Clinical Trial Protocol

	Document Number:	**c26581385-02**
EudraCT No. **EU Trial No.**	N/A	
BI Trial No.	1368-0037	
BI Investigational Medicinal Product(s)	BI 655130	
Title	An open label extension study to assess the long term safety of treatment with BI 655130 administered subcutaneously in adult patients with moderate to severe atopic dermatitis.	
Lay Title	A study to test the long-term safety of BI 655130 in patients with atopic eczema who took part in study 1368-0032	
Clinical Phase	II	
Clinical Trial Leader	[redacted] Tel: [redacted] Fax: [redacted]	
Coordinating Investigator	N/A	
Status	Final Protocol (Revised Protocol based on Global Amendment 1)	
Version and Date	**Version: 2.0**	**Date: 23 March 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	07 May 2019
Revision date	23 Mar 2020
BI trial number	1368-0037
Title of trial	An open label extension study to assess the long term safety of treatment with BI 655130 administered subcutaneously in adult patients with moderate to severe atopic dermatitis.
Coordinating Investigator	N/A
Trial site(s)	Multi-centre trial
Clinical phase	II
Trial rationale	To provide patients with moderate to severe atopic dermatitis extended access to a potentially beneficial treatment and evaluate long-term tolerability and safety
Trial objective(s)	The primary objective of this trial is to assess the long term safety and efficacy of treatment with BI 655130 in patients with atopic dermatitis who have completed and have responded to treatment in the parent study 1368-0032.
Trial endpoints	Primary Endpoint • Number of patients with treatment emergent adverse events (AEs) at week 48 Secondary endpoints • Percentage change from baseline in the Eczema Area and Severity Index (EASI) Score at Week 48 • Percentage of patients with a 50% improvement from baseline in EASI (EASI50) at Week 48 • Percentage of patients with a 75% improvement from baseline in EASI (EASI75) at Week 48 • Change from baseline in SCORing of Atopic Dermatitis (SCORAD) (%) at Week 48 • Percentage of patients achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in Investigator Global Assessment (IGA) at Week 48
Trial design	An open label extension clinical trial consisting of approximately 4 years of treatment and a 16 week follow-up
Total number of patients randomised	Approximately 40 patients will enter this trial
Number of patients on each treatment	All patients will receive BI 655130
Diagnosis	Adult patients with moderate to severe atopic dermatitis
Main in- and exclusion	Inclusion Criteria

criteria	• Signed and dated written informed consent in accordance with Good Clinical Practice (GCP) and local legislation prior to the start of any screening procedures • Patients who completed the 1368-0032 trial and did not prematurely discontinue treatment prior to week 16, and; In the 1368-0032 re-allocation period (V7 to V11) : ➢ If an original non-responder from week 16 (V7), attained at least an EASI 50 by last infusion (week 28) or by the EOS. ➢ If an original responder from week 16 (V7) completed the last visit Week 28 (EOS) or dropped to an EASI 50 score prior to Week 28. Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly for the duration of the trial and 16 weeks after last administration. A list of contraception methods meeting these criteria is provided in the patient information. (Refer to Section 4.2.2.3) [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. Exclusion Criteria • Women who are pregnant, nursing, or who plan to become pregnant while in the trial. (Refer to Section 4.2.2.3) • Any new documented active or suspected malignancy except appropriately treated basal cell carcinoma, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix. • Use of any restricted medication as specified in Section 4.2.2.1 or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator. • Active systemic infections during the last two weeks prior to first drug administration. • Currently enrolled in another investigational device or drug trial, except for 1368-0032. • Any condition which would prevent the patient continuing on treatment in this trial 1368-0037

	• History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients
Test product(s)	BI 655130
dose	600 mg (4 syringes, 150 mg each) every 4 weeks
mode of administration	Subcutaneous (SC)
Comparator product(s)	N/A
dose	N/A
mode of administration	N/A
Duration of treatment	Approximately 4 years
Statistical methods	Descriptive statistics only

FLOW CHART- YEAR 1

	Open Label Treatment Period- Year 1														Continue year 2 to 4 based on visit type (See Flow Chart for Years 2-4 and Flow Chart for end of treatment and end of study visits.
Visit Number	**1**[2]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	14	
Day	1	29	57	85	113	141	169	197	225	253	281	309	337	365	
Week	1	4	8	12	16	20	24	28	32	36	40	44	48	52	
Visit Window (days)	n/a	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	±14	
Visit Type	**A**	**B**	**B**	**C**	**B**	**B**	**D**	**B**	**B**	**C**	**B**	**B**	**E**	**B**	
Informed consent [1]	X														
Demographics	X														
Medical history	X														
Inclusion/Exclusion/Eligibility	X														
Smoking status/ weight/height[18]	X												X		
Physical exam	X[8,]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[8]	X[9]	
Vital signs[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12 lead-ECG [5]	X												X		
Safety Lab tests[11]	X						X						X		
Pregnancy Testing[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Infection Testing[12]	X												X		
VAS SCORAD [6]	X			X			X			X			X		
[redacted]	[redacted]						[redacted]						[redacted]		
IGA[6,] **EASI** [6,] **SCORAD** [6]	X			X			X			X			X		
[redacted]	[redacted]						[redacted]						[redacted]		
[redacted]	[redacted]						[redacted]						[redacted]		
[redacted]	[redacted]						[redacted]						[redacted]		
All AEs/SAEs/ AESIs[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IRT Call	X[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Administer trial drugs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

