Women of childbearing potential must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient, parent(s) (or patient's legal guardian) information.

Acceptable methods of birth control for this trial are:
- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable).

- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion
- Vasectomised sexual partner with documented absence of sperm.
- Complete sexual abstinence (not to have male-female vaginal sex).

As monoclonal antibodies can be secreted in milk, women should refrain from breastfeeding once they receive the study drug and up to [redacted] weeks after, i.e. until BI 655130 is eliminated. They can start nursing again after this period.

Male Patients:
Contraception of male trial participants and female partners of male trial participants are not required.

4.3 TREATMENT COMPLIANCE

The trial drug will be administered at the clinic site under the supervision of trained site personnel. For the visits with reduced number of assessments (e.g. Weeks [redacted] the trial drug may be administered by the specialized HCP in accordance with the protocol. The measured plasma concentration will provide additional confirmation of compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

The primary, secondary and further endpoints of the study are specified in Sections 2.1.2 and, 2.1.3 and 2.2.2, respectively.

IASI
IASI is a composite score based on the global Congenital Ichthyosis Severity Instrument (CISI) score that captures differences in severity in different body regions as a function of their body surface area, and also standardizes the number of choices within the Likert scales for erythema and scaling. IASI measures erythema and scaling as 0-4+ in severity at each of 4 locations: head and neck (including scalp); arms (including palms); legs (including soles); and trunk, prorated based on body surface area in these sites and the percentage of involvement in each of these sites. The scale has a range of 0-48 (sum of a max score of 24 for erythema and 24 for scaling). A higher score means worse clinical severity [R22-1085].

IGA
IGA for NS will assess the global severity of erythema and scaling in NS using 5-point Likert scale ranging from 0=clear, to 4=severe.

NASA
The NASA represents a modification of the standard Eczema Area and Severity Index (EASI) and assesses the severity of dermatitis over 4 body areas (head and neck, trunk, upper extremities, and lower extremities [R22-0826]. It assigns proportionate body surface areas to the head and neck (10%), trunk (30%), upper extremities (20%), and lower extremities (40%). The area of involvement (affected by inflammation, not including dry skin) of each of

the 4 body regions is represented by a 7-point numeric coded value (0-6). The investigator is required to record the percentage area (0-100%) and suggested to record to nearest 5%.

Score	Area of involvement, %
0	No eruption
1	<10
2	10-29
3	30-49
4	50-69
5	70-89
6	90-100

The head, trunk, upper limbs and lower limbs are assessed separately for erythema (E), infiltration/ papulation (I), lichenification (L), and scaling (S). The average degree of severity of each sign in each of the 4 body parts is assigned a score of 0 to 3 indicating no involvement (0) or mild (1), moderate (2), or severe (3) expression of the clinical sign. A higher score means worse clinical severity.

NRS Pain
The Numeric Pain Rating Scale is a unidimensional measure of pain intensity, including those with chronic pain. The 11-point numeric scale ranges from '0' representing 'no pain' to '10' representing worst pain imaginable.

NRS Itch
The NRS itch is comprised of one item to measure intensity of itch. The scale ranges from '0' representing 'no itch' to 10 'worst imaginable itch'.

DLQI/CDLQI
DLQI is the most commonly used and first dermatology-specific quality of life assessment tool to assess various dermatologic conditions and has been a reliable measure of quality of life. It contains 10 questions and scores from 0 to 30 in total. Response categories include "not relevant" (score of 0), "not at all" (score of 0), "a little" (score of 1), "a lot" (score of 2) and "very much" (score of 3). Question 7 is a "yes"/ "no" question where "yes" is scored as 3. DLQI total score is calculated by summing the scores of each question resulting in a range of 0 to 30. Interpretation can be done by cut points: 0 (score of 0–1), no effect;1 (score of 2–5), small effect; 2 (score of 6–10), moderate effect;3 (score 11–20), very large effect;4 (score 21–30), extremely large effect [R22-1982].

For adolescents, an adapted version of this tool is used, called the Children's Dermatology Life Quality Index (CDLQI). The CDLQI is a questionnaire designed to measure the impact of skin disease on the lives of children and young people. The CDLQI has been developed to resemble the DLQI, with responses ranging from not at all to very much. Data from the two cannot be combined, because the items and score meaning bands are different. CDLQI total score is calculated by summing the scores of each question resulting in a range of 0 to 30. Interpretation can be done by cut points: 0 (scores of 0–1), no effect;1 (scores of 2–6), small effect; 2 (scores of 7–12), moderate effect;3 (scores 13–18), very large effect;4 (scores 19–30), extremely large effect [R24-3537].

5D-Itch-scale
The 5-D itch scale is a multidimensional questionnaire designed to assess itching in clinical trials. The five domains of the questionnaire include: degree, duration, direction, disability, and distribution. The duration, degree and direction domains include one item each, and the disability domain had four items. All items of the first four domains were measured on a five-point Likert scale. The distribution domain includes 16 potential locations of itch, including 15 body part items and one point of contact with clothing or bandages. For the distribution domain, the number of affected body parts is tallied (potential sum 0–16) and the sum is sorted into five scoring bins: sum of 0–2 = score of 1, sum of 3– 5 = score of 2, sum of 6–10 = score of 3, sum of 11–13 = score of 4, and sum of 14–16 = score of 5. [R22-1980].

HADS
HADS is a widely used scale for assessing anxiety and depression in general hospital setting. It has 14 items in total (scoring from 0 to 3), which constitute the overall distress scale (HADS-S), and it groups 7 items each to anxiety subscale (HADS-A) and depression subscale (HADS-D), respectively. The categorisation of severity for both HADS-A and HADS-D subscales are mild (scores 8-11), moderate (scores 12-15), severe (scores 16-21, 21 is the highest score for each subscale). The highest score for HADS-S is 42, and a score over 9 is considered as distress [R22-2030].

Itchy-Qol
Itchy QoL is a pruritus-specific quality-of-life (QOL) instrument that consists of 22 pruritus-specific items (each score from 1 to 5; the sum ranges from 22 to 110) regarding symptoms, functions and emotions [R24-3478].

Patient Global Impression of Severity for Erythema
The Patient Global Impression of Severity for Erythema (PGIS-E) is a single item questionnaire that describes the severity of erythema over the past 24 h when considering skin area affected by NS. Participants will rate how his/her severity of erythema over the past 24 h can be described using a 5-point scale ranging from "None" to "Very Severe".

Patient Global Impression of Severity for Scaling
The Patient Global Impression of Severity for Scaling (PGIS-S) is a single item questionnaire that describes the severity of scaling over the past 24 h when considering skin area affected by NS. Participants will rate how his/her severity of scaling over the past 24 h can be described using a 5-point scale ranging from "None" to "Very Severe".

Patient Global Impression of Change for Netherton Syndrome Skin Symptoms
The Patient Global Impression of Change (PGIC) for Netherton syndrome skin symptoms is a single item questionnaire that describes the change (improvement or deterioration) in skin symptoms overall related to NS since the medication of this study has started. Participants will rate how his/her NS has changed since the beginning of the study using a 5-point scale ranging from "Much better" to "Much worse" with "no change" indicating neither better nor worse.

5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Treatment Emergent Adverse events
- Adverse events of special interest (AESIs)
- Serious adverse events (SAEs)
- Safety lab tests
- Intensity of adverse events will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (refer to ISF for details)
- Physical examination
- Vital signs (blood pressure, pulse rate, body temperature)
- 12-lead ECG
- Infusion reaction
- Immunogenicity (ADA)
- Injection site reactions

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flowchart It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.
Measurement of height and body weight will be performed at the time points specified in the Flowchart.
During remote visits, an abbreviated body system assessment will be conducted by the trained HCP instead of a physical exam. This abbreviated body system assessment will include evaluation of organ systems associated with AE(s) symptoms and is only observational and conversational with patient.

The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flowchart, prior to blood sampling. This includes temperature, respiratory rate, systolic and diastolic blood pressure, and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 min of rest. The results must be included in the source documents available at the site.

At dosing visits for [redacted]

At dosing visits, for [redacted]

The investigator should evaluate the clinical significance of the results. Clinically abnormal findings will be reported as baseline condition or AEs.

Monitoring for hypersensitivity reactions:
Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 1 hour after the i.v. drug administration at Visit 2 and Visit 6. Hypersensitivity reactions should be treated according to medical standards.
Pre-medications for further infusions might be considered and will be agreed on between investigator and BI clinical monitor.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3:1. For the sampling time points please see the Flowchart.
All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.
Patients do not have to be fasted for the blood sampling for the safety laboratory.

Instructions regarding sample collection, sample handling / processing and sample shipping are provided in the Laboratory Manual in the ISF.

According to the EU recommendation [R23-1267], the following applies for adolescent patients in EU countries:

It needs to be assured that the research related blood loss (including any waste) does not exceed 3% of the total blood volume over a period of four weeks, and does not exceed 1% at any single time. This recommendation leads to the allowable sample volumes, indicated in the Appendix 10.3. Total blood volume is approximately 80-90 mL/kg body weight.
With the minimum weight of 35 kg allowed in this study, the maximum blood volume allowed would be 28 mL – 31.5 mL (1%) at a single visit and 84 mL – 94.5 mL (3%) over 4 weeks.

For EU countries, the central laboratory has been set up specifically for adolescents to minimize the blood volume and to not exceed the limits considering a weight of 35 kg. In case additional blood collections are needed, e.g. for DILI, investigators have to take care to stay within the accepted range of blood volume, according to the EU recommendation. Step-wise collection of samples at separate days / visits may be considered, if needed.

For non-EU countries, central laboratory has been set up for adolescents to minimize the blood volumes in a similar way. Step-wise collection of samples at separate days / visits may be considered, if larger volumes of blood need to be collected (e.g. for DILI).

The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the ISF and eCRF system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

The central laboratory will transfer the results of the analysis to the sponsor or delegate.

Table 5.2.3:1 Safety laboratory tests (central lab Assessment)

Category	Test name
Infection testing	Hepatitis B Surface Antigen (qualitative) Hepatitis B core Antibody (qualitative) HBV-DNA PCR (quantitative) at screening and EoS Visit[1] Hepatitis C Antibodies (qualitative)* HIV-1, and HIV-2 Antibody (qualitative) QuantiFERON® (or if applicable, T-Spot®) TB[2,3,4]
Specific gamma-globulin quantification IgE	IgE[5]
Urine-Sediment (only if urine analysis abnormal)	Microscopic examination
Urine Pregnancy test[6]. At the drug administration visits, the test will be performed prior to the administration of study drug	Human Chorionic Gonadotropin in urine
Serum Pregnancy test[6] (only for female patients of childbearing potential)	Human Serum Chorionic Gonadotropin

Table 5.2.3:1 (cont'd) Safety laboratory tests (central lab Assessment)

Category	Test name
Haematology	Haematocrit Haemoglobin Red blood cell count (RBC) White blood cell count (WBC) Platelet count
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Manual differential WBC (if automatic differential WBC is abnormal)	Neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin time (Quick's test and International Normalized Ratio [INR]) Fibrinogen
Enzymes	Aspartate transaminase (AST/GOT) Alanine transaminase (ALT/GPT) Alkaline phosphatase (AP) Gamma-glutamyl transferase (GGT) Creatine kinase (CK) CK-MB, only if CK is elevated Lactate dehydrogenase (LDH) Serum tryptase[7] Amylase Lipase
Substrates	C-Reactive Protein (CRP) Serum albumin Creatinine Total bilirubin Direct bilirubin Total protein Total cholesterol Triglycerides Glucose BUN (blood urea nitrogen) Uric acid eGFR (estimated by CKD-EPI formula) (only at screening) Bilirubin Indirect (if total is elevated) Troponin (Reflex, in case of elevated CK) LDL-Cholesterol HDL-Cholesterol
Electrolytes	Sodium Potassium Chloride Calcium
Urinalysis (dipstick)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine erythrocytes Urine leukocytes Urine pH

[1] An HBV-DNA should be conducted at screening if Hepatitis B core Antibody is positive and Hepatitis B Surface Antigen is negative. If at screening, Hepatitis B core Antibody is positive and Hepatitis B Surface Antigen is negative, HBV-DNA should be repeated at the EOS visit.
[*] A positive Hep C Antibodies test result should be confirmed by PCR.

[2] There is a trial site option to perform a tuberculin skin test (i.e. PPD skin test) or any alternative test/procedure (as per local standards) to rule out TB if the retest QuantiFERON®-TB test result is indeterminate (see footnote 4 below for details).
[3] If the 1 st QuantiFERON® (or if applicable, T-Spot®) -TB test result is indeterminate, a retest should be performed. If the retest QuantiFERON-TB test result is indeterminate, a tuberculin skin test (i.e. PPD skin test) or any alternative test/procedure (as per local standards) to rule out TB should be performed at the site.
<For Japan> T-Spot® TB test may be performed at local labs instead of QuantiFERON®-TB test.
[4] In patients with a negative QuantiFERON®-TB or tuberculin skin test (i.e. PPD skin test) or alternative test/procedure (as per local standards), the test should be repeated on a yearly basis (see Flowchart) and at EoS.
<For Japan> T-Spot® TB test may be performed at local labs instead of QuantiFERON®-TB test
[5] IgE will be taken in case of systemic hypersensitivity including infusion reaction together with ADA (anti-drug antibodies) sample.
[6] Urine and serum pregnancy testing will be performed as indicated in the Flowchart. In case a remote visit is performed by the HCP, the HCP should be provided with urine pregnancy test kits. The kits may be supplied by the trial site or by the sponsor.
[7] Serum tryptase will be assessed only in the event of suspected hypersensitivity reaction.

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the Flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis.
Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.
Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and / or treated as medically appropriate.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

Local Tolerability

Local tolerability at the administration site of spesolimab or placebo will be assessed by the investigator during the trial drug administration visit and at time of AE assessment by questioning retrospectively since the last visit. Any observed local tolerability reaction, e.g. 'swelling', 'induration', 'heat', 'redness', pain', and other findings' should be reported as an adverse event.

All cases of malignancies, sepsis or other serious infections that are detected during the trial will be reported as SAEs.

