Clinical Trial Protocol

	Document Number:	**c23806995-04**
EudraCT No. **EU Trial No.**	N/A	
BI Trial No.	1368-0032	
BI Investigational Medicinal Product(s)	BI 655130	
Title	Phase IIa multicentre, randomized, double-blind, placebo-controlled, study to evaluate the safety, tolerability and efficacy of treatment with BI 655130 in adult patients with moderate to severe atopic dermatitis	
Lay Title	A study in patients with atopic eczema to test how effective BI 655130 is and how well it is tolerated	
Clinical Phase	Phase IIa	
Clinical Trial Leader	[redacted] Tel: [redacted] Fax: [redacted]	
Coordinating Investigator	N/A	
Status	Final Protocol (based on Global Amendment 03)	
Version and Date	**Version: 4.0**	**Date: 12 Feb 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	05 Nov 2018
Revision date	12 Feb 2020
BI trial number	1368-0032
Title of trial	Phase IIa, multicentre, randomized, double-blind, placebo-controlled, study to evaluate the safety, tolerability and efficacy of treatment with BI 655130 in adult patients with moderate to severe atopic dermatitis
Coordinating Investigator	N/A
Trial site(s)	Multi-centre trial
Clinical phase	IIa
Trial rationale	Although the pre-clinical data and rationale for the use of an IL-36R antagonist in atopic dermatitis (AD) are strong, there are no data on the use of an IL-36 receptor antagonist in patients with AD. Thus, a small proof of clinical concept study is planned to assess safety, tolerability and efficacy in patients with moderate to severe AD.
Trial objective(s)	The primary objectives of this trial are to investigate the safety, tolerability and efficacy of BI 655130 in adult patients with moderate to severe atopic dermatitis following repeated intravenous administrations of 600 mg compared to placebo.
Trial endpoints	Primary endpoint • Percentage change from baseline in EASI at Week 16 Secondary endpoint • Number of patients with drug related AEs • Absolute and percentage change from baseline in EASI at Week 4 • Proportion of patients with a 50% improvement from baseline in EASI (EASI50) at Week 4 and 16 • Proportion of patients with a 75% improvement from baseline in EASI (EASI75) at Week 4 and 16 • Change from baseline in SCORAD at Week 4 and 16 • Proportion of patients achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in IGA at Week 4 and 16
Trial design	Double-blind, randomised, placebo-controlled comparison of two groups over 16 weeks
Total number of patients randomised	Approximately 45 patients will be entered in the study
Number of patients on each treatment	30 patients in the active group 15 patients in the placebo group
Diagnosis	Adult patients with moderate to severe atopic dermatitis

Main in- and exclusion criteria	Inclusion Criteria (for complete list refer to Section 3.3.2)
	• Male or female patients, 18 to 75 years of age at screening
	• Diagnosis of atopic dermatitis for at least 1 year
	• Moderate to severe atopic dermatitis defined as:
	  o At least 10% Body Surface Area (BSA) of atopic dermatitis involvement at screening and baseline
	  o Eczema Area and Severity Index (EASI) of at least 12 at screening and at least 16 at baseline,
	  o Investigator Global Assessment (IGA) of at least 3 at screening and baseline
	• Documented history of inadequate response to topical corticosteroid as judged by the investigator
	• Willing to use a standard emollient for the duration of the study
	• Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per International Council on Harmonization (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 information.
	Exclusion Criteria (for complete list refer to Section 3.3.3)
	• Use of topical corticosteroids or other agents for atopic dermatitis within 7 days prior to first dose of trial treatment.
	• Use of systemic corticosteroids or other agents for atopic dermatitis within 4 weeks prior to first dose of trial treatment (for more details refer to Table 4.2.3.1: 1)
	• Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
	• Any documented active or suspected malignancy or history of malignancy within 5 years prior to the screening visit, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix. Use of any restricted medication as specified in Table 4.2.3.1: 1 or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator.
	• History of allergy/hypersensitivity to the systemically

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

	administered trial medication agent or its excipients.
	• Active systemic infections (Fungal and bacterial disease) during the last 2 weeks prior to first drug administration, per investigator assessment.
	• Relevant chronic or acute infections (exception: common cold) including human immunodeficiency virus (HIV) or viral hepatitis. A patient can be re-screened if the patient was treated and is cured from the acute infection.
	• Active or Latent TB:
	  • Patients with active tuberculosis are excluded.
	  • Patients with a positive QuantiFERON TB test during screening are excluded, unless:
	  ○ Patient had previous diagnosis of active or latent TB and has completed appropriate treatment per local practice/guidelines within the last 3 years and at least 6 months before first administration of trial medication under this protocol (patients may be re-screened once to meet this criterion)
	  ○ Patients with suspected false positive or indeterminate QuantiFERON TB result may be re-tested once
	  ○ If QuantiFERON TB test result is not available or providing indeterminate results after repeat testing: A tuberculin skin test reaction ≥10mm (≥5mm if receiving ≥15mg/d prednisone or its equivalent) is considered positive.
	• Evidence of a current or previous disease, medical condition other than atopic dermatitis, surgical procedure, psychiatric or social problems, medical examination finding, or laboratory value at screening outside the reference range that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol, comply with all study visits/procedures or to complete the trial, compromise the safety of the patient or compromise the quality of the data.
	• Major surgery (major according to the investigator) performed within 12 weeks prior to first study drug adminstration or planned during the study (e.g. hip replacement, aneurysm removal, stomach ligation).
	• Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold Upper Limit of Normal (ULN) elevation in AST or ALT or alkaline phosphatase, or >2-fold ULN elevation in total bilirubin.

Test product(s)	BI 655130

dose	600 mg every 4 weeks
method and route of administration	Intravenous (i.v)
Comparator product(s)	Placebo
dose	Matching placebo
method and route of administration	Intravenous (i.v.)
Duration of treatment	Up to 32 weeks
Statistical methods	Restricted maximum likelihood estimation based on a mixed-effect model for repeated measures analysis will be used to obtain adjusted means for the treatment effects of the primary endpoint percent change in EASI Score. This model will include discrete fixed effects for treatment at each visit and stratification factor Asian/Non-Asian, and continuous fixed effects for baseline at each visit. The primary treatment comparisons will be the contrast between treatments at Week 16. To compare proportion of patients reaching EASI 50 or 75, or having IGA 0 and 1, the Cochran-Mantel-Haenszel test will be used. Safety data will be presented using descriptive methods. An interim analysis will be conducted when 75% of the patients have completed at least 4 weeks of treatment.

FLOW CHART

Randomised Treatment Period

Trial Periods	Screening											
Visit	**1**	**2[1]***	**3**	**4**	**5**	**6**	**7[17] Re-allocation**	**8**	**9**	**10 (EoS for R)[2]**	**11 End of Study (EoS)/FU1 (NR) [3,18]**	**End of Study Safety Phone Call (NR)[20]**
Day	-28 to -7	1	15	29	57	85	113	141	169	197	228 - 309	309
Week	-4 to -1		2	4	8	12	16	20	24	28	32 - 44	44
Time window for visits			±3 days	±3 days	±3 days	±3days	±3 days	±3 days	±3 days	±3 days	±3 days	+/- 3 days
Screening/baseline												
Informed consent for main study	X											
Informed consent for PGx Sampling	X											
Demographics	X											
Smoking History	X											
Medical history	X											
Review of in-/exclusion criteria	X	X										
Randomisation		X										
Physician and Patient Assessments												
Investigator Global Assessment (IGA)[17]	X	X	X	X	X	X	X	X	X	X	X	
EASI[17]	X	X	X	X	X	X	X	X	X	X	X	
SCORAD[17]	X[19] (BSA only)	X	X	X	X	X	X	X	X	X	X	
DLQI[17]		X	X	X	X	X	X	X	X	X	X	
All AEs/SAEs/AESIs**	X	X	X	X	X	X	X	X	X	X	X	X
Treatment												
Administer trial drugs		X		X	X	X	X[16]	X[16]	X[16]	X[16]		
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Re-allocation							X					
End of Study Completion Call in IRT										X (R)	X[22] (NR)	X[22] (NR)
Safety												
Physical examination[4]	X[C]	X[T]	X[T]	X[T]	X[T]	X[T]	X[C]	X[T]	X[T]	X[C,T]	X[C]	

Trial Periods	Screening											
Visit	**1**	**2[1]***	**3**	**4**	**5**	**6**	**7[17] Re-allocation**	**8**	**9**	**10 (EoS for R)[2]**	**11 End of Study (EoS)/FU1 (NR) [3,18]**	**End of Study Safety Phone Call (NR)[20]**
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Week	-4 to -1		2	4	8	12	16	20	24	28	32 - 44	44
Time window for visits			±3 days	±3 days	±3 days	±3days	±3 days	±3 days	±3 days	±3 days	±3 days	+/- 3 days
Vital signs[5]	X	X	X	X	X	X	X	X	X	X	X	
Safety Laboratory tests (blood and urine)[6]	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy testing[7]	X[S]	X[U, (S)]		X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[21]
12 lead-ECG (local)[8]	X	X	X	X	X	X	X	X	X	X	X	
Infection Testing[9]	X									X	X	
Biomarker and PK sampling												
Skin Biopsies -Lesional (L) and non lesional (NL)[10]		X (L;NL)		X (L)			X (L)			X(L optional)	X(L optional)	
Photographs of skin lesion[11]		X		X	X	X	X					
Skin Tape stripping[12]		X (L;NL)		X(L)			X(L)			X (L optional)	X (L optional)	
ADA/Nab[13]		X	X	X	X	X	X	X	X	X	X	
PK Sampling[13]		X	X	X	X	X	X	X	X	X	X	
Blood sample for RNA sequencing[13]		X		X	X	X	X					
Blood sample for DNA resequencing[13]		X										
Microbiome sample for 16S sequencing [14]		X (L,NL)		X (L,NL)			X (L,NL)					
Blood sample – soluble protein[13] biomarker		X		X	X	X	X	X	X	X	X	
Blood sample – Optional PGx Sampling[15]		X[15]										

ADA, anti-drug antibody; AE, adverse events; AESI, adverse event of special interest; C, complete physical examination; DLQI, dermatology life quality index; EASI, Eczema Area and Severity Index; ECG, electrocardiogram; EOS, End of Study; L, lesional; PGx, pharmacogenomics; NL, non lesional; PK, pharmacokinetic; SAE, serious adverse event; SCORAD, SCORing of Atopic Dermatitis; T, targeted physical examination; TB, tuberculosis

(*) Day of Randomisation / Day of first intake of randomised medication = Day 1.
(**) After the individual patient's end of the trial the investigator should report only any occurrence of cancer, related SAEs and related AESIs of which the investigator may become aware of and only via the SAE form. Please refer to Section 5.2.5.2.