FLOW CHART- YEARS 2-4

The same visit schedule repeats yearly until the end of year four as follows.
These treatment visits will follow the same ±14 day visit window [redacted]

Year 2													
Visit	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**
Day	393	421	449	477	505	533	561	589	617	645	673	701	729
Week	56	60	64	68	72	76	80	84	88	92	96	100	104
Visit Type	B	B	C	B	B	D	B	B	C	B	B	E	B
Year 3*													
Visit	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**	**40**
Day	757	785	813	841	869	897	925	953	981	1009	1037	1065	1093
Week	108	112	116	120	124	128	132	136	140	144	148	152	156
Visit Type	B	B	C	B	B	D	B	B	C	B	B	E	B
Year 4*													
Visit	**41**	**42**	**43**	**44**	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**EOT (52)**	**EOS (53)**
Day	1121	1149	1177	1205	1233	1261	1289	1317	1345	1373	1401	1429	1541
Week	160	164	168	172	176	180	184	188	192	196	200	204	220
Visit Type	B	B	C	B	B	D	B	B	C	B	B	EOT	EOS

FLOW CHART: END OF TREATMENT AND END OF STUDY VISITS

Visit	EOT[4] (52)	EOS[4] (53)
Day	1429	1541
Week	204	EOT + 16 weeks
Visit Window	±14	+14
Physical examination	X[8]	X[8]
Vital signs	X[10]	X
Smoking status/ /weight	X	X
12 lead-ECG [5]	X[13]	X
Safety Laboratory tests[11]	X	X
Pregnancy Testing[7]	X	X
Infection Testing[12]	X[13]	X
[redacted]	[redacted]	[redacted]
VAS SCORAD[6]	X	X
[redacted]	[redacted]	[redacted]
IGA[6,] EASI[6,] SCORAD [6]	X	X
All AEs/SAEs/ AESIs[3]	X	X
IRT call	X[17]	
Administer study drugs	X[15]	
Concomitant therapy	X	X
Completion of patient participation		X
[redacted]	[redacted]	[redacted]

Flow Chart Visit Type Explanation

Visit types refer to the procedures required per Flow Chart.

Visit Type	Procedures Required
A	Only performed per Flow Chart at Visit 1
B	Shorter visits and contain procedures that are consistently performed at every visit (targeted Physical exam, Vitals, pregnancy testing, IRT call, Trial drug administration, AEs/SAEs/ AESIs, and Concomitant therapy
C	All "B" procedures plus IGA, EASI, SCORAD and VAS SCORAD
D	Approximately 6 month visit in each year. All "B", and "C" procedures plus safety labs, [redacted]
E	Yearly visit. All "B", "C", and "D" procedures plus weight, smoking status, ECG and Infection Testing. A complete physical rather than a targeted exam is to be performed.

Footnotes to Flow Chart:

1. Patients should sign consent on or prior to visit 1 (V1).
2. V1 of this extension trial should be preferably performed during the EOS of the preceding BI 655130 parent trial. When the visits are performed on the same day duplicate procedures across studies are performed once during the EOS/V1. If these visits are not performed on the same day then all V1 procedures need to be performed at that visit. The only exception is Infection Testing which does not have to be repeated if performed at EOS of the parent trial and there is a <12 week gap from EOS of parent trial to V1 of this trial. Refer also to Section 6.2.1
3. After the individual patient's end of the trial the investigator should report only any cancers of new histology and exacerbations of existing cancer, study treatment related SAEs and study treatment related AESIs of which the investigator may become aware of and only via the BI SAE form. Refer to Section 5.2.6.2.1.
4. All patients who receive at least one dose in the trial, including those who discontinue treatment prematurely, should complete the EOT visit as soon as possible and complete the EOS visit 16 weeks after the date of last trial drug administration.
5. Where possible, electrocardiogram (ECG) measurements should precede blood sampling and drug administration. Refer to Section 5.2.4
6. Body Surface Area (BSA) will be calculated from Part A of the SCORAD. All assessments must be done prior to trial drug administration. The questionnaires completed by patients should be done first before the investigator assessments. Refer to Section 6.2
7. Only applicable for women of childbearing potential. Urine pregnancy tests will be performed at all 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. In case of a positive urine pregnancy test, a serum pregnancy test will be performed at the central laboratory.
8. Complete Physical Examination (PE) includes general appearance as well as evaluation of all organ systems.
9. Targeted physical examination includes evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.
10. Vital signs will be assessed pre dose as well as within 1 hour post dose.
11. Safety laboratory tests include clinical chemistry, haematology, coagulation, and urinalysis, and will be performed centrally. Where possible, safety laboratory tests are to be drawn prior to dosing.
12. Infection testing includes tuberculosis, hepatitis B, hepatitis C, and HIV assessments. Refer to Table 5.2.3:1 and Section 6.2.1. During a combined EOS/V1 only hepatitis C and HIV assesments will need to be done while results of tuberculosis and hepatits B will be used from the parent trial.
13. At EOT visit, infection testing and ECG are only required if not done within the past 6 months.
14. [redacted]
15. For patients who complete the trial, the EOT visit will be the last treatment administration. For patients who discontinue early, there will be no treatment administration at the EOT visit.
16. There will be two IRT calls needed at Visit 1. The first is the study enrolment call performed after the patient signs consent; the second call is a "medication assignment" call performed after confirming eligibility to dispense the first dose of medication.
17. If a patient completes the trial and week 204 (Visit 52) is the EOT, then the site will need to make 2 IRT transactions- one transaction to dispense last medication, and another transaction to complete treatment. For patients who discontinue early, there will be 1 IRT call (transaction) to discontinue treatment.
18. Height is collected at Visit 1 only.

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ABBREVIATIONS

AD	Atopic Dermatitis
ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ADCC	Antibody Dependent cellular cytotoxicity
ALQ	Above limit of Quantification
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BI	Boehringer Ingelheim
BLQ	Below limit of Quantification
BSA	Body Surface area
CA	Competent Authority
CDC	Complement dependent cytotoxicity
CK	Creatine Kinase
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as "eCRF")
CRO	Contract Research Organisation
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DILI	Drug Induced Liver Injury
[redacted]	[redacted]
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EASI	Eczema Area and Severity Index
EC	Ethics Committee

ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EDTA	Ethylendiaminetetraacetic acid
EOS	End of Study
EOT	End of Treatment
EudraCT	European Clinical Trials Database
FAS	Full Analysis set
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GMP	Good Manufacturing Practice
GPP	Generalized pustular psoriasis
HA	Health Authority
HBV	Hepatitis B Virus
HCP	Health Care Proffessional
HIV	Human Immunodeficiency virus
IL	Interleukin
i.v.	intravenous
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator Global Assessment
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITE	Indirect Target Engagement
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of the Quantification
LPLT	Last Patient Last Treatment

LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Drug Regulatory Activities
Nab	Neutralizing Antibodies
NOAEL	No-observed-adverse-effect level
[redacted]	
OPU	Operative Unit
PASI	psoriasis area and severity index
PBMC	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamic
PK	Pharmacokinetics
PPP	Palmoplantar pustulosis
PRO	Patient Reported Outcome
RA	Regulatory Authority
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual Effect Period
RNA	Ribonucleic acid
SC	Subcutaneous
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SCORAD	SCORing of Atopic Dermatitis
SD	Standard Deviation
SoC	Standard of Care
SOP	Standard Operating Procedure
STORM	Storage Conditions for Trial Medications
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TMDD	Target-Mediated Drug Disposition
TSAP	Trial Statistical Analysis Plan
ULN	Upper Level of Normal
ULOQ	Upper limit of quantification
VAS	Visual Analog Scale
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 (pruritus). 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 Interleukin (IL)-13, IL-4, IL-33, and IL-22.

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 IL36 (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 from a mouse model 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).

1.2.1.1 Residual Effect Period

The Residual Effect Period (REP) of BI 655130 is 16 weeks. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

1.2.1.2 Key pharmacokinetic characteristics

PK data so far suggest target-mediated drug disposition (TMDD) kinetics for BI 655130. The saturation of the non-linear elimination pathway is likely occurring after 0.3 mg/kg and BI 655130 seems to exhibit linear kinetics from the next dose-level onwards. Based on the PK in normal volunteers and GPP patients, the elimination half-life of BI 655130 in patients is approximately 3 weeks.

[redacted]

1.2.3 Clinical Experience

As of September 2018, 212 subjects have been exposed to single or multiple doses of BI 655130 in completed or ongoing clinical studies. The clinical safety data support the use of BI 655130 in clinical studies with repeat doses up to 20 mg/kg IV q week for 4 weeks. In phase I trials 1368-0001 and 1368-0002, single administration up to 20 mg/kg IV and repeat dosing up to 20 mg/kg IV have been tested. In trial 1368-0003, single doses of 150 or 300 mg SC and 300mg IV have been tested. In trial 1368-0029 single doses of up to 300 mg SC have been tested. All adverse events (AEs) reported were of mild or moderate intensity; drug-related AEs of moderate intensity were only observed in 1 subject in the 20 mg/kg BI 655130 treatment group (these AEs led to study drug withdrawal). All AEs were resolved by trial completion and no relevant changes were observed in safety laboratory tests, vital signs, or ECGs. No dose dependency was observed for all AEs. The incidences of drug related AEs were balanced across treatment groups up to 10 mg/kg dose, while higher incidences were reported in the 20 mg/kg dose group.