5.2.6 Assessment of adverse events

Data and information necessary for the thorough assessment of AEs, SAEs, and AESIs will be reported to the sponsor via eCRF. This may include specific data and information not prospectively specified in this protocol.

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An 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 to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related or not.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- 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.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. 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 hospitalisation or development of dependency or abuse.

For Japan only: An event that possibly leads to disability will be handled as ‘deemed serious for any other reason’ and, therefore, reported as an SAE.

5.2.6.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as defined above.

The latest list of "Always Serious AEs" can be found in the eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.6.2, subsections "AE Collection" and "AE reporting to sponsor and timelines".

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relate 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 trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.1.2.

The following are considered as AESIs:

Potential Severe DILI
A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

- An elevation of AST (Aspartate Aminotransferase) and / or ALT (Alanine Aminotransferase) ≥3x ULN combined with an elevation of total bilirubin ≥2x ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
- ALT and / or AST elevations ≥10x ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary, in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Systemic hypersensitivity including infusion reaction and anaphylactic reaction
Any suspicion of severe infusion reaction systemic / hypersensitivity reaction and of any potential cases of anaphylaxis should be defined and assessed using the criteria discussed in the statement paper from Sampson HA (Appendix 10.1.12; R11-4890). (See Section 4.2.1 for "Other treatments and emergency procedures")

Severe infections (according to CTCAE version 5.0)

Opportunistic and mycobacterium tuberculosis infections
These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, post-transplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal),

cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression [R17-2617]

Peripheral Neuropathy
Any event suspected or diagnosed as peripheral neuropathy would be considered as an AESI. For the treatment interruption rules, please see Section 3.3.4.3 Discontinuation of the trial by sponsor.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of adverse events should be classified and recorded in the CRF according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [R18-1357] and judged based on the following:

Grade 1	Mild
Grade 2	Moderate
Grade 3	Severe
Grade 4	Life-threatening
Grade 5	Death

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the adverse event and the BI investigational compound, 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 that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the trial 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 aetiologies that could explain the event (e.g. pre-existing 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 reduced).

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 trial drug concerned).
- Continuation of the event despite the withdrawal of the medication, considering 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.
- There is an 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 trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.
Per default SAEs/AESIs should be reported via the eCRF in the EDC system. If the EDC system is not or no longer available (e.g. after data base lock), the BI paper SAE form should be used, please see Section 5.2.6.2.2.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial (= the End of Study (EoS) visit):
  all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial drug related SAEs and trial drug related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the AE or SAE eCRF pages, to the sponsor's unique entry point immediately (within 24 h of becoming aware of the event). The country specific process will be specified in the ISF. The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone in addition.

With receipt of any further information to these events, a follow-up report has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up

until they have resolved, have been assessed as “chronic” or “stable”, or no further information can be obtained.

Should the EDC system not be available for more than 24 h, reporting must occur via the BI paper SAE forms.

5.2.6.2.3 Pregnancy

Urine pregnancy testing should be done prior to trial drug administration. Trial drug should only be administered in case of a negative test result. In case of a positive urine pregnancy test, a serum pregnancy test will be done. Women who underwent tubal ligation are still considered of childbearing potential and pregnancy testing is necessary as well. The testing schedule is specified in the Flowchart.

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 h) 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 for Clinical Studies (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and / or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and / or AESI associated with the pregnancy an SAE form must be completed in addition.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Spesolimab concentrations will be reported descriptively. No PK parameters will be calculated. PK data will be incorporated into a larger pharmacometric analysis with other trials of the spesolimab project. Also, ADAs will be measured and their impact on PK will be assessed. The relationship between PK and selected efficacy endpoints, biomarkers and AEs may be assessed. PK and demographic data together with treatment assignments and dosing information may be made available to individuals outside of the trial team for the purpose of PK dataset generation in accordance with sponsor’s standard procedures.

Refer to the Flowchart for the time points of PK and ADA/Nab sample collection. Date and exact time of drug administration and PK and ADA/Nab sampling will be recorded on CRFs. On visits with trial medication dosing, PK and ADA/Nab samples should be collected prior to administration of trial drug.

5.3.2 Methods of sample collection

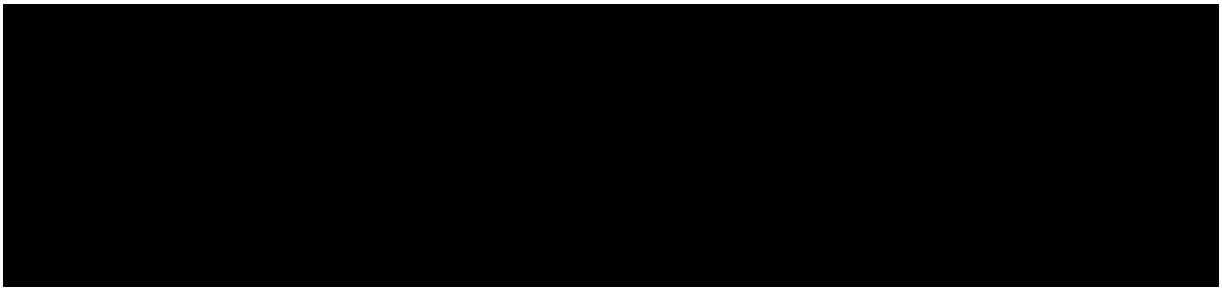
After completion of the trial the plasma/serum samples may be used for further methodological investigations, (e.g. for stability testing, for further investigations to characterize ADA response or to address Health Authority questions regarding the results/methodology). However, only data related to the analyte and / or anti-drug antibodies (if applicable) will be generated by these additional investigations. The samples will be discarded after completion of the additional investigations but not later than 5 years upon the final trial report has been signed.

5.3.2.1 Plasma sampling for PK analysis

For quantification of spesolimab plasma concentrations, blood will be taken from a forearmvein into a K2EDTA (ethylendiaminetetraacetic acid) anticoagulant blood-drawing tube at the time points listed in the Flowchart under plasma PK. Handling procedures can be found in the laboratory manual.

5.3.2.2 Sampling for ADA/Nab assessment

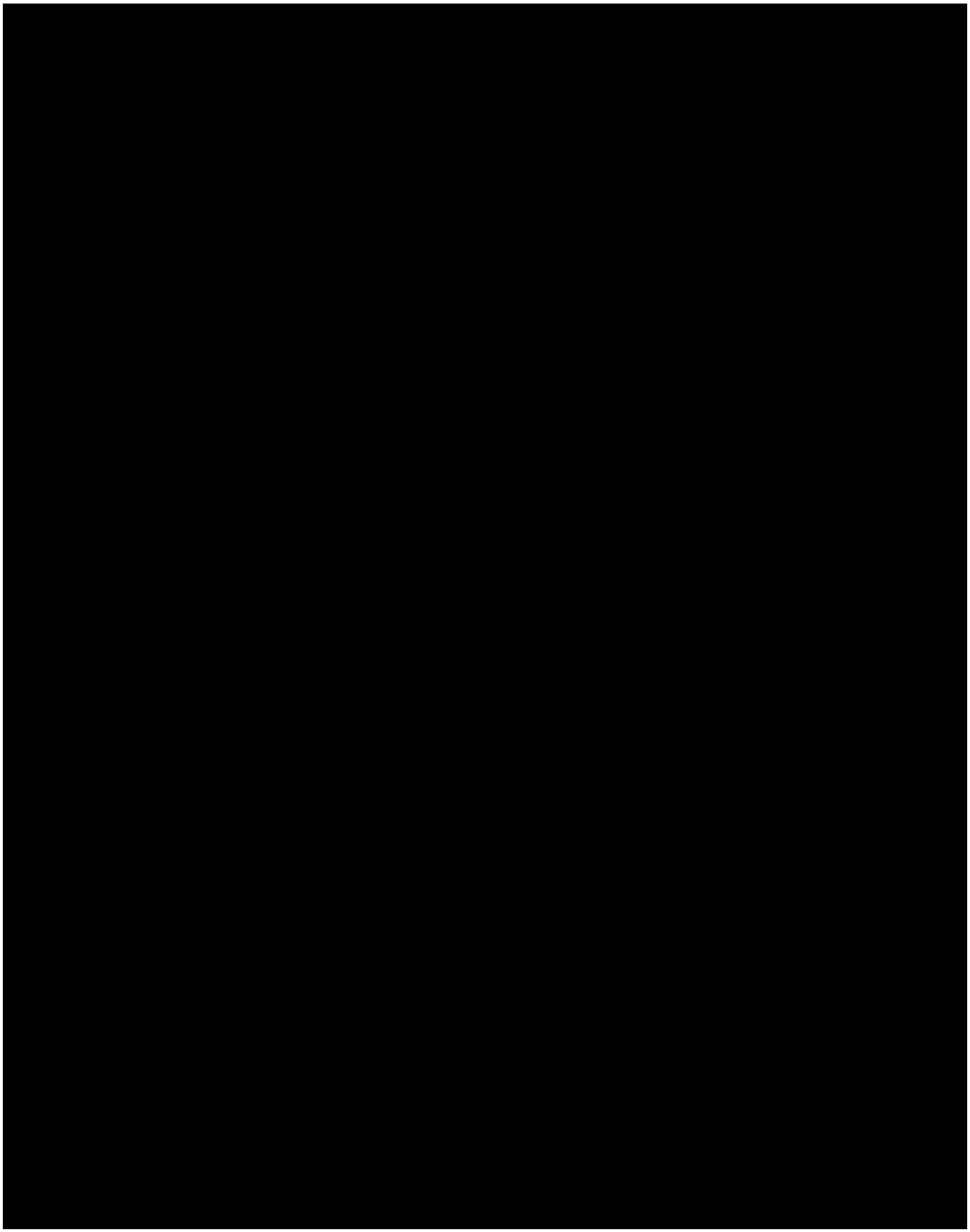
For ADA assessment, blood will be taken from a forearm vein into a K2EDTA anticoagulant blood-drawing tube at the time points listed in the Flowchart under ADA/Nab. For Nab assessment, blood will be taken from a forearm vein into a serum blood-drawing tube at the time points listed in the Flowchart under ADA/Nab. Handling procedures can be found in the laboratory manual.



5.3.4 Pharmacokinetic - pharmacodynamic relationship

No formal analysis of pharmacokinetic/pharmacodynamic relationships is planned. If the data suggest a pharmacokinetic/pharmacodynamic relationship of special parameters, e.g. an exploratory analysis may be performed.
Correlation between drug concentration and response may be made if adequate data are available. In addition, exploratory correlations may also be made between drug concentration and AEs.
Data may also be used to develop pharmacokinetic/pharmacodynamic models using nonlinear mixed effect modeling techniques, if feasible. For this purpose, data may also be combined with data from other trials. Modeling activities will be planned and documented separately according to internal and external guidelines and Standard Operating Procedures (SOP).

This trial is also intended to contribute to modelling of the dose-exposure relationship in children from 12 years to less than 18 years of age (and adults) with Netherton syndrome.



5.5.1 Methods and timing of sample collection

Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. For sampling timepoints see Flowchart.

5.6 OTHER ASSESSMENTS

Photography of skin will be performed in all patients. Front and back trunk, legs and arms, as well as target lesions photographs will be taken preferably at the time points specified in the Flowchart. Instrcutions for taking the photos will be provided in the ISF. Patients must be unrecognizable on the photos (refer to the procedure in the ISF).

5.7 APPROPRIATENESS OF MEASUREMENTS

The safety assessments are standard, are accepted for evaluation of safety and tolerability of both subcutaneous and intravenously administered drug and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure. The biomarkers and pharmacogenomic parameters outlined in Section 5.4 are of exploratory nature only.

Information about race should be obtained from study participants as allowed by local regulations. This is because the prevalence and characteristics of NS may differ between patients of different racial origin. It will thus be worthwhile to assess if patients of different race will respond differently to the study treatment.

6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent of the patient, sponsor and investigator may agree on alternative, back-up or rescue methodology which may include but will not be limited to virtual patient visits and assessments, home healthcare nurse visits, and direct-to-patient shipments of trial treatment. The implementation of these measures will depend on patient's consent, operational feasibility, local law and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.1 VISIT SCHEDULE

All patients should adhere to the visit schedule specified in the Flowchart. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule calculated from randomisation visit (Visit 2).
[redacted] will be instructed to not bath, shower, or apply any topical product to the area that will be tested, 24 h before the visit. Vigorous activity will also be minimized for several hours prior to the visit.

In addition to the scheduled assessments, unscheduled assessments for safety reasons may be performed at any time according to the clinical need.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed as specified in the Flowchart. All efforts should be made to perform the most critical visits e.g. randomisation at Visit 2, primary endpoint at Week 16 and end of treatment at Week [redacted]. These and other visits requiring i.v. administration should always be performed at the investigator site facility whenever possible. The visits with reduced number of assessments and no routine lab sampling, e.g. every second visit during the extended treatment period could be performed remotely or using hybrid approach (assessments performed at home by the specialized vendor/HCP, if applicable) or performed in the investigator site facility, if this is preferable for the patient and the investigational site. Note: [redacted]. drug administration should be performed by the HCP. Patient self-administration is not allowed.

The patients' questionnaires are to be completed by the patient him/herself in quiet area/room without any interpretation by other people, and if possible, before any interaction with the investigator or other member of the trial team. For adolescent patients or if the patient is too sick to complete the questionnaires by him/herself or is illiterate, but is able to reply verbally, a parent/legal guardian or a member of the trial team should read the instructions, questions, and response options aloud to the patient and collect the patient's verbal response in as neutral and unbiased a manner as possible. If this is not possible either, the questionnaires are not to be completed. There is no order of completion.

Whenever possible, the evaluation of efficacy assessments (IASI, IGA, IASI-E, IASI-S, NASA, ISS) are to be conducted by the same investigator throughout the trial.

6.2.1 Screening and run-in period(s)

Screening Period
All patients will need to sign the informed consent form in accordance with the GCP and the local legislation prior to performing any trial related procedures. Only patients with confirmation of NS diagnosis are eligible. The diagnosis of NS is to be done and confirmed by the clinical investigator (either genetic test available in the past or confirmation during the screening).