1- Initiation of randomized treatment at Visit 2 can only begin if the patient meets the criteria for Initiation of Treatment. Please refer to Sections 3.3.2 and 3.3.3.
2- At Visit 10, Non- Responders (NR) will receive their last study drug administration and Responders (R) will have their End of Study (EoS) visit.
3- Should a patient prematurely discontinue before their scheduled EoS every effort should be made to keep the patient in the trial and complete all of the remaining study visits or at a minimum an early EoS visit. Patients who prematurely discontinue before V7/Wk16 are considered Non-Responders.
4- C = Complete Physical Examination (PE) includes general appearance as well as evaluation of all organ systems; T = Targeted physical examination includes evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities. At Visit 10 complete physical examination will be performed for Responders (EOS), targeted physical examination will be performed for Non-Responders. Please refer to Section 5.2.1.
5- Vital signs will be assessed at predose, at approximately 5 minutes after the end of infusion, and 60 mins after the end of infusion at visits with i.v. administration.
6- Safety laboratory tests include clinical chemistry, haematology, coagulation, and urinalysis, and will be performed centrally. Local Labs may to be used for dosing decisions prior to i.v. administration. Please refer to Section 5.2.3.
7- Only applicable for women of childbearing potential. S – serum pregnancy test (performed at screening). U – urine pregnancy tests will be performed at all other visits indicated in the Flow chart. Urine pregnancy testing should be done prior to administration of study drug. Study drug should only be administered in case of a negative test result. (S) - in case of a positive urine pregnancy test, a serum pregnancy test will be done. Please refer to Section 5.2.5.2.
8- ECG measurements should always precede blood sampling and drug administration. Clinically significant abnormal findings should be reported as AEs in the eCRF.
9- Infection testing includes tuberculosis, hepatitis B, hepatitis C, and HIV assessments. Please refer to Table 5.2.3: 1. For the EoS visit only tuberculosis and hepatitis B testing will be performed. For Responders the Infection testing will be conducted at V10 (Week28) which corresponds to their EoS. For Non Responders the Infection testing will be conducted at V11.
10- One (1) lesional (L) and One (1) non-lesional (NL) biopsy will be collected at V2 (baseline), One (1) lesional (L) biopsy will be collected at V4 (Week 4) and at V7 (Week 16). One (1) optional lesional (L) will be collected at EoS (V10 for Responders or V11 for Non-Responders). Each skin biopsy of 4.5 mm punch (split into half for IHC and RNASeq) should be collected prior to trial drug infusion.
11- Photographs of skin lesions are to precede skin biopsies and study drug administration. Please refer to Section 5.6.
12- Skin tape stripping samples will be collected as close as possible to the site of the skin biopsy and at the same timepoint. Skin tape stripping samples must be taken before biopsies are taken and before trial drug infusion. One (1) L and one (1) NL at V2; one (1) L at V4 (Week 4) and V7 (Week 16); and one (1) optional lesional (L) at EoS(V10 for Responders or V11 for Non-Responders) .
13- pre dose PK and ADA and Nab samples will be collected within 2 hour period prior to infusion. In addition, all biomarkers samples will be collected prior to trial drug infusion. Please refer to Section 5.3.
14- Microbiome samples must be taken before biopsies are taken and before trial drug infusion.
15- Deoxyribonucleic acid (DNA) banking sample is optional. Participating patients are required to give informed consent specifically for this banking. Blood sample will be collected in a PAX-gene Blood DNA tube at day 1 (Visit 2). If not possible at Visit 2, this sample may also be collected during a later visit. The DNA banking sample must be collected prior to infusion of the trial drug infusion.
16- At V7 (Week 16) all patients will be evaluated with the EASI score. Non-responders will be re-allocated to receive BI open label trial drug from V7 (Week 16) onward until V10 (Week 28). Responders will be re-assigned to no treatment from V7 (Week 16) onward until V10 (Week 28) but will be expected to come to all visits.

17- All assessments must be done prior to trial drug infusion. The questionnaires completed by patients should be done first before the investigator assessments. Please refer to Section 6.2.
18- For Responders (R) the EoS visit must be completed 16 weeks after last treatment, which is at the latest at Week 28 (V10). Responders (R) may complete EOS at any point after V7 (Week 16) if the patient drops to an EASI 50 score prior to the planned EOS. For Non Responder (NR) patients who have achieved EASI 50 and plan to participate in the extension trial, the EoS visit will be completed no earlier than Week 32. Non Responder patients not participating in the extension trial will complete a V11/FU1 visit between Week 32-44. If a patient should discontinue treatment prematurely every effort should be made to keep the patient in the trial and complete all of the remaining study visits or at a minimum an early EoS visit 16 weeks after last treatment.
19- At V1 (Screening) BSA will be assessed for eligibility. From V2 (baseline) onward BSA will be completed as part of SCORAD assessment.
20- Only Non-Responders not participating in the open label extension trial must complete an End of Study Safety Phone Call. V11 and End of Study Safety Phone call can occur on the same day only if the Residual Effect Period (16 weeks after last trial drug infusion) has been reached (WK44). The phone call cannot be performed before the V11.
21- Patients will be asked about their pregnancy status at the End of Study Safety Phone Call.
22- For Non-Responders participating in the open label extension trial, End of Study completion IRT call is registered at V11 as the End of Study Safety Phone Call is not required. For Non-Responders not participating in the open label extension trial, End of Study completion IRT call is registered only at End of Study Safety Phone Call (WK44). V11 is not registered in IRT.

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ABBREVIATIONS

AD	Atopic Dermatitis
ADA	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALQ	Above limit of quantification
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
CA	Competent Authority
CDC	Complement Dependent Toxicity
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organization
CTL	Clinical Trial Leader
CTP	Clinical Trial Protocol
CTM	Clinical Trial Manager
DBL	Database Lock
DILI	Drug Induced Liver Injury
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EoS	End of Study
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
GCP	Good Clinical Practice

GMP	Good Manufacturing Practice
GPP	Generalised Pustular Psoriasis
HA	Health Authority
i.v.	intravenous
IBD	Inflamatory Bowel Disease
ICH	International Council on Harmonization
IEC	Independent Emmittee
IGA	Investigator's Global Assessment
IHC	Immunohistochemistry
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LLOQ	Lower limit of quantification
LPLT	Last Patient Last Treatment
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed model with repeated measurements
Nab	Neutralizing Antibody
NOAEL	No-observed-adverse-effect level
OPU	Operative Unit
PBMC	Peripheral blood mononuclear cell
PK	Pharmacokinetics
PPP	Palmoplantar Pustulosis
RA	Regulatory Authority
RCTC	Rheumatology Common Toxicity Criteria
REML	Restricted maximum likelihood
REP	Residual Effect Period
s.c.	subcutaneous
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Standard Deviation
SCORAD	SCORing of Atopic Dermatitis
SoC	Standard of Care

SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMDD	Target-Mediated Drug Disposition
TSAP	Trial Statistical Analysis Plan
ULN	Upper Level of Normal
ULOQ	Upper limit of quantification
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Atopic Dermatitis (AD) is an immune-mediated skin disease characterized by chronic or relapsing red and inflamed skin (erythema) and an intense and unrelenting itch (prutitis). In common terminology AD is often referred to as Eczema, the term for a variety of skin conditions, of which AD is the most severe. Diagnosis is based on a patient's medical history, characteristic clinical findings and exclusion of other skin conditions [P18-07868]. The hallmark of AD is pruritus that is responsible for much of the disease burden for patients and their families. Pruritus can be persistent and consequently can disrupt sleep and/or cause anxiety or depression [R18-2681, R18-2680]. Other clinical features of AD include skin dryness, erythema (redness), oozing, crusting, and lichenification (skin that has become thickened and leathery).

Worldwide, the lifetime prevalence of AD has increased over the last 30 years occurring in 10–20% of the population in developed countries. Prevalence is lower, but increasing, in developing countries [R18-2667]. Typically, AD develops during childhood with approximately 60% of cases occurring in the first year of life [P06-08156; R18-2668]. In about 70% of cases, the disease greatly improves or resolves in childhood, but the remaining 30% of patients go on to have a remitting and relapsing condition with repeated flares [R18-2668; R18-2663].

AD appears to have a more heterogeneous pathophysiology than previously thought. Unlike chronic plaque psoriasis that is almost exclusively driven by the Th17 pathway, AD involves multiple immune axes involving expression of multiple cytokines and chemokines, including IL-13, IL-4, IL-33, IL-17 and IL-22. IL-36 is thought to have a pivotal role in amplifying these immune pathways and may be a critical link between S. aureus infection and exacerbation of AD inflammation.

In human skin tissues, IL36R is expressed in keratinocytes, dermal fibroblasts and infiltrating myeloid cells. IL36R activation in skin tissue drives the production of inflammatory mediators (e.g. CCL20, MIP-1β, TNF- β, IL12, IL17, IL23, TGF- β) and modulates the expression of tissue remodeling genes (e.g. MMPs, TGF- β). The link between IL36R and AD is based on data demonstrating upregulation of human IL36R and IL36γ (and IL36α) expression in AD skin biopsies compared to normal control skin as well as data showing IL36R functionality in disease relevant primary human cells. In addition, there is data demonstrating enhanced IL-36 signaling in human macrophages via the TH2 cytokine (IL4) pathway.

Recent data suggest that IL36R may also play a role in the pathogenesis of AD via a specific pathway related to *S. aureus* infection [R18-2666, R18-2669]. These papers show epicutaneous infection with *S. aureus* induces an inflammatory response mediated by IL-36 pathway and that IL36R deficiency or blockade results in a reduction of the skin inflammation induced by *S. aureus* derived virulent PSMα peptides [R18-2666, R18-2669]. These studies demonstrated a clear link to the IL36 pathway suggesting IL36 pathway activation may represent an early and persistent event in the development of AD disease.

1.2 DRUG PROFILE

1.2.1 Mode of Action

BI 655130 is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signaling. Binding of BI 655130 to IL36R is anticipated to prevent the activation of IL36R by cognate ligands (IL36 α, β and γ) and subsequent downstream activation of pro-inflammatory and pro-fibrotic pathways with the aim to reduce epithelial cell/ fibroblast/ immune cell-mediated inflammation and interrupt the inflammatory response that drives pathogenic cytokine production in inflammatory diseases including AD, generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP) and inflammatory bowel disease (IBD).

1.2.2 Nonclinical pharmacology

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 peripheral blood mononuclear cell (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

As BI 655130 does not demonstrate adequate pharmacological activity in common toxicology species, a surrogate antibody (BI 674304) specific for mouse IL36R was developed and used for toxicology assessments. In a 13-week intravenous toxicity study of BI 674304 in mice, no adverse effects of IL36R antagonism were 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. 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.

In intravenous toxicity studies of up to 26 weeks in duration in mice, no adverse effects of IL36R antagonism were seen at a dose that was 5 fold higher than the dose predicted for human studies. Based on these results, the no-observed-adverse-effect level (NOAEL) was considered to be 50 mg/kg/dose.

In developmental and reproductive toxicity studies there was no evidence of effects on fertility or embryonic development in mice after administration of 50 mg/kg/dose of BI 674304 in directed fertility and embryonic development studies.

1.2.3 Clinical experience

As of April 2019, five clinical phase I trials and one clinical phase II trial have been completed for BI 655130; 4 phase I trials were conducted in healthy volunteers (HV), 1 phase I trial in GPP patients and 1 phase II trial in PPP patients.

A total of 187 healthy volunteers have been exposed to single or multiple doses of BI 655130 in 4 phase I studies which assessed safety, tolerability, PK and PD of BI 655130 in healthy volunteers [c09985235-01].

- Study 1368.1 was a single escalating dose trial with i.v. infusions of placebo or BI 655130 up to 10 mg/kg [c09985235-01]. The most frequently reported treatment-emergent AEs were nasopharyngitis (BI 655130: 20.7%; placebo: 15.0%), headache (BI 655130: 8.6%; placebo: 15.0%), influenza like illness (BI 655130: 6.9%; placebo: 10.0%), and diarrhoea (BI 655130: 3.4%; placebo: 10.0%). All AEs were of mild or moderate intensity and were resolved by the end of the trial.There were no serious AEs and no AEs that led to discontinuation of trial drug.
- Study 1368.2 was a multiple rising dose trial with subjects receiving up to 20 mg/kg in a single intravenous infusion weekly for 4 weeks. The incidence of nervous system disorders (especially headache) appeared to be higher in the 20 mg/kg BI 655130 group than in the other treatment groups. Two subjects experienced dyspnoea only in the 20 mg/kg group. Additionally, gastrointestinal disorders (diarrhoea and nausea) and nasopharyngitis appeared to occur more often in subjects who received BI 655130 than in subjects who received placebo. Infusion related reaction, decreased appetite, and anxiety were reported for 1 subject in the 20 mg/kg BI 655130 treatment group.
- Study 1368.3 was a relative bioavailability trial in 36 subjects of a subcutaneous (s.c.) formulation of BI 655130 at two different dose strengths (150 mg and 300mg). The most frequent local events reported were redness and swelling at the injection site, all were mild in intensity, occurred within 30 minutes after injection and completely resolved within 4 hours. There were no reports of injection site pain.
- Study 1368.9 was a single rising dosing trial in 32 Japanese healthy volunteers receiving different i.v. doses of BI 655130 (300 mg, 600 mg, and 1200 mg) or one subcutaneous dose (300 mg). Adverse events by preferred term reported on placebo were vomiting, chest incomfort, 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 first study in patients was conducted as an open-label, single arm phase I study to explore the safety, tolerability, PK and efficacy of BI 655130 in GPP (1368.11). A total of 7 patients with acute GPP were enrolled and treated with a single intravenous dose of BI 655130 (10 mg/kg). Proof-of-concept was achieved with the first 7 patients treated, who showed rapid clinical responses to single administrations of BI 655130 with good safety and

tolerability. The early response in the skin was also accompanied by an early and rapid response in systemic components (C-Reactive Protein [CRP] approaching normalization within 4 weeks). All patients (7/7) reported at least 1 AE while on-treatment and in 4 patients (57.4%) AEs considered drug-related by the investigators were reported. None of the reported AEs was severe, serious or led to discontinuation.The most frequently reported treatment-emergent AE was arthralgia (3 out of 7 patients [42.9%]). Eosinophilia, chills, oedema peripheral, pyrexia, upper respiratory tract infection, and eczema were each reported in 2 patients [28.6%]

Study 1368.15, a randomised placebo controlled study investigated the safety, tolerability, pharmacokinetics, pharmacogenomics and efficacy of 2 intravenous doses of BI 655130 in 59 patients with palmoplantar pustulosis psoriasis. Patients were randomized in a 1:1:1 allocation ratio and received either 900 mg BI 655130, 300 mg BI 655130 or placebo intravenously every 4 weeks over a period of 12 weeks. 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). However, post-hoc subgroup analyses indicated efficacy of both doses of BI 655130 in patients with more severe PPP disease at baseline (above the median PPPASI value of 16.7). In particular, the results on pustule severity were pronounced with a rapid reduction in pustule severity with evidence of a dose response relationship.