PK data suggest target-mediated drug disposition (TMDD) kinetics for BI 655130, with linear kinetics after 0.3 mg/kg. The effective half-life of BI 655130 is approximately 3 weeks in the linear dose range. Indirect target engagement (ITE) of IL36R by BI 655130, using an ex-vivo whole blood stimulation assay, indicates 94% inhibition of MIP-1β compared to baseline for up to 70 days after single dosing and at 90% inhibition for up to 22 weeks after

multiple dosing. Thus, the safety profile was established at doses corresponding with at least 90% target saturation in peripheral whole blood up to 22 weeks after last dose.

In a study of BI 655130 in 7 patients with GPP (1368.0011) who received a single infusion of 10 mg/kg of BI 655130, none of the reported AEs was severe, serious or led to discontinuation and no relevant abnormalities in laboratory values or vital signs were observed. Proof-of-concept was achieved with these 7 patients, who showed rapid clinical responses to single administrations of BI 655130 with good safety and tolerability.

A placebo controlled Phase II study (1368-0015) has also been conducted to in 59 patients with palmoplantar pustulosis (PPP), 38 of whom received infusions of BI 655130 at doses up to 900 mg every 4 weeks (0, 4, 8 and 12 weeks) and were followed-up through week 32. Two Serious AEs (SAEs) were reported (one patient each in the 300 mg BI 655130 and placebo arm). While the majority of AEs were mild or moderate and expected for the population, a severe AE was reported in 2 patients for each of the three study arms (300 mg BI 655130, 900 mg BI 655130 and placebo). Four AEs (10.5%) in patients treated with BI 655130 and three AEs (14.3%) in patients treated with placebo led to discontinuation of trial medication. Three patients in the 900 mg BI 655130 arm and two in the placebo arm experienced a significant AE. No AEs of special interest (AESI) were reported. No clinically relevant abnormalities with respect to safety laboratory and vital signs were observed.

While the proportion of patients who achieved ppPASI50 at Week 16 in the total population was similar in all treatment groups (6 of 19 in 900 mg BI 655130 arm, 6 of 19 in 300 mg BI 655130 arm, and 5 of 21 in placebo arm) the baseline disease severity within the trial population was lower than expected, with half of the patients having a baseline ppPASI total score ≤ 16.70. In patients with baseline disease scores > 16.7, a post-hoc subgroup analyses indicated efficacy for both doses of BI 655130. The mean percent reduction from baseline in pustular severity was 58%, 35% and 8% for the 900 mg BI 655130, 300 mg BI 655130 and placebo groups respectively, indicating a dramatic reduction in pustule severity with evidence of a dose response relationship.

Overall, BI 655130 was safe and well tolerated. Most AEs were of mild or moderate intensity and there were only 2 serious AEs, one of which occurred in a patient receiving placebo. No AE was considered to be dose-limiting and no AEs of special interest occurred. All AEs were resolved by the end of the trial. There were no relevant changes in safety laboratory tests, vital signs, or ECGs. No safety signals have been identified for BI 655130. There is preliminary, non-placebo controlled, efficacy in patients with an acute flare of GPP and a signal of efficacy in PPP patients with baseline disease scores above 16.7.
For further details and most up-to-date results refer to the current "Investigator`s Brochure" (IB) [c03320877-06].

1.3 RATIONALE FOR PERFORMING THE TRIAL

The purpose of the trial is to offer to all patients who completed the clinical trial 1368-0032 as planned, the option to continue to receive BI 655130 treatment if they have responded to treatment and meet all criteria for study entry.

This trial is designed to evaluate the long-term tolerability and safety of BI 655130 in patients with AD. The data generated from this extension trial is anticipated to provide additional safety data of up to approximately four years treatment in approximately 40 patients treated with BI 655130.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

The parent study (1368-0032) is the first use of BI 655130 in patients with AD.
Since this trial is ongoing the efficacy of BI 655130 in AD patients cannot be confirmed at this time. Nonetheless, if patients respond in the parent study they will receive the benefit of continued study medication.

The link between IL36R and AD is based on upregulation of human IL36R and its ligands in skin biopsies from AD patients, as well as data showing IL36R functionality in disease relevant primary human cells. In a mouse model, IL36R plays a role in the pathogenesis of AD via a specific pathway related to S. aureus infection [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.