Demographics:
During the screening visit, demographics information will be collected. This includes:

- Age on the day of informed consent (in years)
- Sex (male, female in order to describe the patient`s sex at birth),
- Ethnicity and race (if allowed by local regulations) will be collected and reported in the eCRF

Screening visit (visit1) is to be performed within 84 days before Visit 2. Screening assessments may be repeated as long as they fall within the Screening visit window. If more than one screening assessment is available, the latest assessment prior to the start of treatment must be used to assess eligibility.

Baseline Conditions
Chronic diseases, current observable conditions, any new clinically relevant findings discovered from the physical examination, ECG, safety labs, and any condition requiring therapy will be reported on the baseline condition eCRF page.
Infections testing will include tuberculosis, hepatitis B, hepatitis C, and HIV assessments (see Table 5.2.3:1)

Medical History:
Medical history of NS, including previous and concomitant treatment will be reported in the eCRF.

Mutation status:
Information on the genetic testing for *SPINK5* causative mutations to confirm the diagnosis of NS will be collected in patient's historical data and reported in the eCRF.

Re screening:
If a patient results in a screen failure, the patient must be registered as a screen failure in IRT system. However, re-screening of patient who has previously failed screening will be permitted. In this situation patient will be allocated a new patient number which will be linked to the previous patient number in the IRT system. Details of IRT procedures can be found in the IRT manual located in the ISF.

Is a patient enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment or misdiagnosed), the sponsor should be contacted immediately.

6.2.2 Treatment period(s)

The investigator must perform a final assessment of eligibility when the results of all screening assessments are available. If the patient does not meet the eligibility criteria, the patient must be recorded as a screen failure.

The eligible patient will be randomised at Visit 2 (Day1) using IRT. Subsequent visits during the treatment period are performed as described in the Flowchart.
Patients may decide to continue receiving the Open Label Extended trial treatment until Week 156.

Physical examination, vital signs Laboratory tests, ECG, local tolerability See Section 5.2.

Blood sampling should be done prior to trial drug administration. Fasting is not required for blood sampling.

Pregnancy test will be conducted for women of childbearing potential only. Serum pregnancy test will be performed at screening and urine pregnancy tests will be performed at all other visits indicated in the Flowchart. Urine pregnancy test should be done prior to study drug administration and trial drug should only be administered in case of a negative test result. In case of a positive urine pregnancy test, a serum pregnancy test will be done (via central lab) and study drug administration will be postponed until negative result of serum pregnancy test is available.

Concomitant medication review
Data concerning concomitant medications will be collected throughout the trial as specified in the Flowchart.

For more details on PK, ADA and Nab, and biomarkers samples collection please refer to Sections 5.3 and 5.4.

Unscheduled visits
The unscheduled visit may include additional collection of blood samples for safety reasons. The unscheduled visit may also include additional assessments deemed necessary by the investigator such as laboratory samples, ECGs, or other procedures which were missed at a previous visit. All unscheduled visits should be described (including the reason for the visit) and documented in the medical/source record, and in the eCRF.

6.2.3 Follow-up period and trial completion

For patients completing the full treatment period up to Week [redacted], a Follow-up Visit should be performed [redacted] weeks after the last administration of trial medication (EoS). Termination of trial medication (EoT) and trial completion (EoS) must be recorded on the corresponding eCRF.

The information collected at the EoS visit should include all follow up of AEs ongoing at EoT and new AEs that occurred after EoT.
Abnormal assessments or lab values judged clinically relevant by the investigator will be monitored until they returned to a medically acceptable level.

Early treatment discontinuation
Patients who discontinue the trial treatment early (prior to Week [redacted]). These patients should be registered as withdrawn from randomized treatment in IRT and the eCRF accordingly. Timepoint of early EoT will be considered the visit when the last dose of IMP was administered. In case of early discontinuation from trial treatment, every effort should be made to keep the patient in the trial and complete all of the remaining visits up to Week [redacted] (without IMP administration in that case). At a minimum, patients should come to an End-of-study Visit (EoS), [redacted] weeks after the last dose to cover full REP.

Early trial discontinuation
The patients who have not reached the End-of-trial Visit (EoS) within the specified window per protocol (e.g. due to withdrawal of consent, administrative reason, lost to follow-up, death etc.).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The study design is described in Section 3.1 and trial objectives are described in Section 2.

7.1 NULL AND ALTERNATIVE HYPOTHESES

Statistical hypothese to be tested for the primary endpoint are:

H_{01}: There is no difference regarding the proportion of the primary endpoint (IASI response, defined as a decrease of at least 50% absolute change in IASI score from baseline at Week 16) between spesolimab versus placebo against H11: There is a difference regarding the proportion of the primary endpoint (IASI response, defined as a decrease of at least 50% absolute change in IASI score from baseline at Week 16) between spesolimab versus placebo. The trial is considered positive, if the null hypothesis of the primary endpoint can be rejected and the result is more favorable for spesolimab versus placebo (proportion in spesolimab group ≥ proportion in placebo group).

Further hypothesis will be tested on the key secondary endpoint in a hierarchical manner if the null hypothesis of the primary endpoint H_{01} has been previously rejected.

Statistical hypothese to be tested for the key secondary endpoint are:

H_{02}: There is no difference regarding the proportion of the key secondary endpoint (IGA response, defined as a decrease of at least 1-grade absolute change in IGA score from baseline at Week 16) between spesolimab versus placebo against H_{12}: There is a difference regarding the proportion of the key secondary endpoint (IGA response, defined as a decrease of at least 1-grade absolute change in IGA score from baseline at Week 16) between spesolimab versus placebo.

No adjustment of the two-sided alpha level of 0.05 is necessary.

7.2 PLANNED ANALYSES

7.2.1 General considerations

The primary analysis of this trial is planned to be performed once all randomized patients have completed the 16 weeks or early discontinued from the trial, to support an early submission; a database lock for the primary analysis will then be performed.

Final analysis is planned to be performed at the end of the trial once all patients have completed the trial (including any follow-up period if applicable).

Details of treatment unblinding for the primary analysis and final analysis are described in

Section 4.1.5. Details of the analysis to be performed will be described in the TSAP.

In general, baseline refers to the last non-missing value prior to first treatment in this study.

There will be two main patient sets in this trial for analyses:

Full analyses set (FAS)
This patient set includes all patients who were randomised and received at least one study treatment in this trial.

Per-Protocol Set (PPS)
This patient set includes all patients in FAS who adhered to the CTP without any important protocol deviations (iPDs) which lead to exclusion from the PPS. This set will be used for sensitivity analysis on the primary endpoint and key secondary endpoint.

Further analysis sets will be defined in the trial statistical plan (TSAP) if necessary.

Important deviations of the protocol will include deviations of the key inclusion and exclusion criteria, concomitant use of restricted medications, and any other deviations of the protocol deemed important by the study team. All decisions concerning important protocol deviations will be made prior to unblinding of the database for the final trial analysis.

Standard statistical parameters (number of non-missing values, mean, standard deviation (SD), median, quartiles, minimum and maximum) or frequency tables (including patient frequencies and percentages) will be calculated where appropriate.

7.2.2 Handling of Intercurrent Events

The expected intercurrent events of interest in this trial are:
- Restricted medications and treatments for NS (see Section 4.2.1)
- Treatment discontinuation due to AE/lack of efficacy/other reasons

The strategy for handling intercurrent events is as follows:

Composite strategy: This is the effect of spesolimab, where intercurrent events of use of restricted medications and treatments for NS will be considered as treatment failure.
Treatment policy strategy: treatment discontinuation will be handled by a treatment policy approach, i.e. the value of the variable regardless of the occurrence of the intercurrent event will be used.

Each analysis will reference the strategy for handling intercurrent events that it will be estimating. The estimand for each main analysis in this protocol is the combination of the relevant detailed clinical objective from Section 2.1 and this strategy.

7.2.3 Primary objective analyses

The analysis for the primary endpoint will be on the FAS, including calculating the proportion of patients achieving IASI response at Week 16 (defined as a decrease of at least 50% absolute change in IASI score from baseline at Week 16). For the estimand concept on

the primary binary endpoint, composite strategy will be applied that occurrence of use of restricted medications and treatments for NS prior to Week 16 will be considered to represent a non-response at the Week 16 timepoint.

Comparisons between treatment groups regarding the binary endpoint variable, the proportions of IASI response at Week 16 will be performed using the exact unconditional Suissa-Shuster Z-pooled test. The risk difference together with 95% confidence intervals will be used to quantify the treatment, comparing spesolimab to placebo.

The patients will be analysed according to the stratum to which they belong (regardless of any mis-assignment to treatment based on identification of the wrong stratum), as such an error occurs before randomization and is therefore consistent with regulatory guidance.

7.2.3.1 Sensitivity Analyses

Sensitivity analyses of the primary endpoint will include:

- A sensitivity analysis utilizing the PPS;
- A sensitivity analysis which utilizes alternative methods for the handling of missing data as described in Section 7.3.
- A sensitivity analysis to adjust for covariates of age group (adult vs. adolescent) and baseline IASI group (classified into 2 equally sized groups by median) using logistic regression model.

Further sensitivity analyses, if any, will be defined in the TSAP.

7.2.3.2 Subgroup Analyses

Subgroup analyses are planned for primary endpoint regarding age (adult vs. adolesent), sex (female/male). Further subgroup analyses, if any, will be defined in the TSAP.

7.2.3.3 Supplementary Analyses

Not applicable.

7.2.4 Secondary objective analyses

For key secondary endpoint, the analyses will be performed on the FAS in the same manner as described for the analysis of the primary endpoint in Section 7.2.3.

For binary secondary endpoints, the analyses will be performed on the FAS in the same manner as described for the analysis of the primary endpoint in Section 7.2.3.

Analyses for the continuous secondary endpoints will be analysed by a restricted maximum likelihood (REML) estimation-based approach using a mixed-effect model with repeated measurements (MMRM) analysis, including calculating the adjusted means and 95% CIs (if applicable) based on FAS. The analysis will include the fixed, categorical effects of treatment at each visit, age group and the fixed continuous effects of baseline at each visit.

Analysis of treatment emergent AEs will be described in Section 7.2.6.

7.2.6 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, defined as 16 weeks after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

The exposure adjusted incidence rate (per 100 patient-years) of a selected treatment emergent adverse event is defined as the number of patients experiencing the adverse event per treatment group during time at risk divided by the total time of patients at risk in that treatment group to contribute the event to the analysis multiplied by 100 (per 100 patient-years), where:

Time at risk [patient-years] = (date of onset of TEAE – study drug start date + 1) /365.25

If, for a patient, the selected treatment emergent adverse event didn't occur then the time at risk will be censored at min (date of death, last contact date per EoS page, drug stop date + 112 days). For each selected treatment emergent AE, the exposure adjusted incidence rate will be calculated as:

Incidence rate [1/100 patient-years (pt-yrs)] = 100 * number of patients with TEAE / Total TEAE-specific time at risk [patient-years].

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the

reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared with findings before start of treatment.

7.2.7 Other Analyses

Not applicable

7.2.8 Interim Analyses

A Data Monitoring Committee (DMC) will be in place with tasks as described in Section 8.7.

The primary analysis of this trial is planned to be performed once all randomized patients have completed the 16 weeks or early discontinued from the trial, to support an early submission; a database lock for the primary analysis will then be performed. Further interim analyses may be conducted during the open label treatment period to support, for example, regulatory interactions and/or regulatory filing. Final analysis is planned to be performed at the end of the trial once all patients have completed the trial (including any follow-up period if applicable).

7.3 HANDLING OF MISSING DATA

For handling missing data on the primary, key secondary and secondary binary efficacy endpoints, a Non-Response Imputation (NRI) will be applied as the primary imputation approach, that is, imputing as a failure to achieve a response, however:

- If there are available data at the visits both before and after the visit with a missing outcome, then impute as a success only if both the preceding and the following observations also represent a success.
- Otherwise, impute as a failure to achieve a response (i.e. no response imputation [NRI]).

NRI is a conservative imputation scheme because it assumes that withdrawal (or missing data due to any other reason) is related to treatment failure. A Best-Response Imputation (BRI) will also be considered, i.e. to impute all missing values based on the best response observed at visits prior to occurrence of intercurrent events/missing data. If there is no non-missing data available, then the missing value will be imputed as a failure.

Missing data will not be imputed for secondary continuous endpoints. The mixed effect model will handle missing data based on a likelihood method under the ‘missing at random assumption’.

For further endpoints, rules for handling of missing data will be specified in the TSAP if necessary. With respect to safety evaluations, it is not planned to impute missing values.

7.4 RANDOMISATION

The trial will be performed as a double-blind design for the randomized treatment period with respect to two blinded treatment groups. Randomisation to the treatment groups of Spesolimab and placebo will be 2:1 and will be stratified by the following factor:

- Adults versus adolecents
- Japan versus China versus other regions

Stratification for Japan versus China versus other regions will be done in order to assure that sufficient patients per treatment group are recruited specifically to support individual country submission in Japan and China; these strata will be treated as operational strata and will not be included into the analyses of efficacy endpoints.

The adolescent patients will be randomised in a 2:1 ratio to two treatment groups (spesolimab and placebo) regardless of blocking factor of Japan versus China versus other regions.

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

The sample size is determined as 39 patients based on feasibility and practical considerations due to the rareness of this disease.

As there is no experience in this ultra-rare disease, the main assumptions for the primary endpoint and key secondary endpoint are, that there is a treatment difference (delta) of 50% between placebo and spesolimab in both endpoints. In addition, the correlation of the two endpoints are assumed to range from 0.3 to 0.7. The power estimates below are derived using R version 4.0.2 with 2-sided type I error of 0.05 when considering 39 patients.

Table 7.5: 1 Power to achieve statistical significance for primary endpoint and key secondary endpoint on spesolimab versus placebo under various scenarios for N=39 (2:1)

Sample size: spesolimab vs. placebo	Placebo/Spesolimab response rate in primary endpoint and key secondary endpoint	Correlation between primary and key secondary endpoint	Power to achieve primary endpoint	Power to achieve primary and key secondary endpoint
26:13	15%, 65%	0.3	89.0%	80.6%
		0.5		81.8%
		0.7		83.3%
26:13	20%, 70%	0.3	88.0%	78.9%
		0.5		80.2%
		0.7		81.9%
26:13	30%, 80%	0.3	88.5%	79.7%
		0.5		80.9%
		0.7		82.6%

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as “protocol deviation”.