In total, 85.7% in the placebo arm and 89.5% in each of the BI 655130 arms (300 mg and 900 mg) reported at least 1 AE while on treatment. There were 3 AEs leading to discontinuation of trial drug in the placebo arm (14.3%), whereas 1 patient in the 300 mg dosing arm (5.3%) and 3 patients in the 900 mg dosing arm (15.8%) discontinued trial medication due to an adverse event. The most frequently reported treatment-emergent AE were nasopharyngitis (placebo 38.1%, 300 mg BI 655130 26.3%, 900 mg BI 655130 42.1%) and headache (placebo 33.3%, 300 mg BI 655130 21.1%, 900 mg BI 655130 31.6%).

PK data indicate target-mediated drug disposition (TMDD) of BI 655130. The saturation of the non-linear elimination pathway is likely occurring after 0.3 mg/kg and BI655130 exhibits linear kinetics at dose-level greater than 0.3 mg/kg. The half-life of BI655130 is approximately 4 weeks in the linear dose range and thus similar to otherIgG1 molecules.

In one patient an infusion related reaction was reported. The patient felt “heat” after the infusion of the trial medication during Visit 3. The event was not accompanied by other symptoms, in particular vital signs remained stable. The patient recovered without treatment. There were no clinically relevant abnormalities on treatment with BI 655130 with respect to safety laboratory and vital signs.

Summary
BI 655130 has been tested and found safe and tolerable in humans in single and multiple rising dose trials 1368.1, 1368.2, 1368.3 and 1368.9 in healthy male and female subjects and in trial 1368.11 in GPP patients and in trial 1368.15 in PPP patients. The most frequently reported treatment-emergent AEs were viral upper respiratory tract infection, nasopharyngitis, headache, influenza like illness and injection site erythema, without any dose-dependency. One potential infusion reaction has been reported in a subject who

discontinued his third infusion of BI 655130 in 1368.2. All AEs were resolved by the end of the trial. There were no relevant changes in safety laboratory tests, vital signs, or ECGs

For further details and most up-to-date results refer to the current "Investigator`s Brochure" [c03320877-05].

1.3 RATIONALE FOR PERFORMING THE TRIAL

Although the pre-clinical data and rationale for the use of an IL-36R antagonist in AD are strong, there are no clinical data on this mechanism of action in AD. Thus, a small proof of clinical concept study is planned to assess safety, tolerability and efficacy in patients with moderate to severe AD.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see Section 5.4). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

The positive efficacy data obtained in GPP (trial 1368.11) confirms BI 655130's mechanism of action of effectively blocking the IL36 pathway thereby providing support for potential benefit in diseases where the IL36 pathway appears to contribute to disease. Furthermore, the clinical safety data support clinical studies in patients with repeat doses up to 20mg/kg IV qw.

There is no direct benefit for individual participants in this study, because efficacy of BI 655130 has not been demonstrated in AD and because some patients will initially be randomised to the placebo arm. Participation in this study may help to generate future benefit for larger groups of patients with atopic dermatitis if BI 655130 proves to be successful in treating this disease. In order to assess any future benefit for atopic dermatitis patients, it is critical to have a placebo control to address potential confounding factors, such as placebo effect, regression to the mean in endpoint scoring or potential investigator bias in safety and efficacy assessments. Patients who are initially randomized to placebo and do not respond will be given the opportunity to receive BI 655130 after the Week 16 primary analysis.

One subject in trial 1368.2 appeared to have an infusion reaction at a dose of 20 mg/kg, thus patients in this trial will be closely monitored for infusion reactions, including measurement of pulse and blood pressure prior to infusion and approximately 5 and 60 minutes after the end of infusion.

Humans with congenital absence of IL36R have no adverse clinical signs or symptoms, including susceptibility to infection or reactivation of chronic infections. Nonetheless, given this is the first trial in patients with atopic dermatitis, patients with active infection or certain chronic infections (HIV, HBV, TB) will be excluded.

The mouse specific analogue of BI 655130 has been tested in embryo-fetal and fertility and early embryonic development studies. There was no evidence of effects on fertility or embryonic development (teratogenicity) in mice after administration of 10 or 50 mg/kg/dose.

Thus, men and women of child bearing potential with appropriate birth control can be included in clinical trials with BI 655130. Women of child bearing potential with appropriate birth control can be included in clinical trials with BI 655130 but must maintain a highly effective method of contraception throughout the course of trials with BI 655130 and up to 16 weeks after the last study drug infusion. Contraception of male trial precipitants and female partners of male trial participants are not required based on the toxicity studies conducted in mice. Due to the outcome of the completed teratogenicity study a double barrier method of contraception is not required.

Currently there are no data available allowing the conduct of clinical trials in pediatric patients, pregnancy and lactation. Until such data are available, these patients will be excluded from this study (1368-0032).

Currently there are no data available to suggest interactions of BI 655130 with other drugs [c03320877-05].

Considering the medical need for development of an effective and well tolerated drug for the therapy of AD, the benefit of this trial is considered to outweigh the potential risks and justifies the administration of multiple doses of BI 655130 to patients with AD to investigate safety, tolerability and efficacy.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this trial is to investigate the safety, tolerability and efficacy of BI 655130 in patients with AD following multiple intravenous administrations of 600 mg compared to placebo.

While the main objective is to assess safety and tolerability of BI55130 in patients with AD, these endpoints can only be analyzed descriptively. Thus, the endpoints to be discussed below will focus on efficacy endpoints that are more amenable to other statistical analyses and where sample size considerations may be more relevant.

A description of the endpoints to be determined, and the observations along with specific information as how to collect the data for that information, is provided in Section 5.

2.1.2 Primary endpoint

The primary efficacy endpoint for this trial is the percentage change from baseline in the Eczema Area and Severity Index (EASI) Score at Week 16.

2.1.3 Secondary endpoint(s)

Secondary efficacy endpoints are

- Number of patients with drug related AEs
- Absolute and percentage change from baseline in EASI at Week 4
- Proportion of patients with a 50% improvement from baseline in EASI (EASI50) at Week 4 and 16
- Proportion of patients with a 75% improvement from baseline in EASI (EASI75) at Week 4 and 16
- Change from baseline in SCORAD at Week 4 and 16
- Proportion of patients achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in IGA at Week 4 and 16

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

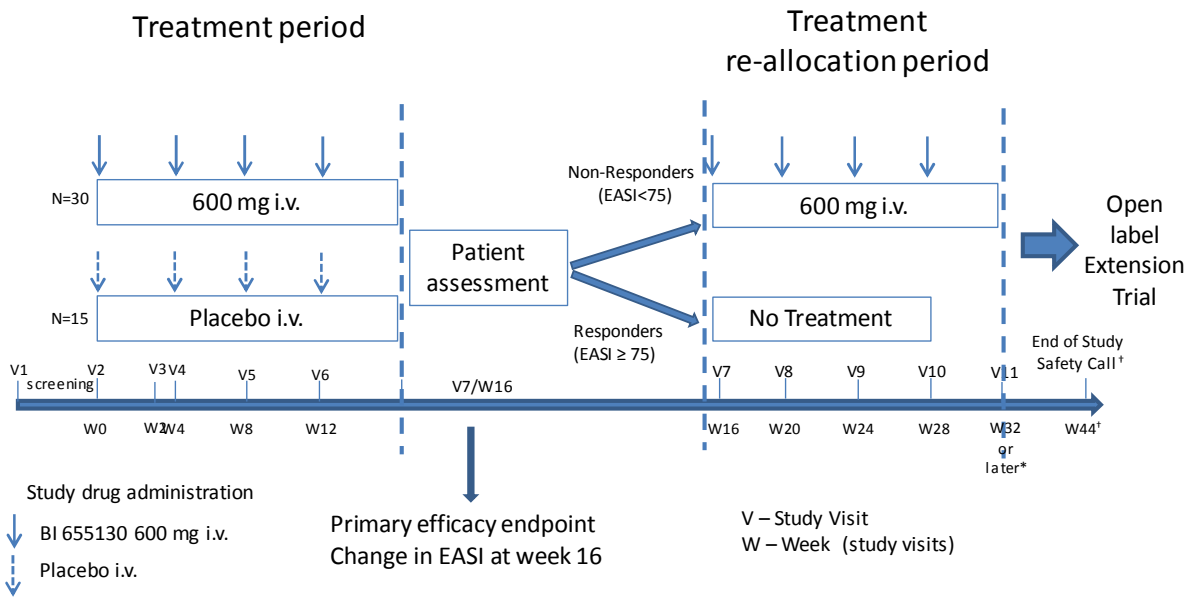
3.1 OVERALL TRIAL DESIGN AND PLAN

This is a double-blind, placebo-controlled study assessing the safety, tolerability and efficacy of 600 mg BI 655130 compared to placebo given intravenously every 4 weeks in patients with moderate to severe atopic dermatitis. Safety and tolerability will be evaluated based on AE data collected and physical examination at every visit. At W16 patients will be evaluated for response to treatment by the change in EASI score compared to baseline. Patients who have responded, defined as having attained at least 75% reduction in EASI score compared to baseline will no longer receive treatment and will be followed at W 20, 24 and 28 to evaluate the sustainability of their response. If this patient reaches a 50% reduction in EASI score compared to baseline prior to the planned EOS at Week 28, they will immediately perform EOS and will be given the opportunity to receive treatment in an open label extension trial.

Patients who have not responded, defined as attained less than 75% reduction in EASI score compared to baseline will receive 600 mg BI 655130 at W16, 20, 24 and 28. Patients re-allocated to treatment, who reach EOS will be offered participation in the extension trial if they meet the eligibility criteria.

After re-allocation at Week 16, a patient will know what treatment they are on but will remain blinded to the treatment received until Week 16.

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 randomization (active: placebo) is warranted in order to maximize the number of patients receiving active treatment and is being controlled for from a statistical standpoint. The rationale for switching responding patients to follow-up with no-treatment at Week 16 is to evaluate the duration of clinical response off treatment. In addition, patients who have not attained at least a 75% reduction in EASI score compared to baseline will have the opportunity to receive (or continue) active treatment.

3.3 SELECTION OF TRIAL POPULATION

3.3.1 Main diagnosis for trial entry

This study will include adult patients diagnosed with atopic dermatitis for at least 1 year who developed moderate to severe atopic dermatitis with documented inadequate response to topical corticosteroid and be willing to discontinue topical corsticosteroid 7 days or systemic corticosteroid 4 weeks before first administration of trial treatment.