Patients in the parent trial (1368-0032) who do not achieve at least a 50% reduction in Eczema Area and Severity Index (EASI) following treatment with BI 655130 will not be enrolled in 1368-0037. Thus, all patients in 1368-0037 will be receiving BI 655130 and will have experienced some reduction in their disease in the parent trial. Since all patients will receive active treatment, most patients have a potential benefit from participating in this long term clinical trial.

1.4.2 Risks

There are no identified or potential safety risks for BI 655130, based on the toxicology programme or any clinical trials conducted for this product to date (Refer to Section 1.2). No other IL-36 receptor antagonist is currently approved, providing information on identified risks in molecules of this class.

Currently there are no data available to suggest interactions of BI 655130 with other drugs [c03320877-06]. Since the drug exposure in this trial is expected to be lower than in the parent trial (1368-0032), there is a risk that some patients will lose response. Rules for discontinuation for these patients are outlined in Section 3.3.4.1.

The risks shown in the table below are hypothetical in nature; these are derived from general safety considerations of immunomodulatory drugs.

In order to protect the patient's safety during conduct of this trial, an independent Data Monitoring Committee has been established for the periodic review of clinical trial safety data.

Table 1.4.2:1 Study Risks

Hypothetical risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product		
Drug Induced Liver Injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´safety. See Section 5.2.6 (AESI)
Systemic Hypersensitivity	After administration of any biologic agent or protein there is a possibility of occurrence of adverse immune reactions which can be local (e.g. redness, pruritus, and or swelling at the injection site) or systemic (e.g. anaphylactic reactions). As patients have already been exposed in the parent trial, the risk of systemic hypersensitivity is low	Patients with a history of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients are excluded from the trial. In case of systemic hypersensitivity reactions including anaphylactic reaction emerging during or after administration of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care (SoC) to interrupt and treat the condition. Systemic hypersensitivity reaction is defined as AESI. It is subject to close monitoring and investigators are requested assess these conditions using the criteria discussed in the statement paper from Sampson HA [R11-4890].
Infections	Inhibition of the immune response with an immune-modulating biologic may increase the risk of infections. A recent characterization of individuals with homozygous IL36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signaling pathway inhibition does not compromise host defenses	Screening procedures for infections will be established for this trial. Patients with any relevant chronic or active acute infections including human immunodeficiency virus (HIV), viral hepatitis or tuberculosis are excluded from the trial. Treatment of infections should be initiated promptly according to standards of care. Severe infections and opportunistic

	[R17-3632].	infections are considered AESI for this trial. These conditions and serious infections are subject to close monitoring. Patients with active systemic infections during the parent 655130 study must delay Visit 1 in this study until the infection has resolved for at least 2 weeks. An independent data monitoring committee (DMC) is in place to periodically evaluate clinical trial safety data.
Malignancies	Inhibition of the immune response with an immune-modulating biologic may increase the risk of a decreased immune defense against malignancies. A recent characterization of individuals with homozygous IL36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signaling pathway inhibition does not compromise host defenses [R17-3632].	Patients with a documented active or suspected malignancy will be excluded from participation in this trial. In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with BI655130. Diagnostics and treatment have to be initiated according to local SoC. Malignancies represent always serious adverse events and are subject to close monitoring.
Inclusion of paediatric, pregnant and lactating patient	Currently there are no data available allowing the conduct of clinical trials in paediatric patients, pregnancy and lactation.	Until such data are available, these patients will be excluded.
Trial procedures		

Blood Sampling and SC injection	The risks of SC injection are expected to be lower than i.v. infusion used in parent trial (1368-0032) There is a risk of mild pain, local irritation, erythema, or bruising at the injection/ puncture site. There is a small risk of lightheadedness and/or fainting. In rare cases the puncture site can also become infected or nerves may be damaged inducing long lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain. Frequent blood collection may cause anaemia (low red blood cell count), which may create a need for blood transfusions.	(a) Close clinical monitoring of AEs (b) selection of experienced sites and site staff; (c) Training.

1.4.3 Discussion

Considering the unmet medical need for development of an effective and well tolerated drug for the therapy of AD this benefit is considered to outweigh the potential risks and justifies the long term administration of BI 655130 to patients with AD.

Based on the limited data currently available, the risks to patients associated with administration of BI 655130 are considered acceptable.

In order to detect and mitigate any safety signals and potential risks described above as early as possible, an independent Data Monitoring Committee (DMC) will oversee this study.

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 assess the long term safety and efficacy of treatment with BI 655130 in patients with AD who have completed and have responded to treatment in the parent study 1368-0032.