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

The investigator will inform the sponsor or delegate immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (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 trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent, and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

For adolescents, the patient will be provided with an age-adapted information sheet wherehis/her assent will be collected according to the regulatory and legal requirements of the participating country. The refusal of an adolescent to participate must be acceptedindependently of the consent of his/her parent(s)/legal guardian.

For patients who may legally consent during the trial participation (turning to the age of legal consent in the participating country), written informed consent must be obtained to confirm the patient's willingness to pursue trial participation. The patient will continue with the assessments for which he/she consented at the beginning of the trial (as an adolescent).

The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient (or patient's parents (s) /legal guardian) must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent/assent of the patient's (or patient's parent(s)/legal guardian) own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent/assent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial patient protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and

ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit / inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)

- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion / exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator / institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents / data, including progress notes, copies of laboratory and medical test results, which must always be available for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor or delegate will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

SAE/AESI are processed in the global Safety Database and assessed for the company causal relationship as well as the expectedness of the event according to the reference safety information. Individual Case Safety Reports (ICSR) are subsequently reported according to local Regulations.

Reporting to the EMA will be done via E2B transmission of ICSRs to the Eudravigilance CT Module**.**

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.

To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a patient identification number instead of the patient's name. The code is only available at the site and must not be forwarded to the sponsor. In case patient's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the patient will be redacted by the site prior to forwarding.

Access to the patient files and clinical data is strictly limited: personalised 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 at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs / IECs and patients will be informed as appropriate.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage have to be in accordance with the separate biobanking informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay / equipment validation depending on the intended use of the biomarker data
- Samples and / or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").

The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A [redacted] will be established. Members of the [redacted] are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician.

The [redacted] will evaluate safety and efficacy data. The [redacted] will receive urgent significant safety concerns, for immediate evaluation. While [redacted] members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular [redacted] meetings will be held at specified intervals. The [redacted] will recommend continuation, modification or termination of the trial as detailed in the [redacted] charter. [redacted] recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs) / Health Authorities (HAs), IrBs / ECs, and to investigators as requested by local law. The tasks and responsibilities of the [redacted] are specified in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their *curricula vitae*) will be filed in the ISF.
The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

In the participating countries the trial will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) based on a contract. The CRO will perform project management, clinical field monitoring, medical monitoring, and reporting.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service, vendor for photo documentation, and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

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10. APPENDICES

10.1 SCALES

10.1.1 IASI- Ichtyosis Area Severity Index

a) Determine mean **INTENSITY** of erythema or scaling in a body region (A1 = head and neck; A2 = upper limbs; A3 = trunk; A4 = lower limbs) through either selecting a representative area of ichthyosis or averaging the intensity within a body region. The intensity of redness/ erythema and scaling of the ichthyosis is assessed as none (0), mild (1), moderate (2), severe (3) or very severe (4).

0	None
1	Mild
2	Moderate
3	Severe
4	Very Severe

b) Determine what percentage of **AREA** within a body region is affected by ichthyosis. In each region, the area is expressed as nil (0), 1-9% (1), 13-29% (2), 30-49% (3), 50-69% (4), 70-89% (5) or 90-100% (6). Many with ichthyosis have generalized involvement with 100% of area affected (e.g., score of 6), but it is possible that areas may be spared (e.g., palms or soles). The mean intensity score (A1-A4 for each site) is multiplied by the number correlating with the percentage within a region with ichthyosis (B1-4).

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

c) Determine **TOTAL EXTENT** by using a multiplier that takes into account the percentage of the total body surface area represented by each body region (C1 = 0.1 for head and neck; C2 = 0.2 for upper limbs; C3 = 0.3 for trunk; C4 = 0.4 for lower limbs).

The **Final score** for each intensity measure (IASI-E or IASI-S) is thus the composite of:

IASI-E: Ichthyosis Area Severity Index – **Erythema**

(A1 erythema x B1 x C1) + (A2 erythema x B2 x C2) + (A3 erythema x B3 x C3) + (A4 erythema x B4 x C4)

IASI-S: Ichthyosis Area Severity Index – **Scaling**

(A1 scaling x B1 x C1) + (A2 scaling x B2 x C2) + (A3 scaling x B3 x C3) + (A4 scaling x B4 x C4)

The composite score **IASI (max potential 48) = IASI-E (max potential = 24) + IASI-S (max potential) = 24**

The **IASI (Ichthyosis Area and Severity Index)** is a modification of the global CISI score that incorporates extent through the techniques used for assessment in the EASI and PASI scores for eczema (AD) and psoriasis, respectively. IASI takes only a few minutes to assess, and the totals are calculated automatically in spreadsheets.

BODY REGION	Erythema (A)	X	Region score (B)	X	Multiplier (C)	Score per body region
Head/Neck (1)		X		X	0.1	
Trunk (2)		X		X	0.3	
Upper extremities (3)		X		X	0.2	
Lower extremities (4)		X		X	0.4	
TOTAL (Sum Score per Region): IASI-E =						

BODY REGION	Scaling (A)	X	Region score (B)	X	Multiplier (C)	Score per body region
Head/Neck (1)		X		X	0.1	
Trunk (2)		X		X	0.3	
Upper extremities (3)		X		X	0.2	
Lower extremities (4)		X		X	0.4	
TOTAL (Sum Score per Region): IASI-S =						

IASI = IASI-E + IASI-S

10.1.2 IGA

Score	Morphological Descriptors
Clear (0)	Normal skin
Almost clear (1)	Light pink erythema and/or minimal scaling
Mild (2)	Pink erythema and/or localized scaling
Moderate (3)	Red erythema and/or generalized fine scaling
Severe (4)	Deep red erythema and/or generalized coarse scaling

10.1.3 NASA- Netherton Area Severity Assessment Score

- Netherton-specific modification of the EASI score that substitutes scaling for excoriation
- NASA score can theoretically vary from 0 to 72

Score	Area of Involvement, %
0	No eruption
1	<10
2	10-29
3	30-49
4	50-69
5	70-89
6	90-100

The calculation of NASA score for children 8 years or older is performed as follows (where the area is defined on the 7-point ordinal scale):

Location	
Head/Neck	(E+I+L+S)×Area×0.1
Trunk	(E+I+L+S)×Area×0.3
Upper limbs	(E+I+L+S)×Area×0.2
Lower limbs	(E+I+L+S)×Area×0.4
NASA score equals:	Sum of the above 4 body areas

eTable. Scoring Signs of Netherton Area Severity Assessment

Sign	Score
Erythema (E)	0=None 1=Mild; faintly detectable erythema: very light pinpoint dots 2=Moderate; full red, clearly distinguishable 3=Severe; deep/dark red
Infiltration/papulation (I)	0=None 1=Mild; barely perceptible elevation 2=Moderate; clearly perceptible elevation but not extensive 3=Severe; marked and extensive elevation
Lichenification (L)	0=None 1=Mild; slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated 2=Moderate; definite thickening of the skin with skin markings exaggerated so that they form a visible criss-cross pattern 3=Severe; thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern
Scaling (S)	0=None 1=Mild 2=Moderate 3=Severe

10.1.4 NRS Pain

Please rate the severity of your Netherton Syndrome (NS) pain in the past 24 hours at its worst?

Please mark the number on the 0 to 10 scale below.

0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

10.1.5 NRS Itch

Please rate the severity of your Netherton Syndrome (NS) itch in the past 24 hours at its worst?

Please mark the number on the 0 to 10 scale below.

0	1	2	3	4	5	6	7	8	9	10
No itch										Worst possible itch

10.1.6 Dermatology Life Quality Index (DLQI) / Children's Dermatology Life Quality Index (CDLQI)

DERMATOLOGY LIFE QUALITY INDEX

Hospital No: Date: DLQI
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ■ one box for each question.

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	 Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐

Please check you have answered EVERY question. Thank you.

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CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

Hospital No
Name: Diagnosis: CDLQI
Age: SCORE:
Address: Date:

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.

1.	Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
3.	Over the last week, how much has your skin affected your **friendships**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
7.	Last week, was it **school time?** ⇒ **If school time**: Over the last week, how much did your skin problem affect your **school work**?	Prevented school Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐ ☐
	OR		
	was it **holiday time?** ⇒ **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐

Please check that you have answered EVERY question. Thank you.

10.1.7 5D-Itch-scale

5-D Pruritus Scale

1. **Duration**: During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree**: Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction**: Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability**: Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

10.1.8 Hospital Anxiety and Depression Scale (HADS)

Name: _____ Date: _____

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edg e of the questionnaire.

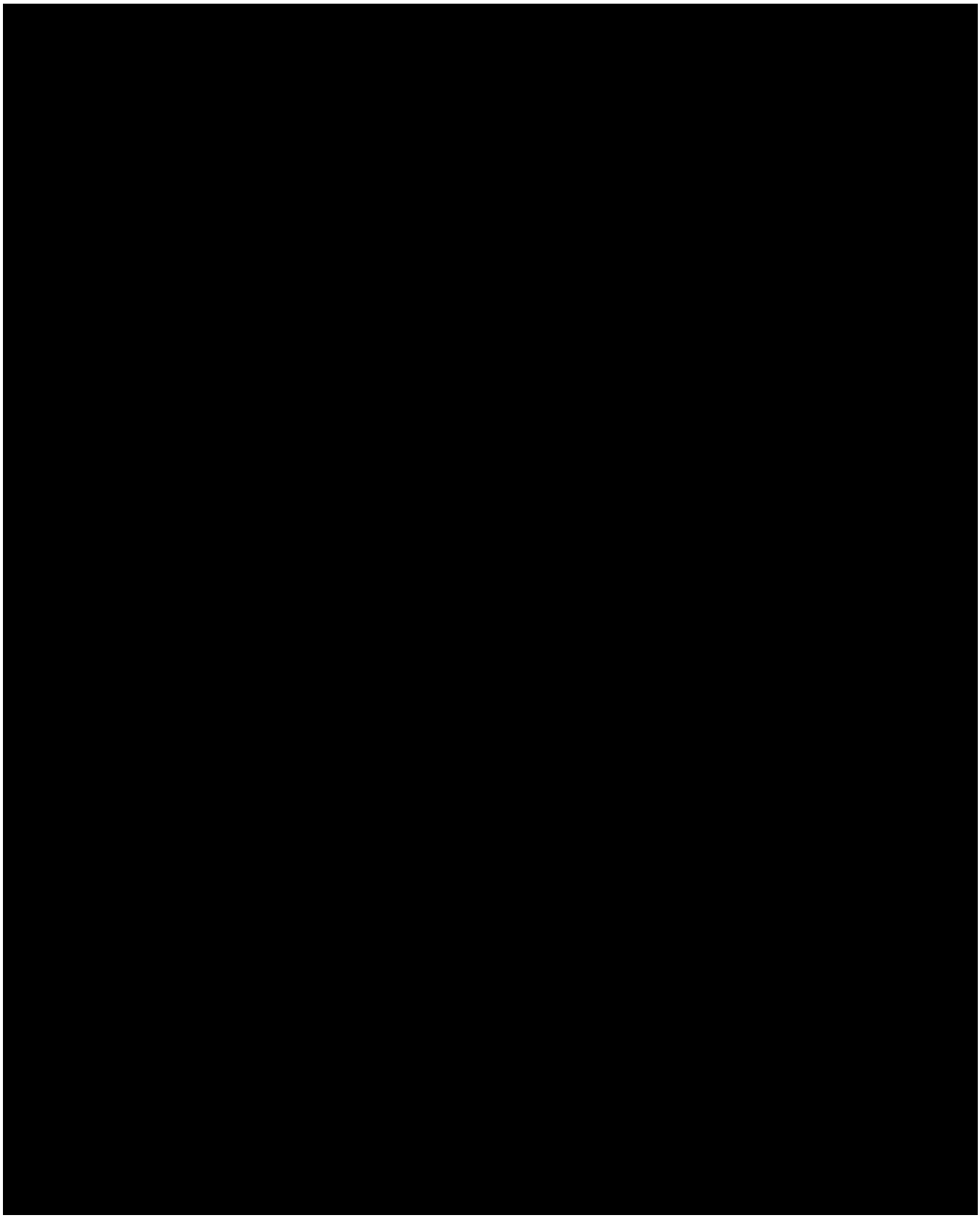
Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