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. Signed and dated written informed consent in accordance with Good Clinical Practice (GCP) and local legislation prior to the start of any screening procedures
2. Male or female patients, 18 to 75 years of age at screening
3. Diagnosis of atopic dermatitis for at least 1 year
4. Moderate to severe atopic dermatitis defined as:
    - At least 10% Body Surface Area (BSA) of atopic dermatitis involvement at screening and baseline
    - Eczema Area and Severity Index (EASI) of at least 12 at screening and at least 16 at baseline
    - Investigator Global Assessment (IGA) of at least 3 at screening and baseline
5. Documented history of inadequate response to topical corticosteroid as judged by the investigator
6. Willing to use a standard emollient for the duration of the study
7. Women of childbearing potential (WOCBP)[2] 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

[2] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.

than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

3.3.3 Exclusion criteria

1. Use of topical corticosteroids or other agents for atopic dermatitis within 7 days prior to first dose of trial treatment.
2. Use of systemic corticosteroids or other agents for atopic dermatitis within 4 weeks prior to first dose of trial treatment (for more details refer to Table 4.2.3.1: 1).
3. Women who are pregnant, nursing, or who plan to become pregnant while in the trial. Women who stop nursing before the study drug administration do not need to be excluded from participating; they should refrain from breastfeeding up to 16 weeks after the last study drug administration (see Section 4.2.3.3)
4. Patient with a transplanted organ (with exception of a corneal transplant > 12 weeks prior to screening) or who have ever received stem cell therapy (e.g., Prochymal).
5. Any documented active or suspected malignancy or history of malignancy within 5 years prior to the screening visit, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
6. Use of any restricted medication as specified in Table 4.2.3.1: 1 or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator.
7. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients.
8. Active systemic infections (Fungal and bacterial disease) during the last 2 weeks prior to first drug administration, per investigator assessment.
9. Relevant chronic or acute infections (exception: common cold) including human immunodeficiency virus (HIV) or viral hepatitis. A patient can be re-screened if the patient was treated and is cured from the acute infection.
10. Active or Latent TB:

Patients with active tuberculosis are excluded.
Patients with a positive QuantiFERON TB test during screening are excluded, unless:

- Patient had previous diagnosis of active or latent TB and has completed appropriate treatment per local practice/guidelines within the last 3 years and at least 6 months before first administration of trial medication under this protocol (patients may be re-screened once to meet this criterion)
- Patients with suspected false positive or indeterminate QuantiFERON TB result may be re-tested once
- If the QuantiFERON TB test result is not available or provides indeterminate results after repeat testing: A tuberculin skin test reaction ≥10mm (≥5mm if receiving ≥15mg/d prednisone or its equivalent) is considered positive.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

11. Currently enrolled in another investigational device or drug trial, or less than 30 days or 5 half lives, whichever is longer since ending another investigational device or drug trial(s), or receiving other investigational treatment(s).
12. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse or any condition) other than AD, surgical procedure, psychiatric or social problems, medical examination finding (including vital signs and 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 study participant unreliable to adhere to the protocol, comply with all study visits/procedures or to complete the trial compromise the safety of the patient or compromise the quality of the data.
13. Major surgery (major according to the investigator) performed within 12 weeks prior to first study drug adminstration or planned during the study (e.g. hip replacement, aneurysm removal, stomach ligation).
14. Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold Upper Limit of Normal (ULN) elevation in AST or ALT or alkaline phosphatase, or >2-fold ULN elevation in total bilirubin.

3.3.4 Withdrawal 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.

Every effort should be made to keep the patients in the trial: if possible on treatment, or at least 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 Electronic Case Report Form (eCRF). If the reason for discontinuation is death, this should be reported on the SAE form as well, regardless of causal relationship.

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, 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 investigational medicinal product or other trial treatment, please see Section 4.2.3.
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy).

- For individual stopping rules related to specific adverse events, please see Section 4.2.

In case of a temporary discontinuation of trial treatment, trial treatment should be restarted as soon as medically justified, please see Section 4.1.4, 4.2.2. Even if the trial treatment is discontinued, the patient remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart 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 (BI) 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. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
3. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

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

The investigational product has been manufactured by BI Pharma GmbH & Co. KG, Biberach, Germany. The BI 655130 molecule is an anti-human IL36 receptor monocloncal antibody heterodimer with a molecular weight of approximately 146 kDa.

BI 655130 solution for infusion (i.v. administration) is formulated at 60 mg/mL presented in a 10 mLvial with a nominal fill volume of 7.5 mL (450 mg).

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Study Compound

Substance:	BI 655130
Pharmaceutical formulation:	Solution for infusion
Source:	BI Pharma GmbH & Co. KG, Biberach, Germany
Unit strength:	BI 655130 450 mg/vial (60 mg/mL), 7.5 mL fill volume
Posology:	600 mg i.v. infusion once every 4 weeks
Method and route of administration:	i.v. infusion

Table 4.1.1: 2 Placebo comparator

Substance:	Placebo
Pharmaceutical formulation:	Solution for infusion
Source:	BI Pharma GmbH & Co. KG, Biberach, Germany
Unit strength:	Placebo to BI 655130 450 mg/vial (60 mg/mL), 7.5 mL fill volume
Posology:	0 mg i.v. infusion once every 4 weeks
Method and route of administration:	i.v. infusion

At the time of use the i.v. solutions for dosing will be prepared as detailed in the instruction in the ISF.

4.1.2 Selection of doses in the trial and dose modifications

A fixed rather than weight-based dose regimen of single dose of 600 mg has been selected. Early trials of therapeutic monoclonal antibodies often investigate body-weight–based regimens to reduce the inter-subject variability in drug exposure. However, there is generally only a modest contribution of body weight to the overall pharmacokinetic (PK) and pharmacodynamic (PD) variability of monoclonal antibodies. Furthermore, monoclonal antibodies are highly target specific and offer a relatively large therapeutic window compared to new chemical entities. Therefore, most monoclonal antibodies are approved at fixed doses in antibody/target excess in order to cover target turnover and maximize efficacy [R10-6267; R13-4749; R13-4753; R13-4750; R13-4754].

4.1.3 Method of assigning patients to treatment groups

An Interactive Response Technology (IRT) will be used to screen and randomise eligible patients, perform subsequent drug assignment, manage initial/re-supply ordering of drug supplies and handle emergency un-blinding. The investigator will receive all necessary instructions to access IRT from the Sponsor or chosen provider. Detailed IRT functions and procedures will be documented in the user requirement specifications mutually agreed to by the sponsor and the IRT vendor. Patients will be randomly assigned to one of the treatment groups through the assignment of medication which will be treatment group-specific (Section 3.1). For technical and statistical features of the treatment allocation process, please see. Sections 4.1.4 and 7.6.

During Visit 2 (W0) and after the patient's eligibility has been confirmed, the treatment will be assigned via IRT. Patients will be randomized to receive BI 655130 600 mg or placebo in a ratio of 2:1. The assignment will occur in a blinded fashion via IRT.

During Visit 7 (W16) patients will be evaluated with the EASI scoring system (see Section 5.1) and based on the response will be reassigned via IRT to receive BI 655130 600 mg or no treatment at all. The re-assignement will occur in an open label fashion.

4.1.4 Drug assignment and administration of doses for each patient

In all patients, the infusion solution is intended to be intravenously administered over a period of 90 minutes. In case of safety concerns, e.g. due to 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 minutes (3 hours). Further based on his/her medical judgment the investigator will provide medications as needed.

The administration of the trial medication will be done under the supervision of the investigating physician or a designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation, if correct dosage cannot be ensured otherwise.

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

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments until after the data base lock (DBL) for the primary analysis. The randomisation code will be kept secret by Clinical Trial Support up to the interim database lock at Week 16.

The randomisation codes will be provided to bioanalytics prior to last patient completed to allow for the exclusion from the analyses of pharmacokinetic (PK) samples taken from placebo patients. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded.

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 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. 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.

Trial medication must be securely stored, e.g. in a locked refrigerator or at a pharmacy. If the storage conditions are found to be outside the specified range, the Clinical Trial Manager

(provided in the list of contacts) must be contacted immediately. Refer to the storage conditions for trial medications (STORM) document in the ISF for additional information.

The medication may only be dispensed to trial patients according to the Clinical Trial Protocol (CTP) by authorized personnel as documented in the trial staff list.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the Institutional Review Board (IRB) / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority (CA),
- 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,
- 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 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

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the patient from participation (see Section 3.3), are permissible. All concomitant medications should be carefully evaluated by the investigator and the Clinical Trial Manager should be contacted when there are questions regarding concomitant medications.

During the trial, if the severity and progression of the disease worsens, the investigator can treat the patient with Standard of Care (SoC) of his/her choice. All efforts should be made to inform the patient of the importance of coming to the protocol specified visits (See Flow Chart) up to the EoS visit. Patients refusing to return to the study site for scheduled visits after the end of treatment should at least provide safety information by phone at the respective visits.

Overall, the choice of the escape treatment i.e Standard of Care treatment will be left at the discretion of the investigator. The sponsor will not provide/supply SoC treatment(s) to the sites. If a patient receives escape treatment the decision to maintain the patient on trial treatment will be decided with discussion between the investigator and sponsor.

4.2.2 Emergency procedures

Infusion reactions including anaphylactic reaction

In case of infusion reactions including anaphylactic reaction emerging during or after infusion of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to:

- Immediately interrupt the infusion
- Treat with systemic anti-histamines, i.v. steroids, and in case of a severe allergic reaction (eg, anaphylactic reaction) epinephrine

Also draw a plasma sample for IgE and ADA as detailed in the Lab Manual (Central laboratory). Consider also the evaluation of histamine, serum tryptase, and complement components.

In case of infusion reaction, based on patient's clinical course and medical judgment, the infusion may be re-initiated in case of mild or moderate infusion reactions (according to Rheumatology Common Toxicity Criteria (RCTC) V2) at lower speed with gradual increase to complete the infusion as detailed in the Instructions for Preparation and Handling of BI 655130 in the ISF. In any case, the total duration of infusion should not exceed 180 minutes (3 hours).

In case of potential systemic allergic reaction, blood samples for determination of serum tryptase will be collected 0.5 h, 2 h, 6 h, 24 h after onset of the event.

In case of suspected drug related anaphylactic reaction (Appendix 10.1.1) the investigator should discontinue treatment permanently with BI 655130.

Severe infections (according to RCTC V2), 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 BI 655130 may be restarted when the patient has recovered according to investigator's assessment.

Overall, the choice of Standard of Care treatment will be left at the discretion of the investigator. The sponsor will not provide/supply SoC treatment (s) to the sites.

4.2.3 Restrictions

4.2.3.1 Restrictions regarding concomitant treatment

The medications (or classes of medications) listed in Table 4.2.3.1: 1 must not have been taken before inclusion for the time periods as specified, and are not permitted throughout the study participation.

Patients are prohibited from receiving the following therapies, during trial treatment and prior to Visit 2 for the duration specified in the Table below.

Patients who are re-allocated as Non-Responders at Visit 7 (Week 16) and have not reached a 50% reduction in EASI score compared to baseline at End of Treatment are prohibited from receiving the following therapies through to End of Study:

Table 4.2.3.1: 1 Restricted medications

Medication or class of medications[1, 2]	**Restriction duration prior to Visit 2**
UVB phototherapy (including self-treatment with tanning beds or therapeutic sunbathing), PUVA	4 weeks
Hydroxyzine, diphenhydramine, doxepin[3]	1 week
Any other topical medication than the provided emollient (e.g. moisturizers containing urea, calcineurin inhibitors, topical corticosteroids)[4]	1 week
Azathioprine	4 weeks
Investigational products (including biologics)	30 days or 5 half-lives (whichever is longer)
IL36R inhibitors	before and during trial participation
All other biologics, including but not limted to: secukinumab (Cosentyx®) tildrakizumab (Ilumya®) rituximab, ustekinumab (Stelara®),	3 months or 5 half-lives (whichever is longer) 5.5 months prior to Visit 2 5 months priot to Visit 2 4 months prior to Visit 2

Medication or class of medications[1, 2]	**Restriction duration prior to Visit 2**
talizumab, alemtuzumab, guselkumab (Tremfya), ixekizumab (Taltz®), adalimumab (Humira®)	3 months prior to Visit 2
brodalumab (Siliq®), efalizumab, visilizumab, briakinumab, infliximab (Remicade®)	2 months prior to Visit 2
etanercept (Enbrel®)	6 weeks
live virus vaccinations	6 weeks
Any other systemic immunomodulating treatments (e.g. corticosteroids, cyclophosphamide), tofacitinib (Xeljanz®), apremilast (Otezla®) Any systemic immunomodulating treatments for atopic dermatitis including JAK inhitibors, PDE4 inhibitors, systemic steroids	30 days
retinoids	4 weeks no treatment initiation or dose escalation Must be discontinued prior to receiving the first dose of BI 65513/placebo

[1]In case of disease worsening, the use of standard of care (physician's choice) is left at the discretion of the investigator (refer to Section 4.2.1). Patient continuation on trial treatment will be reassessed based on the medication used for the disease worsening.
[2]This list is not all inclusive, for any medications that are not listed, contact the Clinical Trial Manager (CTM) for restriction duration
[3] Other antihistamines for indications other than atopic dermatitis can be prescribed on an as-needed basis. Dose should, preferably, be stable within one week prior to V2 and during the course of the study.
[4] No restriction on corticosteroid drops administered in the eye or ear; nasal corticosteroids to treat rhinitis;inhaled corticosteroids to treat asthma; Montelukast (systemic) to treat asthma or allergic rhinitis - if these medications were on stable maintenance dose for 3 months prior to Visit 2.