2.1.2 Primary endpoint

Number of patients with treatment emergent AEs at week 48

2.1.3 Secondary endpoints

Secondary endpoints are:

- Percentage change from baseline in the Eczema Area and Severity Index (EASI) Score at Week 48
- Percentage of patients with a 50% improvement from baseline in EASI (EASI50) at Week 48
- Percentage of patients with a 75% improvement from baseline in EASI (EASI75) at Week 48
- Change from baseline in SCORing of Atopic Dermatitis (SCORAD) (%) at Week 48
- Percentage of patients achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in Investigator Global Assessment (IGA) at Week 48

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-centre, multi-national open label extension clinical trial. It is anticipated that approximately 40 patients with AD will complete the parent clinical trial 1368-0032 as planned and be eligible for enrolment in this extension trial. Patients who withdrew treatment prematurely in 1368-0032 will not be eligible for this extension trial.

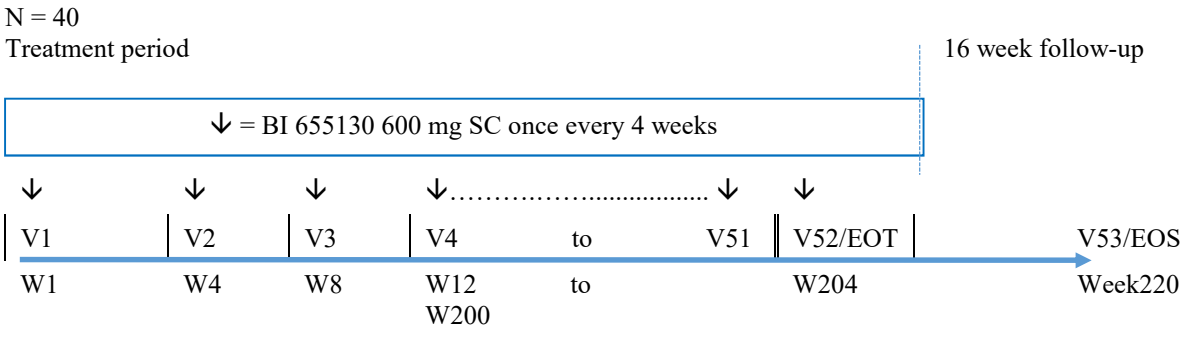
The purpose of the trial is to offer to all patients who completed the clinical trial 1368-0032 as planned, the option to continue to receive BI 655130 treatment if they have responded to treatment and meet all criteria for study entry.

Response to treatment is defined as a 50% or more decrease in EASI in the parent trial. Refer to Section 3.3.1 and Section 3.3.2.

After signing informed consent, and if all eligibility criteria are met, patients will receive the first dose of BI 655130 for this extension trial. All patients will be assigned to receive active treatment, administered subcutaneously (SC).

All patients will return 16 weeks post the last treatment for an End of Study (EOS) visit. The trial is estimated to last approximately 4 years. The trial will end when all patients discontinue treatment, have another means to obtain treatment with BI 655130 or if the development of the drug is terminated. Individual treatment will be stopped if a reason for withdrawal is met.

Figure 3.1:1 Trial Design



V1 is eligibility and first SC injection
V1 should be preferably combined with EOS of trial 1368-0032.
Maximum gap for enrolling is 12 weeks from parent 1368-0032

V = Study Visit
W = Week (study weeks)
EOT = End-of-Treatment
EOS = End-of-Study

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

The trial will be conducted as a prospective, open-label design. The aim of the trial is to allow treatment continuation to individual patients who responded to treatment therefore, randomization, blinding and use or placebo would not be appropriate.

This trial is designed as a long-term extension clinical trial and is expected to generate additional safety information to support registration submissions. Therefore the primary endpoint is focused on safety. Patients who prematurely discontinued blinded treatment (up to Week 16) in the parent trial (1368-0032) are not eligible for this study. In addition only patients who have met the definition of a completed patient and responded to treatment in the parent trial (1368-0032) will be eligible for this study.

Our goal in this study is to obtain additional safety, tolerability and efficacy data following long-term drug administration.

These parameters will be assessed in a descriptive manner, since the trial is open-label and there is no placebo control. Thus, there is no method of controlling observer bias. The duration of the trial is designed to provide additional long term safety data in patients receiving a dose that is at or above the potential to-be-marketed dose. In addition, the trial provides long term access to IP for patients that have responded prior to marketing approval.

3.3 SELECTION OF TRIAL POPULATION

It is anticipated that approximately 40 patients with AD from the parent trial 1368-0032 will be eligible for enrolment in this extension trial. This extension trial will utilize the same sites from the parent trial across the same countries.

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

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

3.3.1 Main diagnosis for trial entry

Patients with AD will be included in this trial if they fulfil all the inclusion and do not present any of the exclusion criteria.

Patients who prematurely discontinued blinded treatment (up to Week 16) in the parent trial (1368-0032) are not eligible for this study. In addition patients from 1368-0032 must have

shown a response in order to be eligible. Patients from the 1368-0032 who were in the non-responder category at week 16, which was defined as less than EASI 75, must have completed the EOS visit and must attain at least an EASI 50 by the last infusion of BI 655130 (Week 28) or by the EOS in order to be eligible for this extension trial.