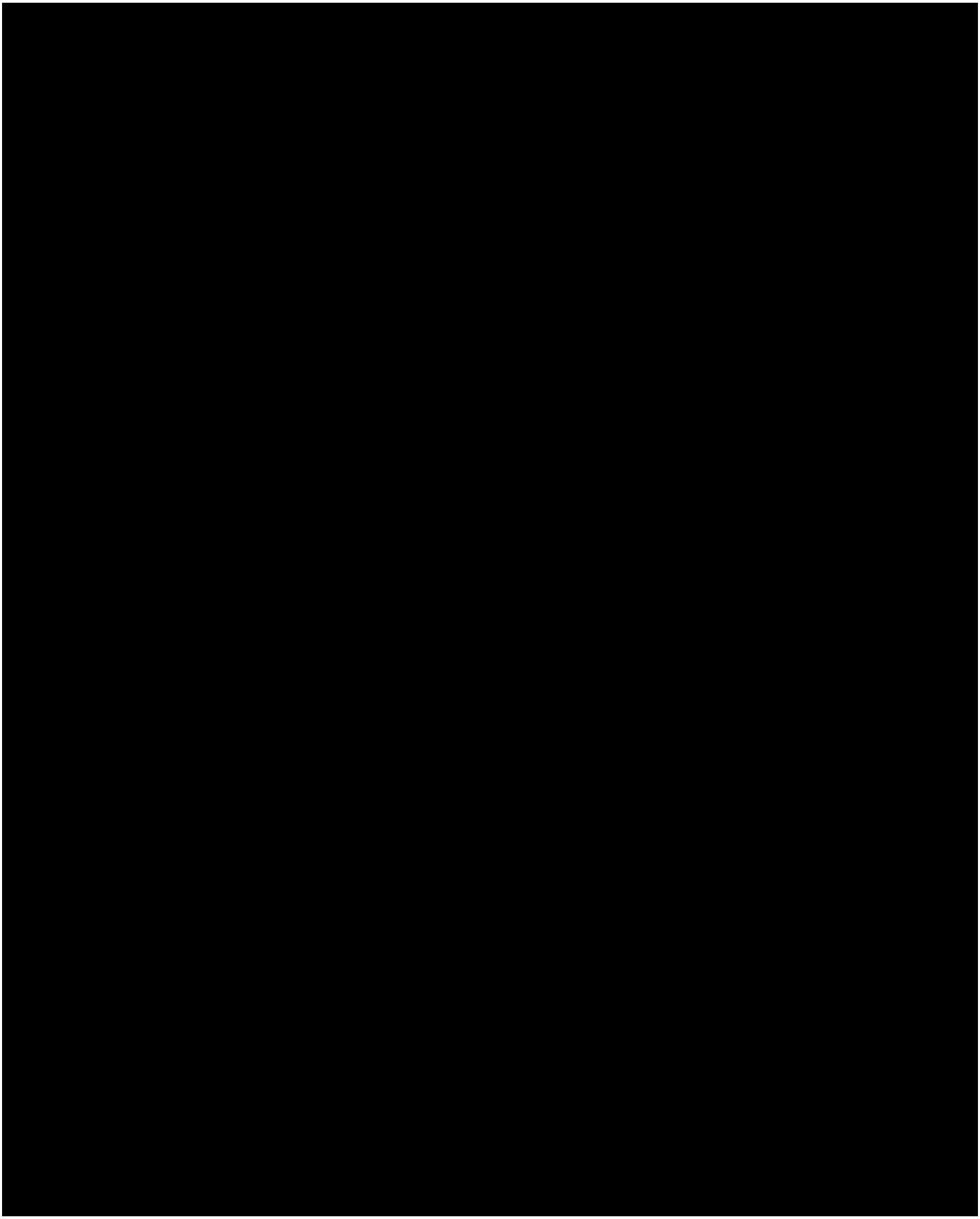
FOLD HERE

A	D			A	D
		I feel tense or "wound up"	**I feel as if I am slowed down**		
3		Most of the time	Nearly all the time		3
2		A lot of the time	Very often		2
1		From time to time, occasionally	Sometimes		1
0		Not at all	Not at all		0
		I still enjoy the things I used to enjoy	**I get a sort of frightened feeling like "butterflies" in the stomach**		
	0	Definitely as much			
	1	Not quite so much	Not at all	0	
	2	Only a little	Occasionally	1	
	3	Hardly at all	Quite often	2	
			Very often	3	
		I get a sort of frightened feeling as if something awful is about to happen	**I have lost interest in my appearance**		
3		Very definitely and quite badly	Definitely		3
2		Yes, but not too badly	I don't take as much care as I should		2
1		A little, but it doesn't worry me	I may not take quite as much care		1
0		Not at all	I take just as much care as ever		0
		I can laugh and see the funny side of things	**I feel restless as if I have to be on the move**		
	0	As much as I always could	Very much indeed	3	
	1	Not quite so much now	Quite a lot	2	
	2	Definitely not so much now	Not very much	1	
	3	Not at all	Not at all	0	
		Worrying thoughts go through my mind	**I look forward with enjoyment to things**		
3		A great deal of the time	As much as I ever did		0
2		A lot of the time	Rather less than I used to		1
1		Not too often	Definitely less than I used to		2
0		Very little	Hardly at all		3
		I feel cheerful	**I get sudden feelings of panic**		
	3	Never	Very often indeed	3	
	2	Not often	Quite often	2	
	1	Sometimes	Not very often	1	
	0	Most of the time	Not at all	0	
		I can sit at ease and feel relaxed	**I can enjoy a good book or radio or television programme**		
0		Definitely			
1		Usually	Often		0
2		Not often	Sometimes		1
3		Not at all	Not often		2
			Very seldom		3

Now check that you have answered all the questions

	A	D
TOTAL		





[redacted]

10.1.12 Diagnosis of Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg +[2 x age] from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years

10.1.13 Itchy QOL

ItchyQoL™

ITCHING QUALITY OF LIFE SURVEY

The following questions concern your feelings about your itchy skin condition. Please check the answer that best describes your experience.	**How often during the past week do these statements apply to you?**				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
1. My itchy skin condition bleeds.	☐1	☐2	☐3	☐4	☐5
2. My skin hurts because of my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
3. My itchy skin condition burns or stings.	☐1	☐2	☐3	☐4	☐5
4. I get scars from my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
5. I need to scratch my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
6. Temperature or seasonal changes aggravate my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
7. I spend a lot of money treating my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
8. My itchy skin condition makes it hard to work or do what I enjoy.	☐1	☐2	☐3	☐4	☐5
9. My itchy skin condition affects my interaction with others. (For example: family, friends, close relationships, etc.)	☐1	☐2	☐3	☐4	☐5

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The following questions concern your feelings about your itchy skin condition. Please check the answer that best describes your experience.	**How often during the past week do these statements apply to you?**				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
10. My itchy skin condition affects how well I sleep.	☐1	☐2	☐3	☐4	☐5
11. My itchy skin condition often makes it difficult to concentrate.	☐1	☐2	☐3	☐4	☐5
12. My itchy skin condition limits the types of clothes I can wear.	☐1	☐2	☐3	☐4	☐5
13. My itchy skin condition forces me to buy special soaps, detergents, and lotions.	☐1	☐2	☐3	☐4	☐5
14. I am frustrated by my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
15. I am embarrassed by my itchy skin condition.	☐1	☐2	☐3	☐4	☐5

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	How often during the past week do these statements apply to you?				
	NEVER	RARELY	SOMETIMES	OFTEN	ALL THE TIME
16. My itchy skin condition drives me crazy/nuts.	☐1	☐2	☐3	☐4	☐5
17. My itchy skin condition makes me angry or irritable.	☐1	☐2	☐3	☐4	☐5
18. My itchy skin condition makes me feel depressed or sad.	☐1	☐2	☐3	☐4	☐5
19. I worry about what other people think about me because of my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
20. I worry that the itching will last forever.	☐1	☐2	☐3	☐4	☐5
21. I feel self-conscious because of my itchy skin condition.	☐1	☐2	☐3	☐4	☐5
22. My personality has changed because of my itchy skin condition.	☐1	☐2	☐3	☐4	☐5

Subject signature _____ Date _____

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10.1.14 Patient Global Impression of Severity for Erythema (PGIS-E)

Please note that erythema refers to the change in the color of your skin, typically turning red or purple, due to Netherton Syndrome.
When considering the skin area (or areas) affected by your disease, please choose the response below that best describes the severity of erythema on your skin over the past 24 h:

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

10.1.15 Patient Global Impression of Severity for Scaling (PGIS-S)

When considering the skin area (or areas) affected by your disease, please choose the response below that best describes the severity of the scaling of your skin over the past 24 h:

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

10.1.16 Patient Global Impression of Change for Netherton Syndrome Skin Symptoms (PGIC)

Please choose the response below that best describes the change in the skin symptoms overall related to your Netherton Syndrome since you started taking the medication of this study:

- ☐ Much better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Much worse

10.2 TRIAL PARTICIPANT FEEDBACK

Optional Trial Participant Feedback Questionnaires:

This trial will include an option for adult participants to complete anonymized questionnaires,'Trial Participant Feedback Questionnaire', to provide feedback on their clinical trial experience. Individual participant level responses will not be reviewed by investigators.

Responses will be used by the sponsor to understand where improvements can be made in the clinical trial process. These questionnaires will not collect data about the participant's disease, symptoms, treatment effect, or AEs and therefore will not be part of the trial data or clinical trial report. The questionnaires will be implemented after local regulatory approval and after consent of the trial participant. Providing feedback is optional and not required for participation in the trial.

10.3 MAXIMUM ALLOWABLE RESEARCH-RELATED BLOOD SAMPLE VOLUMES FOR ADOLESCENTS IN EU COUNTRIES

Body weight (kg)	Circulating total blood volume (ml)	Maximum allowable sample volume over 4 weeks (ml) - 3% of total blood volume	Maximum allowable sample volume at single time (ml) - 1% of total blood volume
30 - 70	**2400 - 5600**	**48 – 168**	**24 – 56**

11. DESCRIPTION OF GLOBAL AMENDMENT

11.1 GLOBAL AMENDMENT 1

Date of amendment		10 JAN 2024
EU number		2022-501104-10-00
UTN		U1111-1289-6825
BI Trial number		1368-0104
BI Investigational Medicinal Product		Spesolimab, BI 655130
Title of protocol		Evasayil™ : A placebo-controlled trial to evaluate the efficacy and safety of spesolimab in the treatment of patients with Netherton syndrome
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Title page
Description of change		The Universal Trial Number (UTN) was added
Rational of change		Updated information
Section to be changed		Several sections
Description of change		Corrected typos and spelling errors
Rationale for change		Administrative change
Section to be changed		Flow Chart, footnote#5 and Section 6.2.1
Description of change		Updated the screening period to [redacted] week Updated the screening period to [redacted] days Footnote#5 was updated as follows: Infection testing at screening includes tuberculosis (QuantiFERON® or T-Spot®), hepatitis B, hepatitis C, and HIV assessments. See Section 5.2.3 for complete list of testing required. For patients who sign the informed consent ≥4 weeks prior to V2, infection testing must be repeated 2 to 4 weeks prior to V2. For patients who continue in the extended treatment period, tuberculosis test is to be repeated at Week [redacted], Week [redacted], and at EOS. Section 6.2.1 was updated with the following added text: Screening visit (visit1) is to be performed within [redacted] days before Visit 2. Screening assessments may be repeated as long as they fall within the Screening visit window. If more than one screening assessment is available, the latest assessment prior to the start of treatment must be used to assess eligibility.
Rationale for change		Updated to account the availability of Spink5 genetic test results and to clarify that tuberculosis test will be repeated during the extended treatment period.
Section to be changed		Flow Chart and footnote#2

Date of amendment		10 JAN 2024
Description of change		Footnote # 2 was updated accordingly to include the following text: After Visit 15 (Week[redacted] each individual patient may continue receiving the trial drug up to [redacted] weeks (approximately 2 years). Patients who do not agree to continue should have their EoT visit at Week [redacted]. If the patients continue in the extended treatment period, then the EoT visit will occur at Week [redacted].
Rationale for change		To allow the patients benefiting from the trial drug to continue receiving Spesolimab after Week [redacted] and for the duration of approxiametely [redacted] weeks
Section to be changed		Flow Chart and footnote#21
Description of change		Added assessments of Itchy Qol, PGIS-E, PGIS-S PGIC, In- trial interviews (sub study-optional). Footnote#21 regarding in-trial interviews was added as follows: Interviews should occur within 4 weeks after the Week [redacted] visit. They can also be at early termination visit if this visit occurs between Week 8 and Week 16. Interviews will be conducted by [redacted]. Consent to participate in the in-trial interviews can be collected at any visit up to Week [redacted] visit included.
Rationale for change		Addition of assessment tools to further capture the pruritus-specific quality of life and patient's experience.
Section to be changed		Flow Chart and footnote #11
Description of change		Footnote #11 collection of ADA and Nab post-dose have been removed and changed to: PK/ADA/Nab samples will be obtained predose at all indicated visits. In addition, post-dose PK samples will be collected right after the[redacted] at Visit 2 and Visit 6.
Rationale for change		To reduce the amount of blood samples collected thoughout the trial.
Section to be changed		Flow Chart and footnote #12
Description of change		Added timepoints for photographies at remote visits V9; V11; V12; V14
Rationale for change		To clarify that during the remote visits, photographies will be taken by the HCP
Section to be changed		Flow Chart footnote#13, footnote#18 and footnote#19
Description of change		Footnote#13: added "After approval of protocol amendment v2.0, skin biopsies will be obtained only from adult patients."

Date of amendment		10 JAN 2024
		Footnote#18: added "and every 12 weeks starting Visit 15." After sentence "The diary should be given to the patient every 4 weeks until Visit 14". Footnote#19: added "During extension treatment phase, visits without clinical efficacy assessments (i.e every second visit starting V16) could be performed at the investigating site or remotely."
Rationale for change		Skin biopsies will not be collected for adolescents to lower the burden associated with trial assessments. Updates about the assessments during extention treatment phase were added.
Section to be changed		Flow Chart footnote #20
Description of change		Added footnote#20: At Visit 15, and at EOT visit, height will be measured only for adolescent patients.
Section to be changed		Flow Chart and footnote#7
Description of change		An extended treatment period from [redacted] up to [redacted] was added to the flow chart. Description about frequency of pregnancy test 106andomizteneded treatment period was added to footnote#7
Rationale for change		Update according to extension of trial
Rationale for change		To monitor growth in adolescent patients
Section to be changed		Section 1.4.1 Benefits
Description of change		As of September ~~2022~~ **2023**, an estimated ~~734~~ **863 subject**s have been exposed to spesolimab, out of a total of ~~936~~ **966 subject**s in the clinical development programme.
Rationale for change		Number of subjects exposed to spesolimab has increased since the original CTP
Section to be changed		Section 1.4.2 Risks
Description of change		Added "Blood volumes for safety analysis will be reduced for adolescent patients in this trial. In EU, the total blood volume collected will be in line with the EU recommendations for clinical trials on medicinal products conducted with minors across the study (R23-1267).
Rationale for change		Added for according to the EU recommendations
Section to be changed		Section 2.1.4 Secondary endpoint-Efficacy
Description of change		Moved the original secondary efficacy endpoint "Occurrence of bacterial or fungal mucocutaneous infection through Week 16" to further endpoint
Rationale for change		Number of bacterial or fungal mucocutaneous infection occurrences might end up being so small which could make interpretation of results or conclusions difficult. Also, distribution of these occurrences between the arms might end