4.2.3.2 Restrictions on diet and life style

No specific restrictions on diet or life style of the patients are required
Patients should avoid prolonged exposure to sunlight and artificial UV light. Patients should only be using supplied emollient as instructed by the trial physician, instruction will be provided (see Section 6.2.2).

4.2.3.3 Contraception requirements

Women of childbearing potential (WOCBP) 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 information.

Female Patients:
Acceptable methods of birth control for this trial are:

- Combined (estrogen and progestogen containing) hormonal birth control associated with inhibition of ovulation.
- Progestogen-only hormonal birth control associated with inhibition of ovulation.
- Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS).
- Bilateral Tubal occlusion (blocking of the fallopian tubes).
- Vasectomy of sexual partner (proven effective by absence of sperm on the ejaculation).
- 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 16 weeks after, i.e. until BI 655130 is eliminated. They can start nursing again after this period.

4.3 TREATMENT COMPLIANCE

Administration of the trial medication will be done in the study center under the supervision of the investigator or a designee. The measured plasma concentrations will provide additional confirmation of compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Efficacy will be assessed using standard criteria that have been used in numerous AD studies, including the Eczema Area and Severity Index (EASI), the scoring of atopic dermatitis (SCORAD), Investigator Global Assessment (IGA) and Dermatology Quality of Life Index (DLQI).

The primary efficacy endpoint for this trial is percent change in EASI Score at Week 16 compared to Baseline. Secondary endpoints include EASI 50, EASI 75, SCORAD and IGA. An interim analysis of change in EASI at Week 4 will be conducted when 75% of patients have completed the Week 4 visit. The details of these assessments are described below.

EASI

The EASI scoring system is based on the psoriasis area and severity index (PASI) used routinely in patients with psoriasis to describe signs and severity of the disease. The principle of integrating disease extent and severity to describe disease led to the definition of the EASI [R18-2665]. The EASI score assesses the extent of disease at four body sites and measures four clinical signs: (1) erythema, (2) induration/papulation, (3) excoriation, and (4) lichenification, each on a scale of zero to three. The EASI score confers a maximum of 72 and evaluates two dimensions of AD: disease extent and clinical signs. The suggested severity strata for the EASI are as follows: 0 = clear; 0.1–1.0 = almost clear; 1.1–7.0 = mild; 7.1–21.0 = moderate; 21.1–50.0 = severe; 50.1–72.0 = very severe [R18-2851]. The EASI score does not assess symptoms like pruritus and sleep loss [R18-2670].

SCORAD

The SCORAD index will also be included in the clinical trials and has three elements: extent of disease, disease severity and subjective symptoms. These combine to give a maximum possible score of 103. The commonly used SCORAD strata to classify AD severity are mild = 0–25, moderate = 26–50 and severe = 51–103 [R18-2664, R18-2679].

IGA

The IGA scale allows investigators to assess overall disease severity at one given time point, and it consists of a five-point severity scale from clear to severe disease (0= clear,1 =almost clear, 2 = mild, 3 = moderate, 4= severe). The IGA scale uses clinical characteristics of erythema, infiltration, papulation, oozing and crusting as guidelines for the overall severity assessment [R18-2670].

DLQI

The DLQI is a patient-administered, ten-question, quality of life questionnaire that covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment [R05-2548]. The DLQI has a one-week recall period. 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 where 0-1 = no effect on patient's life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, and 21-30 = extremely large effect on patient's life. The higher the score, the more the quality of life is impaired. A 4-point change from baseline is considered a clinically important difference [R18-1988].

5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Adverse events (including drug-related AEs)
- Adverse events of special interest (AESI)
- Serious adverse events (SAEs)
- Safety laboratory tests
- Physical examination
- Vital signs (blood pressure, pulse rate, body temperature)
- 12-lead ECG
- Infusion site reactions
- Immunogenicity (ADA)

5.2.1 Physical examination

Complete and targeted physical examinations will be performed at visits as described in the Flow Chart. Height and weight of the patient will be recorded at the Screening Visit only.

Complete physical examination will include general appearance as well as evaluation of all organ systems. Targeted physical examination will evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.

Clinically relevant abnormal findings will be reported as baseline conditions or AEs.

5.2.2 Vital signs

Vital signs evaluations will be performed at visits as shown in the Flow Chart. This includes measuring temperature, pulse rate and systolic/diastolic blood pressure. Vital signs will be measured after patients have been sitting comfortably for at least 5 minutes. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible. Measurement of vital signs should precede blood sampling to avoid the impact of blood sampling on the vital measurements.

At visits with i.v. administration, vital signs will be assessed pre-dose, at approximately 5 minutes after the end of infusion and 60 minutes after the end of infusion.

During i.v. drug administration, patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 1 hour after the end of study drug administration.

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 CTM.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart.

The parameters that will be determined are listed in Table 5.2.3: 1. The laboratory tests will be performed at a central laboratory.

However, local labs may be used for dosing decisions at visits involving i.v. administration of BI 655130 or placebo. The lab tests listed in Table 5.2.3: 1 can be collected and assessed locally by the investigator prior to study drug infusion to allow for immediate subject management; however, split or concurrent samples will be drawn and sent to the central laboratory for analysis.

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.5.2 and the Drug Induced Liver Injury (DILI) Checklist provided in the ISF and the electronic data capture (eDC) system). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

Clinically relevant abnormal findings (e.g. anemia, hypoproteinemia, hypoalbuminemia, hypocalcemia etc.) will be reported as baseline conditions or AEs. A clinically relevant value may be either in- or outside the reference range. Clinically relevant abnormal laboratory test results must be confirmed using an unscheduled visit laboratory kit and should be repeated until normalization or stabilization or until an alternative explanation has been found. Abnormal laboratory values will also be graded for intensity by using RCTC Version 2.0 criteria [R13-3515].

Instructions regarding sample collection, sample handling/processing and sample shipping are included in the laboratory manual in ISF.

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

Category	**Test Name**
Haemtology	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)
Substrates	C-Reactive Protein (CRP) Serum albumin Creatinine Total bilirubin or Direct bilirubin Bilirubin Indirect (if total is elevated) Total protein Total cholesterol Triglycerides Plasma glucose BUN (blood urea nitrogen) Troponin (Reflex, in case of elevated CK) LDL-Cholesterol (if total cholesterol is elevated) HDL-Cholesterol (if total cholesterol is elevated)
Electrolytes	Sodium Potassium Chloride Calcium

Category	Test Name
Urinalysis (Stix)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine erythrocytes Urine leukocytes Urine pH
Urine-Sediment (only if urine analysis abnormal)	microscopic examination
Infection testing [1]	Hepatitis B Surface Antigen (qualitative[7] Hepatitis B core Antibody[7] HBV-DNA (quantitative) at baseline and EoS[2] QuantiFERON®-TB[3,4,7] Hepatitis C Antibodies (qualitative) HIV-1, and HIV-2 Antibody (qualitative)
Specific gamma-globulin quantification IgE	IgE[5]
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 if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin

[1] For eligibility refer to exclusion criteria Section 3.3.3 for details regarding infection testing.
[2] An HBV-DNA test should be conducted if Hepatitis B core Antibody is positive and Hepatitis B Surface Antigen is negative. These evaluations should be conducted at screening and EOS.
[3] If the 1st QuantiFERON®-TB test result is indeterminate, a retest should be performed.
[4] In patients with a negative QuantiFERON®-TB test, the test should be repeated at EOS.
[5] IgE will be taken in case of infusion reaction together with ADA (anti-drug antibodies) sample.
[6] Urine and serum pregnancy testing will be performed as indicated in the Flow Chart.
[7] Also performed at EoS visit

5.2.4 Electrocardiogram (ECG)

ECG measurements will always precede blood sampling to avoid impact of sampling on the ECG results. The 12-lead ECGs will be recorded and reviewed prior to dosing as scheduled in the Flow Chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis. No central laboratory will be used for ECG recording.

Additional ECGs may be recorded for safety reasons. The electronic version, if applicable, or dated and signed printouts of the ECG, will be regarded as source data and will be stored in the patient's medical file.

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

Other Safety Parameters:

In case of an infusion reaction, monitor the patient per standard of care, grade the intensity of the reaction according to RCTC V2 grading (cf. ISF) and proceed as described in Section 4.2.1.

All cases of malignancies that are detected during the trial will be reported as SAEs.

5.2.5 Assessment of adverse events

5.2.5.1 Definitions of AEs

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 or not considered related to the medicinal product.

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,
- requires 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.

AEs considered "Always Serious"

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in Section 5.2.5.2, subsections "AE Collection" and "AE reporting to sponsor and timelines".

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has developed a list of further 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.

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this 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 below.

The following are considered as AESIs:

Hepatic injury

Hepatic Injury, is defined by the following alterations of hepatic laboratory parameters:

- An elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
- Aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN

Any patients with these lab abnormalities need to be followed up according to the DILI Checklist provided in the ISF. In case of a DILI, it will be up to the investigator to keep the patient in the trial as long as he considers he/she can perform all planned procedures. 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.

Infusion reactions including anaphylactic reaction

Any suspicion of severe infusion reaction and of any potential cases of anaphylaxis should be defined and assessed using the criteria discussed in the statement paper from Sampson HA et al [R11-4890].

Severe infections (according to RCTC grading in the ISF)

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].

Protocol-specified AESI can be classified as serious or non-serious but all AESI must be reported in an expedited manner similar to serious adverse events on a SAE form (i.e. non serious AESI must be reported on the SAE form and follow the same reporting timelines as for serious AEs).

Intensity (severity) of AEs

The intensity grading of AEs will be performed according to RCTC Version 2.0 developed by the Outcome Measures in Rheumatology (OMERACT) organization [R13-3515]. Refer to the ISF for intensity/severity classification.

Intensity options are:

Grade 1 mild
Grade 2 moderate
Grade 3 severe
Grade 4 life-threatening

Causal relationship of AEs

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

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative 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 drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.5.2 Adverse event collection and reporting

AE Collection

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

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:
  - 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 related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however not be reported in the CRF.

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 BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process will be provided 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. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required

For each AE, the investigator should provide the information requested on the appropriate eCRF pages and, if applicable, the BI SAE form. The investigator should determine the causal relationship to the trial medication.

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

- 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 pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only. All (S)AEs, including those persisting after a 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.

Pregnancy

Urine pregnancy testing should be done prior to study drug administration. Study 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 Flow Chart. The patient will also be asked about their pregnancy status at the End of Study Safety Phone Call.

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 hours) 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 Studies (Part B).

The ISF will contain the Pregnancy Monitoring Form for 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 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.

Exemptions to SAE reporting

For this study there are no exemptions to SAE reporting.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

BI 655130 concentrations will be reported descriptively. It is not intended to calculate PK parameters; however, if appropriate PK parameters might be calculated. PK data may be incorporated into a larger pharmacometric analysis with other trials of the BI 655130 project.

Also, ADAs and neutralizing antibody (Nabs) 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 Flow Chart for the time points of PK, ADA and Nab. Date and exact time of drug administration and PK, ADA and Nab will be recorded on CRFs. On visits with study medication dosing, PK, ADA and Nab should be collected within 2 hour period prior to administration of study drug.

5.3.2 Methods of sample collection

5.3.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 655130 plasma concentrations, blood will be taken from a forearm vein into a K_2EDTA (ethylendiaminetetraacetic acid) anticoagulant blood-drawing tube at the time points listed in the Flow Chart under PK sampling.