Patients from the 1368-0032 who were in the responder category at week 16 (V7) which was defined as an EASI 75 or greater, are eligible as long as they have completed the (EOS) visit. If this patient drops to an EASI 50 score prior to the planned EOS at Week 28, they will immediately perform EOS in 1368-0032 and enter into this extension trial.

Patients should enrol into the extension trial as soon as possible after conclusion of the parent trial. It is preferred that the end of study (EOS) visit from parent trial (1368-0032) will be combined with Visit 1 of this trial which includes the first SC dose of trial drug.
The Sponsor must be notified if enrolment is delayed. Patients must be enrolled within a maximum of 12 weeks after the EOS visit from 1368-0032. (Refer to Section 6.2.1 for more detailed information on study procedures).

The results of the safety labs as well as Infection Testing will be available/reported after the patient has entered and received the first dose of study medication in this trial. Refer to Section 3.3.4.1 for discontinuation of treatment rules.

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. Patients who completed the 1368-0032 trial and did not prematurely discontinue treatment prior to week 16, and;
   In the 1368-0032 re-allocation period (V7 to V11):
   - If an original non-responder from week 16 (V7), attained at least EASI 50 by last infusion (week 28) or by the EOS.
   - If an original responder from week 16 (V7) completed the last visit Week 28 (EOS) or dropped to a EASI 50 score prior to Week 28.

3. Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly for the duration of the trial and 16 weeks after last study drug administration. A list of contraception methods meeting these criteria is provided in the patient information. (Refer to Section 4.2.2.3)

[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.

3.3.3 Exclusion Criteria

1. Women who are pregnant, nursing, or who plan to become pregnant while in the trial. Refer to Section 4.2.2.3

2. Any new documented active or suspected malignancy except appropriately treated basal cell carcinoma, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.

3. Use of any restricted medication as specified in Section 4.2.2.1 or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator.

4. Active systemic infections during the last two weeks prior to first drug administration. Refer to Section 1.4.2 and Section 4.2.1

5. Currently enrolled in another investigational device or drug trial, except for 1368-0032.

6. Any condition which would prevent the patient continuing on treatment in this trial 1368-0037.

7. 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.

8. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients.

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 Section 3.3.4.1 and Section 3.3.4.2.

Every effort should be made to keep the patients in the trial.

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 misses more thaan 3 consecutive doses of trial treatment.
- The patient is unable to discontinue use of a restricted medication (Section 4.2.2.1) or requires other concomitant therapy that in the opinion of the investigator may interfere with trial treatment.
- The patient requires rescue medication for the treatment of unstable or worsening of AD. Refer to Section 4.2.2.1
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, and other diseases.) For individual stopping rules related to specific adverse events, please see Section 4.2.1 other treatments and emergency procedures.
- Malignancies during the trial. Refer to Section 4.2.1
- Severe, progressive, or uncontrolled hepatic disease during trial.
- The patient becomes pregnant during the trial.
- Confirmed active tuberculosis during the trial.
- The patient tests positive for HIV or Hepatitis B or C during the trial.

If a patient permanently discontinues trial treatment, the patient should return for the end of treatment (EOT) procedures as well as the end of study (EOS) procedures as outlined in the Flow Chart and Section 6.2.3.

Discontinuation due to pregnancy

If a patient becomes pregnant during the trial the investigator must follow the AE reporting procedure as noted in Section 5.2.6.2.3. The patient must discontinue drug and perform EOT and EOS procedures accordingly. The patient will be followed up until birth or otherwise termination of the pregnancy.

The data of the patient will be collected and reported in the clinical trial report (CTR) until last patient last visit (LPLV) and that any events thereafter will be reported in the BI Pharmacovigilance database.

It is per the Investigator opinion and judgment when trial medication can be temporarily interrupted and then reinstated for certain medical reasons such as surgery, adverse events

and other diseases. In these cases of a temporary discontinuation/interruption of trial treatment, trial treatment should be restarted as soon as medically justified. (Refer to Section 4.1.4 and Section 4.2.1).

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.
If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
3. Deviations from 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

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product

Substance:	BI 655130
Pharmaceutical formulation:	Solution for SC injection
Source:	BI Pharma GmbH & Co. KG, Biberach, Germany
Unit strength:	150mg/mL, 1mL prefilled syringe
Posology:	600mg once every 4 weeks
Method and route of administration:	Subcutaneous

4.1.2 Selection of doses in the trial and dose modifications

The dose selected for this extension trial is 600 mg SC every 4 weeks. The exposure from a single dose of 600 mg SC.is expected to be approximately 60% of the 600 mg i.v. given in the parent trial. The rationale for this dose relates to the feasibility of administering more than 600 mg (4 x 1mL syringe) at a single visit. Thus, it is expected that 600 mg SC will be at or above the to-be-marketed dose. If the data from the non-treatment portion of the parent trial indicates that a different posology is efficacious, the trial will be updated with this new posology, i.e. every 6 or 8 weeks.