Date of amendment		10 JAN 2024
		up being disproportionate, purely by chance, which also could make any interpretation of results or conclusions difficult.
Section to be changed		Section 2.1.4 Secondary endpoint-Efficacy
Description of change		Moved the original secondary efficacy endpoint "Percent change from baseline in NASA score at Weeks 4, 8, 12 and 16" to further endpoint, and changed it to "Percent change from baseline in NASA score up to Week [redacted] and by visit up to Week [redacted]"
Rationale for change		Update of endpoint
Section to be changed		Section 2.1.4 Secondary endpoint-Efficacy
Description of change		The original secondary efficacy endpoint "IASI subscore response, defined as a decrease of at least 50% absolute change in IASI-E subscore AND a decrease of at least 50% absolute change in IASI-S subscore from baseline at Weeks 4, 8, 12 (Yes/No)" was splited to two endpoints "IASI-E subscore response, defined as a decrease of at least 50% absolute change in IASI-E subscore at Weeks 4, 8, 12, 16 (Yes/No)" and "IASI-S subscore response, defined as a decrease of at least 50% absolute change in IASI-S subscore from baseline at Weeks 4, 8, 12, 16 (Yes/No)"
Rationale for change		Clarification to separately evaluate the IASI subscore response
Section to be changed		Section 2.1.4 Secondary endpoint-Safety
Description of change		"The occurrence of treatment emergent adverse events" was change to "The occurrence of treatment emergent adverse events **including serious and/or opportunistic infections"**
Rationale for change		As per PDCO recommendation, opportunistic infection should be added as a secondary endpoint for all studies involving pediatric subjects
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		

Date of amendment		10 JAN 2024
Description of change		[redacted]
Rationale for change		
Section to be changed		Section 3.1 Overall Trial Design
Description of change		Contents (texts and Figure 3.1:1) were updated due to the implementation of the extended treatment period after Week 52
Rationale for change		Update according to the extended trial duration
Section to be changed		Section 3.2 Discussion of Trial Design including the choice of control group(s)
Description of change		The following texts were added: In addition, the extended treatment period after Week [redacted] is included to provide trial patients with continued treatment and assessments, and to collect further efficacy and safety evaluation. As part of the trial, patients may participate to the Qualitative Interview sub-study to understand their experience with the received treatment during the clinical trial. Participation in the interview is optional and details will be described in an optional informed consent form/Assent. The interview will be conducted after a separate patient interview informed consent has been given in accordance with local ethical and regulatory requirements. Further details will be provided in a separate In-trial interview Manual. This trial will also include an option for participants and/or participant caregivers to complete anonymized questionnaires to provide feedback on their clinical trial experience. Providing this feedback is not required for trial participation, and information collected from these questionnaires will not be analysed as part of the clinical data for the trial (see Appendix 10.2).
Rationale for change		Update of trial design
Section to be changed		Section 3.3.4.1 Discontinuation of trial
Description of change		Wording amended (second bullet point) The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of ~~*both*~~ the investigator ~~*and sponsor representative*~~, the safety of the

Date of amendment		10 JAN 2024
		patient cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
Rationale for change		Request by the Competent Authorities to change the wording from "the opinion of both the investigator and sponsor representative to "the opinion of the investigator".
Section to be changed		Section 4.1.4 Drug assignment and admistration of doses for each patient
Description of change		The bolded text is added to sentence "During the visits with reduced number of assessments e.g. Weeks [redacted], **and extended treatment period**, patients will be offered to receive spesolimab s.c. at home or closer to the patient's home, administered by a specialized vendor/HCP if applicable."
Rationale for change		Updated according to change in trial design
Section to be changed		Section 4.1.5.1 Blinding
Description of change		The primary analysis of this trial is planned to be performed once all randomized patients have completed the 16 weeks or early discontinued from the trial, to support an early submission: a database lock for the primary analysis will then be performed and treatment will be unblinded to the sponsor. Patients, investigators and central reviewers, ~~and everyone~~ involved in trial conduct ~~or analysis or with any other interest~~ in this double-blind trial will remain blinded regarding the randomised treatment assignments until the database is declared ready for **final** analysis according to the sponsor's SOPs. Further details regarding the timepoint of unblinding the database for analysis is documented in the TSAP. ~~If the primary analysis and the final analysis are performed separately (see Section 7.2.1),~~ ~~then a database lock for the primary analysis will be done and treatment will be unblinded to~~ ~~trial and project team members. Details will be described in the primary analysis logistics~~ ~~plan~~. … The randomisation codes ~~will~~ **may** be provided to bioanalytics before the last patient completed the trial ~~to exclude placebo samples from~~ **for** the PK and ADA analysis. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial has been officially un-blinded to the sponsor.

Date of amendment		10 JAN 2024
Rationale for change		Clarified the unblinding at primary analysis and final analysis
Section to be changed		4.1.6 Packaging, labelling, and re-supply
Description of change		Added: In accordance with the Clinical Trial regulation (EU) No 536/2014 and the corresponding Annex VI, omitting of label content with the following justifications: -the translation of country specific label text may differ from the Master Label Text based on specific local requirements. This could include the omission, addition or revision of some text per local regulation compliance - the Investigator name was omitted from the label due to IRT System
Rationale for change		Clarification added to comply with EU regulation on labels content in Clinical trials
Section to be changed		Section 4.2.1.1 Other treatments
Description of change		The following text were added: For skin care: Emollients must not include urea or salicylic acid, should not be keratolytics and should not be medicinal products (i.e. no treatment indications).
Rationale for change		To clarify the type of emollients allowed
Section to be changed		Section 4.2.2 Restrictions
Description of change		Table 4.2.2.1: 1 Restricted medications and treatments Include **urea** as one of the Topical retinoids, topical calcineurin inhibitors, keratolytics for the restricted mediation usage.
Rationale for change		Clarification
Section to be changed		Section 5.1 Assessment of Efficacy
Description of change		Added the following text for DLQI/CDLQI assessment: Response categories include “not relevant” (score of 0), “not at all” (score of 0), “a little” (score of 1), “a lot” (score of 2) and “very much” (score of 3). Question 7 is a “yes”/ “no” question where “yes” is scored as 3. DLQI total score is calculated by summing the scores of each question resulting in a range of 0 to 30. Added the following text for the 5D-Itch-scale assessment: For the distribution domain, the number of affected body parts is tallied (potential sum 0–16) and the sum is sorted into five scoring bins: sum of 0–2 = score of 1, sum of 3– 5 = score of

Date of amendment		10 JAN 2024
		2, sum of 6–10 = score of 3, sum of 11–13 = score of 4, and sum of 14–16 = score of 5.  Added the following assessment: **Itchy-Qol** Itchy QoL is a pruritus-specific quality-of-life (QoL) instrument that consists of 22 pruritus-specific items (each score from 1 to 5; the sum ranges from 22 to 110) regarding symptoms, functions, emotions, and self-perception [R22-2031]. **Patient Global Impression of Severity for Erythema** The Patient Global Impression of Severity for Erythema (PGIS-E) is a single item questionnaire that describes the severity of erythema over the past 24 h when considering skin area affected by NS. Participants will rate how his/her severity of erythema over the past 24 h can be described using a 5-point scale ranging from "None" to "Very Severe". **Patient Global Impression of Severity for Scaling** The Patient Global Impression of Severity for Scaling (PGIS-S) is a single item questionnaire that describes the severity of scaling over the past 24 h when considering skin area affected by NS. Participants will rate how his/her severity of scaling over the past 24 h can be described using a 5-point scale ranging from "None" to "Very Severe". **Patient Global Impression of Change for Netherton Syndrome Skin Symptoms**

Date of amendment		10 JAN 2024
		The Patient Global Impression of Change (PGI-C) for Netherton syndrome skin symptoms is a single item questionnaire that describes the change (improvement or deterioration) in skin symptoms overall related to NS since the medication of this study has started. Participants will rate how his/her NS has changed since the beginning of the study using a 5-point scale ranging from "Much better" to "Much worse" with "no change" indicating neither better nor worse.
Rationale for change		Updated the assessment
Section to be changed		Section 5.2.3 Safety laboratory parameters and Appendix 10.3
Description of change		Contents (texts and Appendix 10.3) were added to include blood collection instructions for adolescent patients according to EU recommendation [R23-1267]. Footnotes of Table 5.2.3.1 were updated. Added Appendix 10.3 maximum allowable research-related blood volumes for adolescents in EU countries
Rationale for change		Clarification
Section to be changed		Section 5.2.6.2.2 AE reporting to the sponsor and timelines
Description of change		The following texts were modified: The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the AE or SAE eCRF pages, ~~according to the process used, EDC/eCRF or paper,~~ to the sponsor's unique entry point immediately (within 24 h of becoming aware of the event). The country specific process will be specified in the ISF. With receipt of any further information to these events, a follow-up ~~SAE form~~ reports have to be provided.
Rationale for change		Typos corrections
Section to be changed		Section 5.3.4: Pharmacok–netic - pharmacodynamic relationship
Description of change		The following texts were added: This trial is also intended to contribute to modelling of the dose-exposure relationship in children from 12 years to less than 18 years of age (and adults) with Netherton syndrome.
Rationale for change		Text updated to align the wording with other submission documents
Section to be changed		Section 5.4.3 Methods of sample collection
Description of change		The following text was added: After approval of protocol amendment v2.0, skin biopsies will be obtained only from adult patients.
Rationale for change		To lower the burden associated with the trial assessments for adolescent patients

Date of amendment		10 JAN 2024
Section to be changed		5.4 Assessment of Biomarker(s)
Description of change		The following text was added: [redacted]
Rationale for change		To clarify how long biomarker samples will the be stored
Section to be changed		Section 6.2 Details of trial procedures at selected visits
Description of change		Updated texts due to the inclusion of extended treatment period. Updated texts to specify assistance from other people is applicable during the questionnaires collection. The following texts were added: For adolescent patients or if the patient is too sick to complete the questionnaires by him/herself but is able to reply verbally, a parent/legal guardian or a member of the trial team should read the instructions, questions, and response options aloud to the patient and collect the patient's verbal response in as neutral and unbiased a manner as possible. If this is not possible either, the questionnaires are not to be completed.
Rationale for change		Updated texts due to the inclusion of extended treatment period and specify assistance from other people is applicable during the questionnaires collection.
Section to be changed		Section 6.2.1: Screening and run-in period (s)
Description of change		The following text was updated: Screening visit (visit1) is to be performed within [redacted] **day**s before Visit 2. **Screening assessments may be repeated as long as they fall within the Screening visit window. If more than one screening assessment is available, the latest assessment prior to the start of treatment must be used to assess eligibility.**
Rationale for change		Clarification to reflect the extension of the screening period
Section to be changed		6.2.2 Treatment period(s)
Description of change		The following text was updated: Patients may decide to continue receiving the Open Label Extended trial treatment until [redacted]. Similar edits regarding inclusion of open label extension were also applied in Section 6.2.3 for updated definitions of EoT and early treatment discontinuation.
Rationale for change		Update according to change in trial design
Section to be changed		7.1 Null and Alternative Hypotheses
Description of change		Wording was corrected:

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		H02: There is no difference regarding the **odds** ~~proportion of patients~~ of the key secondary endpoint (IGA score of 0 or 1 at Week 16) between spesolimab versus placebo against H12: There is a difference regarding the ~~proportion of patients~~ **odds** of the key secondary endpoint (IGA score of 0 or 1 at Week 16) between spesolimab versus placebo
Rationale for change		correction
Section to be changed		Section 7.2.2 Handling of Intercurrent Events
Description of change		Updated one of the expected intercurrent events of interest as: Treatment discontinuation ~~(~~due to AE/~~ or due to~~ lack of efficacy/~~)~~**other reasons.** Updated was made to clarify treatment discontinuation will be handled by treatment policy, but not composite strategy. See updated text below: Composite strategy: This is the effect of spesolimab, where intercurrent events of use of restricted medications and treatments for NS ~~and treatment discontinuation~~ will be considered as treatment failure. **Treatment policy strategy: treatment discontinuation will be handled by a treatment policy approach, i.e. the value of the variable regardless of the occurrence of the intercurrent event will be used.** ~~All intercurrent events will be handled using the composite approach and handled as treatment failure.~~
Rationale for change		Update of intercurrent event and clarification. Update of policy and clarification based on health authority feedback and spesolimab experience.
Section ot be changed		Section 7.2.3 Primary objective analyses
Description of change		The following text was added: For the estimand concept on the primary binary endpoint, composite strategy will be applied that occurrence of ~~any intercurrent events (i.e.~~ use of restricted medications and treatments for NS~~, treatment discontinuation~~ prior to Week 16 will be considered to represent a non-response at the Week 16 timepoint. Additional updates in Section 7.2.3: Comparisons between treatment groups regarding the binary endpoint variable, the proportions of IASI response at

Date of amendment		10 JAN 2024
		Week 16 will be performed using a logistic regression model adjusting for the categorical covariate age group (adult vs. adolescent) and the categorical covariate baseline IASI score (classified into ~~4~~ **2** equally-sized ~~quartiles~~ **groups by median**). The likelihood-ratio test will be used to test for difference between treatments. Adjusted **odds ratio and** risk differences together with 95% confidence intervals will be used to quantify the effect of treatment, comparing spesolimab to placebo as the reference. **Procedures to follow if the analysis fails to converge will be described in the TSAP.**
Rationale for change		Update of analysis and clarification.
Section ot be changed		Section 7.2.4 Secondary objective analyses
Description of change		The following texts were updated: For key secondary endpoint, the analyses will be performed on the FAS in the same manner as described for the analysis of the primary endpoint in Section 7.2.3 but excluding baseline IASI score **and including baseline IGA** as covariate. ~~Analyses for the continuous secondary endpoints will be evaluated descriptively, including calculating the means and 95% CIs (if applicable) based on FAS.~~ Analyses for the continuous secondary endpoints will be analysed by a restricted maximum likelihood (REML) estimation-based approach using a mixed-effect model with repeated measurements (MMRM) analysis, including calculating the adjusted means and 95% CIs (if applicable) based on FAS. The analysis will include the fixed, categorical effects of treatment at each visit, age group and the fixed continuous effects of baseline at each visit.
Rationale for change		Added the clarification
Section ot be changed		7.2.6 Safety analyses
Description of change		Was corrected: If, for a patient, the selected treatment emergent adverse event didn't occur then the time at risk will be censored at min (date of death, last contact date per EoS page, drug stop date + 112 days, ~~date of rescue medication if spesolimab 900 mg i.v. is given~~). For each selected treatment emergent AE, the exposure adjusted incidence rate will be calculated as: Incidence rate [1/100 patient-years (pt-yrs)] = 100 * number of patients with TEAE / Total TEAE-specific time at risk [patient-years].