Samples will be stored in a freezer set at the analytical laboratory until the finalization of the clinical trial report (CTR). The plasma samples may be used for further methodological investigations (e.g. for stability testing) however, only data related to the analyte will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.3.2.2 Sampling for ADA/Nab assessment

For ADA assessment, blood will be taken from a forearm vein into a K_2EDTA anticoagulant blood-drawing tube at the time points listed in the Flow Chart. For Nab assessment, blood will be taken from a forearm vein into a serum blood drawing tube at the time points listed in the Flow Chart.

Samples will be stored in a freezer set at the analytical laboratory until they are analyzed. The Plasma/serum samples may be used for further methodological investigations, e.g. for stability testing, however only data related to the anti-drug antibodies will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the final study report has been signed.

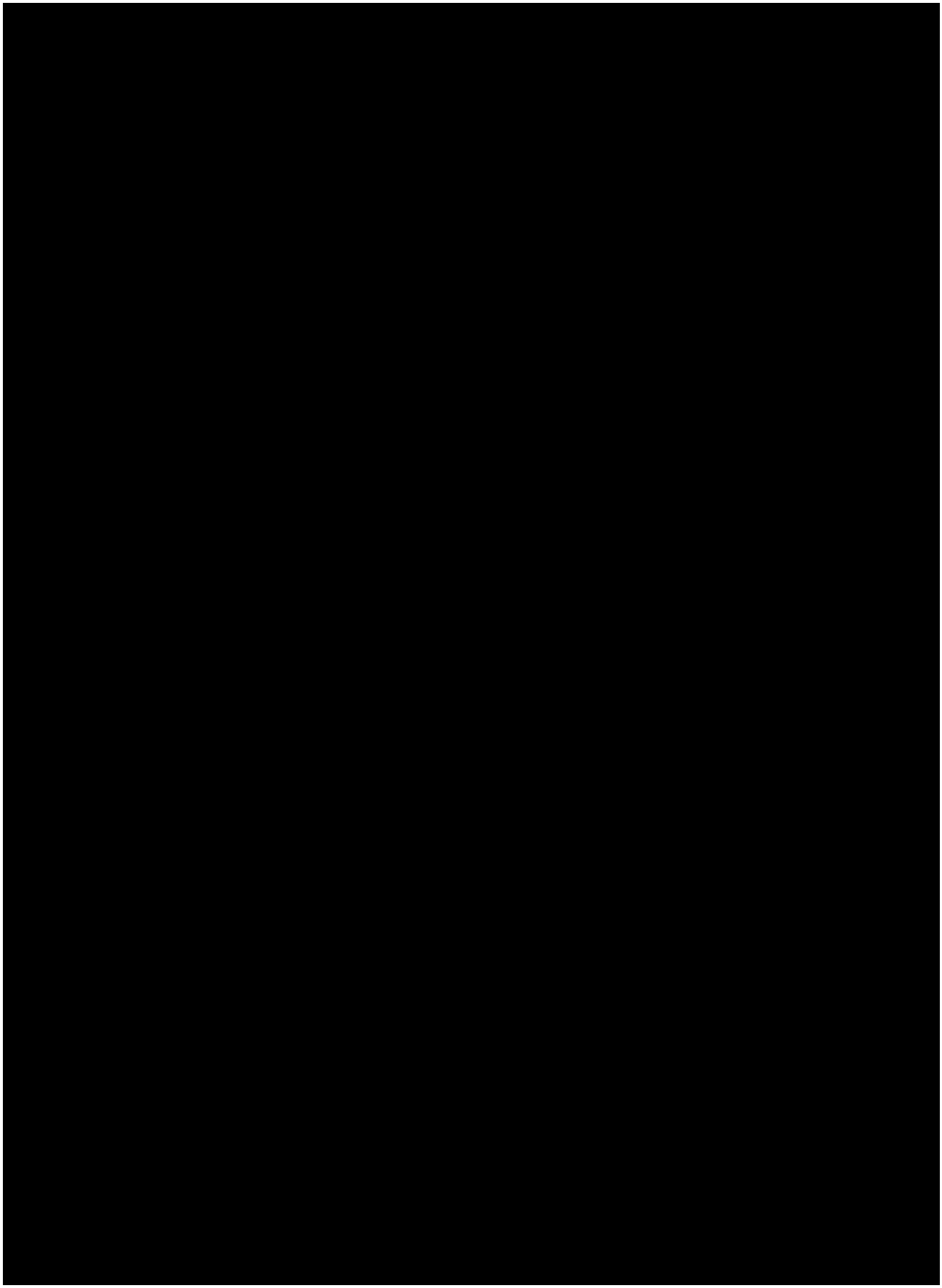
5.3.4 Pharmacokinetic – pharmacodynamic relationship

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. It is not intended to include these data into the final report. However, the data may be part of the report if the available data allows for such correlation.

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 Procesures (SOP).



[redacted]

5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Sample collection and biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

One (1) blood sample will be used for DNA Banking which will be stored at Boehringer Ingelheim. The stored DNA may be retrospectively analysed, e.g. to identify whether there are other genetic factors that could contribute to a better therapeutic outcome or a higher risk of developing treatment related adverse drug reactions.

This blood sample will be collected in a PAXgene Blood DNA tube at Visit 2. If not possible at Visit 2, this sample may also be collected at a later visit.

[redacted]

5.7 APPROPRIATENESS OF MEASUREMENTS

The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG variables that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an 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 are outlined in Section 5.4 are of exploratory nature only.

Information about race should be obtained from all study participants as allowed by local regulations. This is because the prevalence and characteristics of atopic dermatitis 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

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule specified in the Flow Chart. Each visit date (with its window) is to be counted from Day 1 (V2).

All deviations from the planned visit schedule are to be documented. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Additional visits for the purpose of retesting of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

For detailed description of the trial procedures, please refer to the Flow Chart.

Details relating to study drug administration are provided in Section 4.1.4.

Study measurements and assessments are scheduled to occur 'before' trial medication administration at dosing visits and are to be performed and completed prior to the trial drug administration (including pre-dose on Day 1 for PK, ADA, Nab and biomarkers). For planned individual plasma concentration sampling times refer to the Flow Chart. At non-dosing visits sampling should be done after other study procedures have concluded. Sampling times will be recorded and used for pharmacokinetic analysis.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart and respective sections of this protocol. Refer to Section 5 for explanations of the specified assessments and procedural details.

Based on the investigator's clinical judgment, patients may be hospitalized prior to, during or following first study drug administration. Subsequent visits will be conducted in accordance with the protocol and the investigator's judgment (For details, see Flow Chart and Section 3.1).

The patients' questionnaires (DLQI, VAS for pruritus and Sleep loss in SCORAD) are to be completed by the patient him/herself, without any help from or interpretation by other people. The VAS SCORAD should be completed before the DLQI.

Separate from the PROs above, the evaluation of efficacy assessments (EASI, SCORAD, and IGA) are to be conducted preferably by the same physician, whenever possible, throughout the study.

The following procedures should be completed in the following order prior to trial drug infusion:

1. Pruritus and Sleep Loss SCORAD VAS
2. DLQI
3. SCORAD, EASI and IGA
4. Photographs of skin lesions
5. Tape stripping
6. Skin biopsies

Refer to ISF (applicable processing manual) for sample preparation and shipment instructions.

6.2.1 Screening

Screening Period

After patients have been informed about the trial, written informed consent in accordance with GCP and the local legislation must be obtained prior to performing any study related procedures.

Once consent is obtained, the patient is considered to have started the screening process, and is assigned a unique patient number by the IRT system. The patient is to be recorded on the enrolment log and be registered in the IRT system as a screened patient. Study requirements, including the procedure for the follow-up of prematurely withdrawn patients, must be fully explained to the patient and written informed consent obtained prior to initiating any study-related evaluation. The importance of staying in the study until completion of all requirements is to be emphasized. No study procedures are to be done unless the patient has provided consent to take part in the study.

Demographics:
Informed consent date, gender, ethnicity and race (if allowed by local law) will be collected and reported in the eCRF.

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 (excluding AD) will be reported on the Baseline Condition eCRF page.

Infection screening:
Infection testing will include tuberculosis, hepatitis B, hepatitis C, and HIV assessments (see Table 5.2.3: 1).

Medical History:
Information on clinically significant previous and concomitant illnesses, other than AD, or any clinically significant signs or symptoms that are present before informed consent, or pre-existing conditions identified through findings from assessments and examinations done during the screening visits will be recorded as medical and surgical history at screening.

Regarding AD, a detailed history of the disease will be collected and reported in the eCRF. Also, previous and concomitant treatment for AD will be recorded.

Re-screening:
If a patient results in a screen failure (i.e. does not meet the eligibility criteria) the patient must be registered as a screen failure in IRT system. However, re-screening of a previously screen failed patient will be permitted once. Details of IRT procedures can be found in the IRT manual located in the ISF.

For the comprehensive list of the trial procedures required at the Screening Visit (Visit 1) please refer to the Flow Chart.

6.2.2 Randomization Visit and Treatment Visits

Patients will be randomized to receive 600 mg BI 655130 or placebo in a 2:1 randomisation ratio (2:1) at Visit 2. Patients will be stratified according to race i.e Asian vs non-Asian.

The first study drug administration is at Visit 2 (Day 1). Thereafter, patients will receive blinded trial drug at V4, V5 and V6. At V7 patients will be evaluated with EASI scrore and responders will be re-assigned to no treatment whereas non-responders will be re-assigned to BI 655130 600 mg. The re-assignement will be un-blinded.

For information pertaining to PK, ADA, Nab and biomarkers, see Sections 5.3 and 5.4. Fasting is not required for blood sampling. For information pertaining to laboratory tests, ECG, vital signs, and physical examination, see Sections 5.2.1 to 5.2.5.

DNA banking is optional and is only to be done for patients who have provided informed consent for this specific procedure.

Skin lesion photographs will be taken at all visits on site and are to be taken prior to any skin biopsies or study drug administration.

At Visit 1, patients will be provided with emollient and instructions on how to apply. Emollient will be provided to each patient as required for the duration of the study.

Study drug allocation via the IRT system and administration of study drug should be the last activity at Visit 2 with the exception of post dose vital signs assessments.

For women of child-bearing potential, pregnancy testing will be done as specified in the Flow Chart. The patient will also be asked about their pregnancy status at the End of Study Safety Phone Call.

6.2.2.1 Clinical monitoring after study drug administration

During i.v. drug administration, vital signs will be assessed pre-dose, at approximately 5 minutes after the end of infusion, and 60 minutes after the end of infusion. Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 1

hour after the end of infusion. Hypersensitivity reactions should be treated according to medical standards (See Section 4.2.2).

6.2.2.2 Unscheduled visits

During the treatment period patients may be seen at an unscheduled visit if they experience worsening of the disease or have AEs that in the opinion of the investigator need intervention (e.g. escape or rescue treatment) or repeated laboratory testing.

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 that were missed at a previous visit. All unscheduled visits (including the reason for the visit) should be described and documented in the medical/source record, and in the eCRF.

6.2.2.3 End of Study Visit and Safety Phone Call

For the list of trial procedures required at the End of Study visit, please refer to the Flow Chart.

For Non-Responder patients:

At Visit 11, if the patient has any ongoing or newly diagnosed clinical relevant changes in safety laboratory tests, vital signs, ECG or AEs/SAEs/AESIs, the patient should be followed-up as deemed necessary based on medical judgement of the investigator.

An End of Study Safety Phone Call will be completed for Non-Responder patients not participating in the open label extension trial. At any time from Visit 11 to the End of Study Safety Phone Call, if the patient reports any new or ongoing AEs/SAEs/AESIs that based on medical judgement of the investigator require further follow-up, an unscheduled visit should be planned for follow-up or patient referral.

6.2.3 Trial Completion and End of Residual Period

For all randomized patients termination of trial medication and trial completion must be recorded on the corresponding eCRF.

For the comprehensive list of the trial procedures required following the end of treatment, please refer to Flow Chart.

Trial Completion:
Trial completion is defined as a patient having reached the EoS visit within the specified window per protocol.

Treatment Completion:
Treatment completion is defined as a patient receiving four (4) infusions of trial drug (BI 655130 or placebo) at V2, V4, V5 and V6.

In the re-allocation period (V7 to V11) treatment completion is defined as:

- non-responder patient receiving 4 infusions of BI 655130 at V7, V8, V9, V10 and continuing in the trial until the last visit (V11) – End of Study/FU1 (Week 32 - 44).
- responder continuing in the trial until the last visit (V10) – Week 28 or until they reach a 50% reduction in EASI score compared to baseline

Early Treatment Discontinuation:
In case the infusion of study drug is permanently discontinued before the whole amount of prepared solution has been administered to the patient, every effort should be made to keep the patient in the trial and complete all of the remaining study visits. If this is not possible, assessments of the primary endpoint V7 (Week16), should be completed or at a minimum an early EoS visit. Please refer to the Flow Chart.

Early Trial Discontinuation:
A patient not having reached the EoS visit within the specified window per protocol (e.g. due to withdrawal of consent, lost to follow-up, death etc.).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is an exploratory trial in patients with atopic dermatitis. It is designed as a 2:1 randomised, double-blind, placebo-controlled trial with 2 parallel groups (1 dose of BI 655130 and placebo (2:1)).

The primary objective of this trial is to explore the safety, tolerability and efficacy of BI 655130 in comparison to placebo in patients with atopic dermatitis.

The primary efficacy endpoint for this trial is Percent change in Eczema Area and Severity Index (EASI) Score at Week 16 compared to Baseline.

Due to the potential for different pathophysiology in different ethnic groups, randomisation will be stratified by race (Asian vs. Non-Asian patients). The primary endpoint will be analysed using a restricted maximum likelihood estimation based on a mixed-effect model for repeated measures analysis to obtain adjusted means for the treatment effects. This model will include discrete fixed effects for treatment at each visit and stratification factor Asian/Non-Asian, and continuous fixed effects for baseline at each visit. The primary treatment comparisons will be the contrast between treatments at Week 16.

After Week 16 there will be a treatment re-allocation based on EASI75 outcome. In case of EASI75 reached, no treatment will be given, otherwise BI 655130.

7.2 NULL AND ALTERNATIVE HYPOTHESES

One of the aims of this trial is to investigate whether BI 655130 has any therapeutic effect in atopic dermatitis patients, in other words to have the proof of clinical concept. Superiority of BI 655130 to placebo will be tested by the comparison of mean percentage change in the EASI score for BI 655130 and placebo, at Week 16.

The following hypothesis testing will be performed having an alpha level of 10% (two-sided), or $\alpha = 0.05$ (one-sided):

H_0: Mean percent change of EASI score at Week 16 (BI 655130)

$\leq$ Mean percent change EASI score at Week 16 (Placebo)

H_1: Mean percent change EASI score at wWeek 16 (BI 655130)

$>$ Mean percent change EASI score at Week 16 (Placebo)

As this is an exploratory trial, the result of this hypothesis testing will be discussed in the context with all results, both safety and efficacy.

7.3 PLANNED ANALYSES

The efficacy analyses will be performed for the Full Analysis Set (FAS), which is based on the intent-to-treat principle, and comprises all participants who were randomised, received at least one dose during the trial, and had a baseline measurement for the primary endpoint. Efficacy analyses will be based on the planned treatment (i.e., the treatment assigned at randomisation). Safety analyses on patients who were randomised, and received at least one dose during the trial will be based on the actual treatment received at the randomisation visit; this set of patients is called the Safety Analysis Set (SAF). All efficacy analyses will be conducted on the FAS. All safety analyses will be conducted on the SAF. With regard to efficacy and safety endpoints, "baseline" refers to the measurement recorded at randomisation (Visit 2), if data at Visit 2 is missing, then data from Visit 1 will be considered baseline.

Important deviations of the protocol will include key inclusion and exclusion deviations, incorrect medications taken, compliance with study medication, 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 un-blinding of the database for the primary week 16 analysis. This is an exploratory trial and sensitivity analyses may need to be done to investigate the effects of potential confounding factors.

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.

7.3.1 Primary endpoint analyses

The primary analysis is a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) comparing the percent change from baseline of the EASI score after 16 weeks of treatment.

The analysis will include the fixed, categorical effects of treatment at each visit, stratification factor Asian/Non-Asian and the fixed continuous effects of baseline at each visit. Visits will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.10$ (two-sided 90% confidence intervals (CI)). The primary treatment comparison will be the contrast between treatments at Week 16.

The primary analysis will be performed on the FAS. Patients will be analysed according to the stratum to which they belong (regardless of any miss-assignment to treatment based on identification of the wrong stratum), as such an error occurs before randomisation.

Procedures to follow if the analysis fails to converge will be described in the TSAP.

To assess the homogeneity of the treatment effect on the primary endpoint across the levels of Asian/Non-Asian, the same MMRM model will be fitted but replacing the treatment-by-visit term by a treatment-by-Asian/Non-Asian-by-visit term. A descriptive p-value of treatment effect homogeneity at Week 16 will be calculated. No overall treatment effect will be estimated from this model, as it is not interpretable.

7.3.2 Secondary endpoint analyses

The endpoint change from baseline in SCORAD will be analysed using the same model as used for the primary endpoint (MMRM).

For the primary endpoint variable, the EASI score, responder analyses will be performed. A patient is defined as EASI50/75 responder when percent change from baseline of the EASI score is ≥50% or ≥75%, resulting in binary variable with values of 1 (=response) or 0 (=non-response). A logistic regression model will be used to predict the response rates and to calculate the risk difference for BI 655130 versus placebo. As a sensitivity analyses, the Cochran-Mantel-Haenszel (CMH) test adjusted by randomization stratum (Asian/Non-Asian) will be used.

For the proportion of patients with IGA 0 or 1 at weeks 4 and 16, also the CMH test will be used.

7.3.4 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 residual effect period (REP), a period of 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.

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 to findings before start of treatment.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

Refer to Section 5.3.1 and Section 5.3.4.

7.4 INTERIM ANALYSES

An interim analysis will be conducted when 75% of the patients have completed at least 4 weeks of treatment. The results of the analysis will be used for internal decision making only and individuals involved in the conduct of the trial will not be made aware of the results. There will be no changes of the design of the trial because of this interim analysis at Week 4.

The time-point of this interim analysis is triggered by the availability of all EASI and SCORAD data in the database on the first 75% of the patients. For this interim analysis an interim analysis SAP and an interim analysis logistics plan will be developed, including a list with individuals and roles who will have access to unblinding information.

7.5 HANDLING OF MISSING DATA

Every effort will be made to collect complete data at all visits. However, missing data will still occur and approaches to handle this are proposed below.

With respect to safety evaluations, it is not planned to impute missing values.

If a patient misses a visit, for continuous endpoints the missing data will not be imputed. The mixed effect model will handle missing data based on a likelihood method under the "missing at random" assumption.

For all binary endpoints (i.e. endpoints that are either 1 (patient responded) or 0 (patient did not respond)), the following will be performed:

- If there are data at visits both before and after the visit with a missing outcome, then impute as success only if both neighbouring visits also represent a success;
- Otherwise, impute as a non-responder

[redacted]

Further sensitivity analyses to assess the robustness of the results may be performed and as such will be described in the TSAP.

7.6 RANDOMISATION

The trial will be performed as a double-blind design with respect to placebo and the active dose group of BI 655130. Patients will be randomised in blocks to the 2 trial treatments in a 2:1 at baseline visit. The randomisation will be stratified by race (Asian versus Non-Asian patients). If necessary, and depending upon global distribution, entry of patients into a stratum may be capped.

The randomisation of patients to the treatment groups will be performed via IRT. BI will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator and a supplied seed number so that the resulting allocation of medication numbers to treatment is both reproducible and non-predictable. The block size will be documented in the CTR. Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

[redacted]

Based on experience with Dupilumab, it is estimated that the standard deviation of percent change from baseline in EASI Score after 16 weeks of treatment is 30%. The delta used for sample size calculation is 25%. Source for the estimate of the the standard deviation is clinicaltrials.gov, searching was performed using the following condition 'Dupilumab | Studies With Results | Atopic Dermatitis'.

The other parameters for sample size calculation are a power of 80% and a two-sided alpha of 10%. With these parameters, a sample size of at least 42 patients is needed, with at least 28 patients on BI 655130 600mg and 14 patients on placebo.

Table 7.7: 1 Several scenarios for sample size calculation (10% two-sided alpha), based on change from baseline for EASI Score

Delta (%)	SD (%)	Power (%)	N total (active/placebo)
25	25	80	30 (20/10)
30	25	80	21 (14/7)
35	25	80	18 (12/6)
25	30	80	42 (28/14)
30	30	80	30 (20/10)
35	30	80	24 (16/8)
25	35	80	57 (38/19)
30	35	80	42 (28/14)
35	35	80	30 (20/10)
25	35	69	24 (16/8)
25	40	59	24 (16/8)
20	30	63	24 (16/8)
22.5	30	72	24 (16/8)

In addition, with the chosen sample size, the following probabilities we have with this trial. Assuming a treatment effect of 35% in the population, the probability to observe a difference of 25% or more in our study is 85% and the probability to observe a difference of 20% or less in our study only is 6%.

If there would be no difference (delta=0%), the probability to observe a difference of 25% or more in our study only is 1%, also almost 98% to observe a difference of 20% or less.

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) and other relevant regulations. Investigators and site staff must adhere to these principles.

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

The investigator will inform the sponsor 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 finalization 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 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."

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 must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or his 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.

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 subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan 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 three documented attempts to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Copies of patients' source documents will be provided to the sponsor. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's

name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

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 be available at all times for review by the Clinical Research Associate (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 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 Investigator Site File (ISF)) according to contract or the local requirements valid at the time of the end of the trial (whichever period 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.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in Section 8.7.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the Wolrd Health Organization (WHO) GCP handbook.

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.

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 has 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 (HA) request.

The IEC / CA 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.

A project-independent external Data Monitoring Committee (DMC) will be established to assess the safety and efficacy of BI 655130 in this clinical trial at specified intervals through the final time-point (End of Study Visit). Measures will be put in place to ensure blinding of the sponsor and all other trial participants. The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC 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 DMC 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 clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a Clinical Trial Leader (CTL), 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 Manager (CTM), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries 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) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

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 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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9.2 UNPUBLISHED REFERENCES

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10. APPENDICES

10.1 INSTRUCTIONS FOR USE

10.1.1 Diagnosis of Anaphylaxis

Clinical criteria for diagnosing anaphylaxis [R11-4890]

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.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		05 Nov 2018
EudraCT number **EU number**		NA
BI Trial number		1368-0032
BI Investigational Product(s)		BI 655130
Title of protocol		Phase IIa multicentre, randomized, double-blind, placebo-controlled, study to evaluate the safety, tolerability and efficacy of treatment with BI 655130 in adult patients with moderate to severe atopic dermatitis
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Title Page
Description of change		Administrative change to Lay Title
Rationale for change		To provide a more accurate description of the protocol title

11.2 GLOBAL AMENDMENT 2

Date of amendment		05 Jul 2019
EudraCT number **EU number**		NA
BI Trial number		1368-0032
BI Investigational Product(s)		BI 655130
Title of protocol		Phase IIa multicentre, randomized, double-blind, placebo-controlled, study to evaluate the safety, tolerability and efficacy of treatment with BI 655130 in adult patients with moderate to severe atopic dermatitis
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		**All Sections**
Description of change		Participants in this trial will be refered to as patients instead of subjects. This has been corrected throughout the protocol
Rationale for change		Correction
Section to be changed		**Title Page**
Description of change		Administrative changes for CTL, document number, version and date

Rationale for change		To reflect the change in CTL for the study, document number, version number and date of new version
Section to be changed		**Clinical Trial Protocol Synopsis**

Description of change		Removed striked-through text.
		