Date of amendment		10 JAN 2024
Rationale for change		Correction
Section to be changed		7.2.8 Interim analyses
Description of change		Was added: The primary analysis of this trial is planned to be performed once all randomized patients have completed the 16 weeks or early discontinued from the trial, to support an early submission; a database lock for the primary analysis will then be performed. Multiple analyses may be conducted during the open label treatment period to support, for example, regulatory interactions. Final analysis is planned to be performed at the end of the trial once all patients have completed the trial (including any follow-up period if applicable).
Rationale for change		The primary analysis to be consistent with the description from Section 7.2.1
Section to be changed		Section 7.3 Handling of missing data
Description of change		The following texts were updated: For handling missing data on the primary, key secondary and secondary **binary** efficacy endpoints, a Non-Response Imputation (NRI) will be applied as the primary imputation approach, ~~The primary imputation strategy of missing values of secondary continuous endpoints is LOCF, i.e. impute the missing outcome as the last available value (including baseline) prior to the missing outcome.~~ Missing data will not be imputed for secondary continuous endpoints. The mixed effect model will handle missing data based on a likelihood method under the 'missing at random assumption'.
Rationale for change		Update of analysis.
Section to be changed		Section 7.4 Randomisation
Description of change		The following text was added: The adolescent patients will be randomized in a 2:1 ratio to two treatment groups (spesolimab and placebo) regardless of blocking factor of Japan versus China versus other regions.
Rationale for change		To apply PIP requirement.
Section to be changed		Section 8.4 Expedited reporting of adverse events
Description of change		Was added: SAE/AESI are processed in the global Safety Database and assessed for the company causal relationship as well as the expectedness of the event according to the reference safety information. Individual Case Safety Reports (ICSR) are subsequently reported according to local Regulations.

Date of amendment		10 JAN 2024
		Reporting to the EMA will be done via E2B transmission of ICSRs to the Eudravigilance CT Module
Rationale for change		Request by the Competent Authorities to describe the procedures for reporting of suspected unexpected serious adverse reactions to the Eudravigilance database as set out in CTR Annex I paragraph D, subsection 20c.
Section to be changed		Section 10.1 Scales
Description of change		Updated the assessment according to the change in main text
Rationale for change		Adaption to the change in main text
Section to be changed		Section 10.2 Trial Participant Feedback
Description of change		Added the whole section
Rationale for change		To align with BI standards for Clinical Trial Protocols
Section to be changed		Section 9.1 pubished references
Description of change		Added reference R23-1267
Rationale for change		Admistrative
Section to be changed		Protocol synopsis
Description of change		The synopsis was updated according to the main text changes in the protocol
Rationale for change		Admistrative

11.2 GLOBAL AMENDMENT 2

Date of amendment		24 Sep 2024
EU trial no.		2022-501104-10-00
UTN		U1111-1289-6825
BI Trial number		1368-0104
BI Investigational Medicinal Product		Spesolimab, BI 655130
Title of protocol		Evasayil™ : A placebo-controlled trial to evaluate the efficacy and safety of spesolimab in the treatment of patients with Netherton syndrome
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Title page
Description of change		[redacted]

Date of amendment		24 Sep 2024
		[redacted] Phone: [redacted]
Rationale of change		To update clinical trial leader's name and contact information.
Section to be changed		Clinical Trial Protocol Synopsis, Trial Endpoints
Description of change		Updated key secondary endpoint as follows: The key secondary endpoint is IGA response, defined as **a decrease of at least 1-grade absolute change in IGA score from baseline** ~~IGA score of 0 or 1~~ at Week 16 (Yes/No).
Rationale for change		Due to new learnings from experts, case report from dupilumab and IGA development report, 0 or 1 on IGA is most likely not achievable. This was also mentioned in the FDA Written feedback from 2022 - FDA would be open to 1 or 2 grade improvement (if it is clinically meaningful to patients).
Section to be changed		Clinical Trial Protocol Synopsis, Trial Endpoints
Description of change		Text was updated as follows: o IGA ~~response, defined as IGA~~ score of 0 or 1 at Weeks 4, 8, 12, and **16** (Yes/No)
Rationale for change		To update secondary endpoint.
Section to be changed		Clinical Trial Protocol Synopsis, Trial Endpoints
Description of change		Text was updated as follows: o Absolute change from baseline in DLQI~~/CDLQI~~ score at Weeks 8 and 16 o **Absolute change from baseline in CDLQI score at Weeks 8 and 16**
Rationale for change		To split DLQI and CDLQI score into two endpoints.
Section to be changed		Clinical Trial Protocol Synopsis, Statistical methods
Description of change		Text was updated from: ~~Logistic regression will be used to test if there is a difference between treatments regarding the binary primary endpoint variable, adjusting for the categorical covariate age and categorical baseline IASI score.~~ To: **Suissa-Shuster Z-pooled test will be used to test if spesolimab is different from placebo regarding the binary endpoint variable (the proportions of IASI response at Week 16).**

Date of amendment		24 Sep 2024
Rationale for change		Due to the small number of patients in this trial for an ultra rare disease and fewer responses observed so far than assumed, the original primary analysis logistic regression model has a higher risk of non-convergence, i.e. cannot be fitted to the data. The primary analysis model is changed to an exact test (Suissa-Shuster Z-pooled test) which is an appropriate method for small sample size. The original primary analysis model will be run as a sensitivity analysis if it converges.
Section to be changed		Flow chart, photographs
Description of change		Crosses at Visits 9, 11, 12, 14 were removed.
Rationale for change		The possibility to conduct Visits 9, 11, 12 and 14 remotely was removed. Therefore, no photos will be taken by the home care nurse at these visits.
Section to be changed		Flow Chart
Description of change		Flow chart 1, Footnote #2 was updated as follows: [2] After Visit [redacted]), each individual patient may continue receiving the trial drug up to Week [redacted]). **EoT will be at Week [redacted]. All patients who stop treatment prior to Week 156 will be considered early discontinued. Timepoint of early EoT will be considered the visit when the last dose of IMP was administered.** ~~Patients who do not agree to continue should have their EoT visit at Week 52. If the patients continue in the extended treatment period, then the EoT visit will occur at Week 156.~~ ~~Should a patient prematurely discontinue from the trial treatment before scheduled EoT visit,~~ **In case of early discontinuation from trial treatment,** every effort should be made to keep the patient in the trial and complete all of the remaining visits**-up to Week [redacted] (without IMP administration in that case). At a minimum, patients should come to** ~~or at a minimum,~~ an End-of-study Visit (EoS)~~,~~ [redacted] weeks after the last dose **to cover full REP.**
Rationale for change		To clarify wording regarding EoT and early EoT.
Section to be changed		Flow Chart
Description of change		In Flow chart 1, Footnote #3, the following text was added: **Regularly, EoS is [redacted] weeks after last dose of trial medication to cover REP. If a patient discontinues early from trial treatment and continues with original visit schedule (without receiving treatment), EoS could also take place beyond [redacted] weeks after last treatment dose. EoS visit would be performed as the last patient visit in that case.**
Rationale for change		To clarify timepoint of EoS in case of early EoT.
Section to be changed		Flow chart
Description of change		Flow chart 1, Footnote #12 was updated as follows:

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		[12]Photographs of skin lesions are to precede skin biopsies and trial drug administration. In addition to photographs of skin lesions, biopsy site photographs will also be taken at Visit 2 and Visit 6. ~~If a remote visit is performed at visits 9, 11, 12 and 14, photographies of skin lesions will be taken by the Health Care Personnel (HCP) and transmitted electronically to the Investigator for skin assessments. If these visits are performed at the clinic then collection of photographs is not needed.~~
Rationale for change		To remove wording related to remote visits 9, 11 12 and 14, as these were not set-up due to lack of interest by sites, as well as logistical constraints.
Section to be changed		Flow chart
Description of change		Flow chart 1, Footnote #19 was updated as follows: 19~~Visits~~**During extension treatment phase, visits** with reduced number of assessments (i.e ~~Visits 9, 11, 12 and 14~~ **every second visit starting Visit 16 and up to Visit 40**) could be either performed at the investigational site or remotely by a trained Health Care ~~Personnel~~ **Professional** (HCP) at the patient's home ~~or at a facility closer to the patient's home~~. During extension treatment phase. ~~During extension treatment phase, visits without clinical efficacy assessments (i.e. every second visit starting V16) could be performed at the investigating site or remotely.~~ **During remote visits, an abbreviated body system assessment will be conducted by the trained HCP instead of a physical exam. This abbreviated body system assessment will include evaluation of organ systems associated with AE(s) symptoms and is only observational and conversational with patient.**
Rational for change		To remove option to perform visits 9, 11, 12, 14 remotely; clarify that trained HCP will do an abbreviated body system assessment instead of a complete physical exam during remote visits.
Section to be changed		Flow chart
Description of change		Flow chart 2 was added.
Rationale for change		To provide detailed overview of assessments per individual visits during extension treatment phase.
Section to be changed		Section 2.1.3 Key secondary endpoint(s)
Description of change		In efficacy section, text was updated as follows: The key secondary endpoint of this trial is: o IGA response, defined as **a decrease of at least 1-grade absolute change in IGA score from baseline** ~~IGA score of 0 or 1~~ at Week 16 (Yes/No)
Rationale for change		Due to new learnings from experts, case report from dupilumab and IGA development report, 0 or 1 on IGA is most likely not achievable. This was also mentioned in the FDA Written feedback from 2022 - FDA would be open to 1 or 2 grade improvement (if it is clinically meaningful to patients).

Date of amendment		24 Sep 2024
Section to be changed		Section 2.1.4 Secondary endpoint(s)
Description of change		IGA ~~response, defined as IGA~~ score of 0 or 1 at Weeks 4, 8, 12 **and 16** (Yes/No)
Rationale for change		To update description of secondary endpoint.
Section to be changed		Section 2.1.4 Secondary endpoint(s)
Description of change		Text was changed as follows: o Absolute change from baseline in DLQI~~/CDLQI~~ at Weeks 8 and 16 o **Absolute change from baseline in CDLQI score at Weeks 8 and 16**
Rationle for change		To split DLQI and CDLQI score into two endpoints
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 3.1 Overall Trial Design
Description of change		In section "open label period", the following sentences were updated as follows: Patients who have responded (responders), defined as having more than or equal to 50% reduction in IASI score at Week 32 compared with baseline will receive a reduced dose of spesolimab, [redacted] every 4 weeks [redacted].

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		… The dose escalation should be applicable only once [redacted] The beginning of the section "extended treatment period" updated as follows: (from Week [redacted]). In section “extended treatment period” the text was modified as follows: After completing the first [redacted] weeks of treatment, the patients ~~may be~~ **are** offered to continue their assigned treatment at Visit 1**6**~~5~~ (i.e. Spesolimab [redacted]) in the extended treatment period up to [redacted] weeks. **Starting Week 56:** ○ **Patients receiving 600 mg of spesolimab and experiencing a reduction of less than 50% on IASI compared with Visit 2 for two consecutive visits should be discontinued from the trial treatment. These two consecutive visits should be at least 4 weeks apart. Down-titration from 600 mg to 300 mg spesolimab will not be permitted during extended treatment period.** ○ **Patients who are receiving spesolimab 300 mg and experience a reduction of less than 50% on IASI should not be discontinued, but up-titrated to 600 mg first. Only if the patient still shows reduction of less than 50% on IASI on 600 mg for two consecutive visits, patient should be discontinued.** ~~During the extended treatment period, dose escalation to [redacted] will be permitted once for patients who were receiving spesolimab [redacted] and experience a reduction of less than 50% on IASI. [redacted] of spesolimab will not be permitted. Patients receiving [redacted] of spesolimab and experience a reduction of less than 50% on IASI for two consecutive visits should be discontinued from the trial treatment. These two consecutive visits should be at least 4 weeks apart~~. Patients who prematurely discontinue **from** the trial drug will be encouraged **to complete all of the remaining visits up to Week [redacted] (without IMP administration in that case). At a minimum, patients should come to an End-of-study Visit (EoS), [redacted] weeks**

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		after the last dose to cover full REP. ~~perform an unscheduled visit and will then enter the 16-week follow-up period (see Figure 3.1: 1).~~ … Patients who prematurely discontinue **from** the trial drug will be encouraged to **continue with the original visit schedule up to Week [redacted] (without IMP administration in that case). EoS (End of Study) visit will be performed as the last patient visit in that case. At a minimum, patients should come to an EoS Visit [redacted] weeks after the last dose to cover full REP** ~~perform an unscheduled visit and will then enter the [redacted] follow-up period~~ (see Figure 3.1:1).
Rationale for change		To clarify information related to open-label and extended treatment period, as well as to the follow-up period.
Section to be changed		Section 3.2 Discussion on trial design, incl. the choice of control group(s)
Description of change		Text was updated as follows: This trial will also include an option for **adult** participants ~~and/or participant caregivers~~ to complete anonymized questionnaires to provide feedback on their clinical trial experience.
Rationale for change		To clarify that the questionnaires are only available for adult trial participants.
Section to be changed		Section 3.3.4.1 Discontinuation of trial treatment
Description of change		Text was updated as follows: ~~In case the infusion of trial drug is permanently discontinued before the whole amount of the prepared solution has been administered to the patient, every effort should be made to complete all remaining study assessment.~~ In case the study drug administration is permanently discontinued before EoT visit, all efforts should be made to keep the patient in observation **for the remaining trial visits up to regular EoT visit at Week [redacted], according to flow chart.** EoS visit will be performed as the last patient visit in that case. **As a minimum** ~~for at least~~**, the patient should come back for an EoS Visit [redacted]** weeks after the last dose of the study drug.
Rationale for change		To clarify the follow-up of patients with early treatment discontinuation
Section to be changed		Section 3.3.4.3 Discontinuation of the trial by the sponsor
Description of change		The following reason was added: **4. Termination of development of compound in this indication**

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Rationale for change		To add termination of development of compound in NS as a possible reason for trial discontinuation by the sponsor, as this is part of standard CTP template.
Section to be changed		Section 4.1.4 Drug assignment and administration of doses for each patient
Description of change		The following text was removed: ~~For the remote visits, if applicable the HCP, will be provided with at home urine pregnancy test kits.~~ ~~The s.c. injection should avoid sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses. If injections are administered in the same area, it should be at least 2 cm apart and should not be close to a vein.~~
Rationale for change		To remove text related to pregnancy kits and to remove instructions related to s.c injection of IMP to avoid duplication. Detailed instructions are provided in a separate instruction document in the ISF.
Section to be changed		Section 4.2.1.1 Other treatments
Description of change		In restricted medications and treatments for NS section, the text was updated as follows: If the patient experiences an intolerable worsening of NS during the course of the trial, the patient will be discontinued from trial treatment to receive alternative medication ~~and/~~or **receive** treatment for NS **(including restricted medications with the exception of biologs, immunoglobulins and investigational products, in which case the patient needs to be discontinued from trial treatment)** as deemed appropriate by the investigator. ~~These patients~~ **In case of early discontinuation from trial treatment, the patient will** ~~complete early EOT visit and continue~~ **be followed up as described in the Flow Chart 1 (Footnote 2) for early EoT.** ~~to be followed for all regular scheduled follow-up visits for safety and efficacy assessments.~~
Rationale for change		To clarify wording.
Section to be changed		Section 5.1 Assessment of efficacy
Description of change		In section "DLQI/CDLQI," the following text was added: **For adolescents, an adapted version of this tool is used, called the Children's Dermatology Life Quality Index (CDLQI). The CDLQI is a questionnaire designed to measure the impact of skin disease on the lives of children and young people. The CDLQI has been developed to resemble the DLQI, with responses ranging from not at all to very much. Data from the two cannot be**

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		combined, because the items and score meaning bands are different. CDLQI total score is calculated by summing the scores of each question resulting in a range of 0 to 30. Interpretation can be done by cut points: 0 (scores of 0–1), no effect;1 (scores of 2–6), small effect; 2 (scores of 7–12), moderate effect;3 (scores 13–18), very large effect;4 (scores 19–30), extremely large effect [R24-3537].
Rationale for change		To add description of CDLQI score
Section to be changed		Section 5.1 Assessment of efficacy
Description of change		**In section "Itchy-Qol," the text was updated as follows:** **Itchy-Qol** Itchy QoL is a pruritus-specific quality-of-life (QOL) instrument that consists of 22 pruritus-specific items (each score from 1 to 5; the sum ranges from 22 to 110) regarding symptoms, functions~~,~~ **and** emotions ~~and self-perception~~. [R24-3478].
Rationale for change		To correct description of Itchy-QOL
Section to be changed		Section 5.2.1 Physical examination
Description of change		The following text was added: **During remote visits, an abbreviated body system assessment will be conducted by the trained HCP instead of a physical exam. This abbreviated body system assessment will include evaluation of organ systems associated with AE(s) symptoms and is only observational and conversational with patient.**
Rationale for change		To clarify that an abbreviated body system assessment will be conducted by the trained HCP instead of a physical exam during remote visits.
Section to be changed		Section 5.2.3 Safety laboratory parameters
Description of change		Footnote 1 of Table 5.2.3:1 was updated as follows: [1]A HBV-DNA should be conducted **at screening** if Hepatitis B core Antibody is positive and Hepatitis B Surface Antigen is negative. ~~These evaluations should be conducted at screening and~~ **If at screening, Hepatitis B core Antibody is positive and Hepatitis B Surface Antigen is negative, HBV-DNA should be repeated** at the EOS visit.
Rationale for change		To clarify wording related to HBV infection testing at EoS
Section to be changed		Section 5.7 Appropriateness of measurements

Date of amendment		24 Sep 2024
Description of change		Text was added as follows: **This is because the prevalence and characteristics of NS may differ between patients of different racial origin. It will thus be worthwhile to assess if patients of different race will respond differently to the study treatment.**
Rationale of change		To add rationale why race is collected in this trial.
Section to be changed		Section 6.2 Details of trial procedures at selected visits
Description of change		Text was updated as follows: All efforts should be made to perform the most critical visits e.g. randomisation at Visit 2, primary endpoint at Week 16 and end of treatment at Week ~~52~~[redacted]. These and other visits requiring i.v. administration should always be performed at the investigator site facility whenever possible. The visits with reduced number of assessments and no reoutine lab sampling, e.g. ~~Weeks 28, 36, 40 and 48 and~~ **every second visit** during the extended treatment period could be performed remotely or using hybrid approach (assessments performed at home ~~or at the remote facility closer to the patient's home~~ by the specialized vendor/HCP, if applicable) or performed in the investigator site facility, if this is preferable for the patient and the investigational site.
Rationale for change		To update wording related to home care services.
Section to be changed		Section 6.2 Details of trial procedures at selected visits
Description of change		Text was updated as follows: For adolescent patients or if the patient is too sick to complete the questionnaires by him/herself **or is illiterate**, but is able to reply verbally, a parent/legal guardian or a member of the trial team should read the instructions, questions, and response options aloud to the patient and collect the patient's verbal response in as neutral and unbiased a manner as possible.
Rationale for change		To add illiteracy.
Section to be changed		Section 6.2.3 Follow-up period and trial completion
Description of change		Text related to regular EoT was updated as follows: For patients completing the **full** treatment period up to Week [redacted], ~~the EoT vsit is to be scheduled at Visit 15 (Week [redacted]) or after the extended~~

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		~~treatment period (Week [redacted]),~~ a follow- up visit should be performed [redacted] weeks after the last administration of trial medication (EoS). Text related to early treatment discontinuation was updated as follows: Patients who discontinue the trial treatment early (prior to Week [redacted]). These patients should be registered as withdrawn from randomized treatment in IRT **and the eCRF accordingly**. **Timepoint of early EoT will be considered the visit when the last dose of IMP was administered. In case of early discontinuation from trial treatment, every effort should be made to keep the patient in the trial and complete all of the remaining visits up to Week [redacted] (without IMP administration in that case). At a minimum, patients should come to an End-of-study Visit (EoS), [redacted] weeks after the last dose to cover full REP.**
Rationale for change		To clarify wording related to regular and early EoT.
Section to be changed		Section 7.1
Description of change		Text in Null and alternative hypotheses section was updated as follows: H_{01}: There is no difference regarding the **proportion** ~~odds~~ of the primary endpoint (IASI response, defined as a decrease of at least 50% absolute change in IASI score from baseline at Week 16) between spesolimab versus placebo ~~(i.e. odds ratio of spesolimab versus placebo is equal to 1)~~ against H_{11}: There is a difference regarding the ~~odds~~ **proportion** of the primary endpoint (IASI response, defined as a decrease of at least 50% absolute change in IASI score from baseline at Week 16) between spesolimab versus placebo ~~(i.e. odds ratio of spesolimab versus placebo is not equal to 1)~~. The trial is considered positive, if the null hypothesis of the primary endpoint can be rejected and the result is more favorable for spesolimab versus placebo (~~odds~~ **proportion** in spesolimab group ≥ **proportion** ~~odds~~ in placebo group). … H_{02}: There is no difference regarding the ~~odds~~ **proportion** of the key secondary endpoint (**IGA response, defined as a decrease of at least 1-grade absolute change in IGA score from baseline at Week 16)**~~IGA score of 0 or 1 at Week 16)~~ between spesolimab versus placebo against H_{12}: There is a difference regarding the ~~odds~~ **proportion** of the key secondary endpoint (**IGA response, defined as a decrease of at least 1-grade absolute change in IGA score from**

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		baseline at Week 16~~IGA score of 0 or 1 at Week 16~~) between spesolimab versus placebo.
Rationale for change		To align with new primary analysis method and key secondary endpoint.
Section to be changed		Section 7.2.1 General considerations
Description of change		In section "per-protocol set (PPS)," text was updated as follows: **Per-Protocol Set (PPS)** This patient set includes all patients in FAS who adhered to the CTP without any important protocol deviations (iPDs) which lead to exclusion from the PPS. This set will be used for sensitivity analysis on the primary endpoint **and key secondary endpoint**.
Rationale for change		To clarify that PPS will also be used for sensitivity analysis on key secondary endpoint.
Section to be changed		Section 7.2.3 Primary objective analyses
Description of change		Text was updated from: ~~Comparisons between treatment groups regarding the binary endpoint variable, response rate at Week 16 in IASI response will be performed using a logistic regression model adjusting for the categorical covariate age group (adult vs. adolescent) and the categorical covariate baseline IASI score (classified into 2 equally sized groups by median). The likelihood-ratio test will be used to test for difference between treatments.~~ ~~Adjusted odds ratio and risk differences together with 95% confidence intervals will be used to quantify the effect of treatment, comparing spesolimab to placebo as the reference.~~ ~~Procedures to follow if the analysis fails to converge will be described in the TSAP.~~ To: **Comparisons between treatment groups regarding the binary endpoint variable, the proportions of IASI response at Week 16 will be performed using the exact unconditional Suissa-Shuster Z-pooled test. The risk difference together with 95% confidence intervals will be used to quantify the treatment, comparing spesolimab to placebo.**
Rationale for change		Due to the small number of patients in this trial for an ultra rare disease and due to the number of patients within each strata and the number of responses observed in the blinded data so far, the original primary analysis logistic regression model has a very high risk of non-convergence, i.e. it is very likely that it cannot be fitted to the data. The primary analysis model is therefore changed to an exact unconditional Suissa-Shuster Z-pooled test which is an appropriate method for small sample size. The original primary analysis model will be run as a sensitivity analysis if it converges.

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Section to be changed		Section 7.2.3.1 Sensitivity Analyses
Description of change		The following text was added: • **A sensitivity analysis to adjust for covariates of age group (adult vs. adolescent) and baseline IASI group (classified into 2 equally sized groups by median) using logistic regression model.** • **Further sensitivity analyses, if any, will be defined in the TSAP.**
Rationale for change		To align with new primary analysis method, the original primary analysis model will be run as a sensitivity analysis if it converges.
Section to be changed		Section 7.2.4 Secondary objective analyses
Description of change		Text was updated as follows: For key secondary endpoint, the analyses will be performed on the FAS in the same manner as described for the analysis of the primary endpoint in Section 7.2.3 ~~but excluding baseline IASI score and including baseline IGA as covariate~~. For binary secondary endpoints, the analyses will be performed on the FAS in the same manner as described for the analysis of the primary endpoint in Section 7.2.3 ~~but replacing the baseline IASI score with each respective baseline endpoint as covariate~~.
Rationale for change		To align with new primary analysis method.
Section to be changed		Section 7.2.8 Interim analyses
Descrition of change		Text was updated as follows: ~~No interim analysis is planned but a~~**A** Data Monitoring Committee (DMC) will be in place with tasks as described in Section 8.7. The primary analysis of this trial is planned to be performed once all randomized patients have completed the 16 weeks or early discontinued from the trial, to support an early submission; a database lock for the primary analysis will then be performed. Further **interim** analyses may be conducted during the open label treatment period to support, for example, regulatory interactions **and/or regulatory filing**. Final analysis is planned to be performed at the end of the trial once all patients have completed the trial (including any follow-up period if applicable).
Rationale for change		To clarify that interim analyses are planned in this trial.

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Section to be changed		Section 8.1 Trial approval, patient information, informed consent
Description of change		One sentence was added: **The patient will continue with the assessments for which he/she consented at the beginning of the trial (as an adolescent).**
Rationale for change		To clarify that adolescents who achieve age of legal consent will continue with the assessments for which they consented at the beginning of the trial.
Section to be changed		Section 9.1 published references
Description of change		The following changes were made to the reference section: R22-2031 was updated: ~~Krause K, Kessler B, Weller K, *et al.* German version of ItchyQoL: validation and initial clinical findings. Acta Derm Venereol. 2013;93(5):562-568.~~**Desai NS, Poindexter GB, Monthrope YM, Bendeck SE, Swerlick RA, Chen SC. A pilot quality-of-life instrument for pruritus. J Am Acad Dermatol. 2008;59(2):234–44.** R24-3478 was added: R24-3478 **Desai NS, Poindexter GB, Monthrope YM, Bendeck SE, Swerlick RA, Chen SC. A pilot quality-of-life instrument for pruritus. J Am Acad Dermatol; 2008; 59(2); 234-244.** R24-3537 was added: R24-3537 **Lewis-Jones MS, Finlay AY. The children's dermatology life quality index (CDLQI): initial validation and practical use. Br J Dermatol; 1995; 132(6); 942-949**.
Rationale for change		To update list of references.
Section to be changed		Section 10.1.10 ISS – Combination of IASI & VISS
Description of change		Description of ISS was updated.
Rationale for change		To correct inconsistency.
Section to be changed		Section 10.2 Trial participant feedback
Description of change		The text was updated as follows: This trial will include an option for **adult** participants to complete anonymized questionnaires,'Trial Participant Feedback Questionnaire', to provide feedback on their clinical trial experience. Individual participant level responses will not be reviewed by investigators.

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Rationale for change		To clarify that the questionnaire is only available for adult participants.
Section to be changed		Section 10.2 Trial participant feedback
Description of change		The following text was removed: **Optional Caregiver Feedback Questionnaires:** If applicable, this trial will include an option for caregivers to complete anonymized questionnaires, 'Caregiver Feedback Questionnaire', to provide feedback on the clinical trial experience. Individual caregiver level responses will not be reviewed by investigators. Responses will be used by the sponsor to understand where improvements can be made in the clinical trial process. These questionnaires will not collect data about the participant's disease, symptoms, treatment effect, or AEs and therefore will not be part of the trial data or clinical trial report. The questionnaires will be implemented after local regulatory approval and after consent of the caregiver. Providing feedback is optional and not required for participation in the trial.
Rationale for change		A questionnaire for caregivers is not available. Therefore the related text to caregivers was removed.
Section to be changed		Several sections
Description of change		Corrected typos and spelling errors
Rationale for change		Administrative change

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

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