		Exclusion Criteria
		• Use of systemic corticosteroids or other agents for atopic dermatitis within 4 weeks prior to first dose of trial treatment (for more details refer to Table 4.2.3.1: 1)
		• Any documented active or suspected malignancy or history of malignancy within 5 years prior to the screening visit, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
		• Active or Latent TB:
		  • Patients with active tuberculosis are excluded.
		  • Patients with a positive QuantiFERON TB test during screening are excluded, unless:
		  ○ Patient had previous diagnosis of active or latent TB and has completed appropriate treatment per local practice/guidelines within the last 3 years and at least 6 months before first administration of trial medication under this protocol (patients may be re-screened once to meet this criterion)
		  ○ Patients with suspected false positive or indeterminate QuantiFERON TB result may be re-tested once
		  ○ If QuantiFERON TB test result is not available or providing indeterminate results after repeat testing : A tuberculin skin test reaction ≥10mm (≥5mm if receiving ≥15mg/d prednisone or its equivalent) is considered positive ~~and patients will be excluded.~~

Rationale for change		To clarify some sections of the criteria and align with project standard

Section to be changed		**Flow Chart**
Description of change		Added section headers and grouped assessments; Added "X" for Investigator Global Assessment (IGA), EASI and SCORAD – BSA only) at Screening Visit; Added 'C' for Physical examination at V10; Added 'S' for Pregnancy testing at all visits after Screening; Added 'X' for Blood sample-soluble protein biomarker at V11 Footnotes: Added clarifications for Physical Examination, Vital Signs, ECG measurements, Blood Sampling – Optional PGx Sampling, End of Study Visit for Responders (V10) and Non-Responders (V11) Added footnote 19 to reflect collection of BSA assessment at all visits
Rationale for change		Assessments were rearranged to more accurately reflect the order of assessments performed in the clinic. Assessments remained unchanged. Timepoints where procedures are to be completed were updated to be aligned throughout study protocol Added protein biomarker at V11 as this was omitted in error in the initial protocol <u>Footnotes:</u> Clarifications and corrections made to be aligned throughout study protocol. Removal of rescue visits which are not applicable to the study. Footnote 15: Reinforce that this sample is optional and separate consent is required.
Section to be changed		**Section 1.1**
Description of change		Added IL-17 to list of cytokines and chemokines that are expressed by AD. Added statement: IL-36 is thought to have a pivotal role in amplifying these immune pathways and may be a critical link between S. aureus infection and exacerbation of AD inflammation.
Rationale for change		To provide further clarification on the medical background of AD
Section to be changed		**Section 1.2.3**
Description of change		Updated information to include more recent clinical

		trial experience
Rationale for change		To be in alignment with the Investigator Brochure v6.0 dated 04Apr2019
Section to be changed		**Section 1.4**
Description of change		Added information from recent BI clinical trials. Removed the word 'minimal' from the following sentence: Considering the medical need for development of an effective and well tolerated drug for the therapy of AD, the benefit of this trial is considered to outweigh the potential ~~minimal~~ risks and justifies the administration of multiple doses of BI 655130 to patients with AD to investigate safety, tolerability and efficacy.
Rationale for change		To be in alignment with the Investigator Brochure v6.0 dated 04Apr2019
Section to be changed		**Section 3.1**
Description of change		Added clarification on when patients may be withdrawn from the trial or complete End of Study Visit before being given the opportunity to enrol in the extension trial.
Rationale for change		Provided more clarification on the trial design
Section to be changed		**Section 3.3.3**
Description of change		Exclusion Criteria 2. Use of systemic corticosteroids or other agents for atopic dermatitis within 4 weeks prior to first dose of trial treatment (for more details refer to Table 4.2.3.1) 5. Any documented active or suspected malignancy or history of malignancy within 5 years prior to the screening visit, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix. 10. Active or Latent TB: Patients with active tuberculosis are excluded. Patients with a positive QuantiFERON TB test during screening are excluded, unless: • If the QuantiFERON TB test result is not available or provides indeterminate results after repeat testing: A tuberculin skin test reaction ≥10mm (≥5mm if receiving ≥15mg/d prednisone or its equivalent) is considered positive

		~~and patients will be excluded~~. 11. Currently enrolled in another investigational device or drug trial, or less than 30 days or 5 half lives, whichever is longer since ending another investigational device or drug trial(s), or receiving other investigational treatment(s).
Rationale for change		Clarification of criteria; removed inaccurate information
Section to be changed		**Section 4.1.5.2**
Description of change		The following text was removed from Section 4.1.5.2 : ~~An emergency code break (envelope) will be available to the investigator. This code break may only be opened 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. If the code break for a patient is opened, the sponsor must be informed immediately about the unblinding. The treatment allocation should not be disclosed to the sponsor unless this is explicitly requested. The reason for opening the code break must be documented on the envelope and/or appropriate CRF page.~~
Rationale for change		Removed inaccurate information
Section to be changed		**Section 4.2.1**
Description of change		The following text was revised: Patients refusing to return to the study site ~~(during the follow-up period)~~ for scheduled visits after the end of treatment should at least provide safety information by phone at the respective visits. The following text was added: If a patient receives escape treatment the decision to maintain the patient on trial treatment will be decided with discussion between the investigator and sponsor.
Rationale for change		Reinforce the requirement for patients to complete all study visits. Provided clarification on how decisions will be made if patients use escape treatment during the trial
Section to be changed		**Section 4.2.3.1:1** **Table 4.2.3.1:1**

Description of change		Added the following sentence: Patients are prohibited from receiving the following therapies, during trial treatment and prior to Visit 2 for the duration specified in the Table below: Washout periods for restricted medications were updated or added Footnote: Added the following: • Clarification that patients receiving standard of care treatment for disease worsening will be reassessed to continue on trial treatment • This list is not all inclusive, for any medications not listed, contact the Clinical Trial Manager for restricted duration • Antihistamines for indications other than atopic dermatitis can be prescribed on an as needed basis. Dose should, preferably, be stable within one week prior to V2 and during the course of the study • No restriction on use of corticosteroid drops, nasal and inhaled corticosteroids, Montelukast to treat conditions listed – if medications are on stable dose for 3 months prior to Visit 2.
Rationale for change		Clarify how patient treatment administration will be managed in patients who use standard of care in case of worsening disease. Added restricted medications and clarified washout periods to include common treatments for AD which may be used by patients.
Section to be changed		**Section 5.1**
Description of change		Removed striked-through text. ~~The EASI Instrument is provided in Appendix 10.1.2.~~ ~~The SCORAD Instrument is provided in Appendix 10.1.3.~~ ~~The IGA Instrument is provided in Appendix 10.1.4~~ ~~The DLQI Instrument is provided in Appendix 10.1.5.~~ IGA: Removed ‘disease’after each classification
Rationale for change		To prevent confusion for sites over which format to

		use; Removed inaccurate information
Section to be changed		**Section 5.7**
Description of change		Information about race should be obtained from all study participants as allowed by local regulations. This is because the prevalence and characteristics of ~~psoriasis~~ atopic dermatitis 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 for change		Correction of the disease
Section to be changed		**Section 6.2.2**
Description of change		Removed striked-through text: At Visit ~~2~~1~~before study drug administration~~, patients will be provided with emollient and instructions on how to apply. Emollient will be provided to each patient as required for the duration of the study.
Rationale for change		To correct the timing for when emollient is to be provided to the patient
Section to be changed		**Section 6.2.3**
Description of change		For the comprehensive list of the trial procedures required following the end of treatment please refer to Flow Chart.
Rationale for change		Accurately describe the period between end of treatment and end of study
Section to be changed		[redacted]
Description of change		[redacted]
Rationale for change		[redacted]
Section to be changed		**Section 10.1.2**

Description of change		Removed Eczema Area and Severity Index (EASI)
Rationale for change		To prevent confusion for sites over which format to use
Section to be changed		**Section 10.1.3**
Description of change		Removed SCOring of Atopic Dermatitis (SCORAD)
Rationale for change		To prevent confusion for sites over which format to use
Section to be changed		**Section 10.1.4**
Description of change		Removed Investigator Global Assessment (IGA)
Rationale for change		To prevent confusion for sites over which format to use
Section to be changed		**Section 10.1.5**
Description of change		Removed Dermatology Life Quality Index (DLQI)
Rationale for change		To prevent confusion for sites over which format to use

11.3 GLOBAL AMENDMENT 3

Date of amendment		12 Feb 2020
EudraCT number **EU number**		NA
BI Trial number		1368-0032
BI Investigational Product(s)		BI 655130
Title of protocol		Phase IIa multicentre, randomized, double-blind, placebo-controlled, study to evaluate the safety, tolerability and efficacy of treatment with BI 655130 in adult patients with moderate to severe atopic dermatitis
Global Amendment due to urgent safety reasons		
Global Amendment		X
COMMENT: The main purpose of this amendment is to give patients re-allocated as Non-Responders at V7 (Week 16) an opportunity to participate in the open label extension trial earlier after treatment completion.		
Section to be changed	Flow Chart	
Description of change		Renamed V11 End of Study Reduced time for when V11 End of Study visit should be completed after treatment completion, for Non-Responder patients. Added End of Study Safety Phone call for Non-Responder patients who do not continue in open label extension trial.

		Updated Footnotes 3 and 9 Updated footnote 18 to include End of Study and Follow-up visit for Non-Responder patients. Footnotes 20-22 added Added line item for End of Study Completion Call in IRT Infection Testing: Removed HBV DNA at V10 and V11 Section header: Physician and Patient Assessments removed
Rationale for change		To distinguish visit for Non-Responder patients, depending on if they continue in open label extension trial To allow Non-Responders to complete End of Study visit sooner after treatment and if eligible, continue in the open label extension trial. To ensure patients re-allocated as Non-Responders and not continuing in open label extension trial, complete a safety assessment at the end of the residual period. Footnote 3 updated to clarify status of patients who discontinue treatment prematurely Footnote 9 updated to explain which infection tests are performed at EoS visits. Footnotes 18, 20-22 added/revised to clarify when the V11 End of Study/Follow-Up 1 visit and End of Study Safety Phone call should be completed for Non-Responder patients End of Study Completion Call in IRT added to clarify when EoS should be registered for the patient HBV DNA removed from Infection Testing for correction Section header removed to prevent confusion

Section to be changed	[redacted]	[redacted]
Description of change		[redacted]
Rationale for change		
Section to be changed	3.1	**Overall Trial Design and Plan**
Description of change		Updated Figure 3.1.1 Trial design with new time point for when V11 should be completed and added Safety Follow-up Phone Call
Rationale for change		To remain consistent with all protocol amendment changes
Section to be changed	4.2.3	**Table 4.2.3.1:1 Restricted Medications**
Description of change		Duration of restricted medication extended to End of Study Visit for Non-Responders under the specified condition
Rationale for change		Ensures Non-Responder patients who reach EASI 50 (while only on active treatment) by End of Study Visit, are eligible to continue in the open label extension trial
Section to be changed	5.2	**Assessment of Safety**
Description of change		Table 5.2.3:1 Footnote 1 updated and 7 added
Rationale for change		Footnote 1 updated for correction Footnote 7 added to clarify Infection tests performed at EoS visit
Description of change		5.2.5.2 Adverse event collection and Reporting: Updated instructions on the method of reporting SAEs, AESIs and non-serious AEs Updated Pregnancy section to include collection of pregnancy status at the Safety Follow-up phone call
Rationale for change		To allow an alternative method of SAE report transmission (instead of fax) if implemented in this trial To ensure an appropriate safety assessment is completed at the end of the residual period
Section to be changed	6.2	**Details of Trial Procedures at Selected Visits**
Description of change		6.2.2 Randomization Visit and Treatment Visits: For women of child-bearing potential, added the collection of pregnancy status at the Safety Follow-up call. 6.2.2.3 End of Study Visit and Safety Follow-up Phone Call added Trial Completion: Updated the time point (week) when V11 – End of Study should be completed

Rationale for change		To remain consistent with all protocol amendment changes To include details on the safety assessment for Non-Responder patients after treatment completion
Section to be changed	7.3	**Planned Analysis**
Description of change		[redacted]
Rationale for change		Correction and clarification on endpoint analysis

APPROVAL / SIGNATURE PAGE

Document Number: c23806995 **Technical Version Number:4.0**

Document Name: clinical-trial-protocol-version-04

Title: Phase IIa, multicentre, randomized, double-blind, placebo-controlled, study to evaluate the safety, tolerability and efficacy of treatment with BI 655130 in adult patients with moderate to severe atopic dermatitis

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist	[redacted]	14 Feb 2020 16:47 CET
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Approval-Team Member Medicine		14 Feb 2020 17:56 CET
Approval-[redacted] Medicine		14 Feb 2020 19:32 CET
Approval-Clinical Trial Leader		16 Feb 2020 15:39 CET
Approval-Biostatistics		18 Feb 2020 16:49 CET

(Continued) Signatures (obtained electronically)

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