For the parent trial, a fixed rather than weight-based dose regimen of single dose of 600 mg was 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) system will be used in this trial in order to dispense medication kits as well as manage initial/re-supply ordering of medication kits. The study site will be required to complete the appropriate module within the IRT system.
The investigator will receive all necessary instructions to access the IRT system from the Sponsor or chosen provider. Detailed IRT transactions and procedures will be documented in the user requirement specifications mutually agreed to by the sponsor and the IRT provider.
All medication kit assignments will occur in an open label fashion.

4.1.4 Drug assignment and administration of doses for each patient

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.

A total dose of 600 mg of BI 655130 will be administered to each patient every 4 weeks starting with Visit 1 until the End of Treatment (Week 204). IRT will dispense 4 medication kits at each drug administration. Each kit will contain one syringe. Each patient will receive all 4 syringes (4 injections) of study drug. Each of the four 1mL prefilled syringes will contain 150mg/mL of BI 655130 for a total dose of 600mg.

Study drug will be administered exclusively at the study site by a Health Care Professional (HCP) which will be the investigator or other authorized study personnel (e.g. study nurse). Study drug will be administered as a SC injection in the abdomen or thighs. Injections being given in the same area should be at least 2 cm apart and should not be close to a vein. The injection site should avoid sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses.

Dose modifications or adjustments are not permitted.
Interruption of trial treatment may be needed to treat AEs (ie. Infections) and trial treatment should be restarted as soon as medically justified. See Section 4.2.1.

Refer to Section 6.2.2 for rules for dosing limitations within a 14 day period

There are no dietary requirements needed.

In the eCRF, the study drug administration time is always the time of the first injection.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is an open label trial thus the patient, investigator and everyone involved in the trial conduct or analysis will be aware of the treatment assignment.

The study treatment (BI 655130 or placebo) in which the patient received through Week 16 in the parent trial will be blinded until the database lock (DBL) of the parent trial.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by Boehringer Ingelheim (BI) or a designated Clinical Research Organization (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 IRB / ethics committee (EC)
- 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,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator (if applicable)
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics unless there is Sponsor approval. All patients will be dosed in the clinic and will not be taking investigational product home.
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 site of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator or designee must verify that all unused drug supplies have been returned by the clinical site staff and all used or partially used drug supplies have been destroyed on site 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 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 patients' AD worsens the investigator can treat the patient with rescue treatment i.e.Standard of Care (SoC) of his/her choice. The sponsor will not provide/supply SoC treatment(s) to the sites. Refer also to Section 4.2.2.1.

Patients with active systemic infections during the parent 655130 study must delay Visit 1 in this study until the infection has resolved for at least 2 weeks.

Severe infections according to Rheumatology Common Toxicity Criteria (RCTC) grading, serious infections, and opportunistic or mycobacterium tuberculosis infections:
Treatment of the infection should be initiated promptly according to local SoC. 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.

Malignancies
In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with the trial medication, and notify the Clinical Trial Manager (CT Manager). Diagnostics and treatment should be initiated according to local SoC.

Systemic Hypersensitivity including anaphylactic reaction

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

1. Stop further injection(s)
2. Treat with systemic anti-histamines, i.v. steroids, and in case of a severe allergic reaction (e.g., anaphylactic reaction) epinephrine

Also draw a plasma sample for IgE and Antidrug antibodies (ADA) as detailed in the laboratory manual and consider the evaluation of histamine, serum tryptase, and complement components.

In case of systemic hypersensitivity, based on patient's clinical course and medical judgment, injections may be cautiously re-initiated or continued in case of mild or moderate systemic hypersensitivity (according to RCTC grading, provided in the ISF).

In case of anaphylactic reaction based on the criteria discussed in the statement paper from Sampson HA (Appendix 10.1, R11-4890) suspected to be caused by the trial medication, the investigator should discontinue treatment with study drug.

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

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The medication (or classes of medications) listed in Table 4.2.2.1:1 are restricted for the entire study participation (V1 through to EOS). In the event that EOS/V1 cannot be done on the same day and a gap is needed from EOS of the 1368-0032 to visit 1 of this trial, restricted medication allowed and washout periods are noted in the right column of table.

Table 4.2.2.1: 1 Restricted Medications

Medication or class of medications during study[1]	Washout periods prior to V1
Dupilumab, UVB phototherapy, PUVA	Not allowed during gap
Hydroxyzine, diphenhydramine, doxepin	Must be stopped 1 week before Visit 1
Any other topical medication particularly moisturizers containing urea or high potency topical steroids[3]	Must be stopped at Visit 1
Methotrexate, cyclosporine, retinoids, azathioprine	Must be stopped 4 weeks prior to Visit 1
IL36R inhibitors	Not allowed during gap
All other biologics, including but not limited to etanercept (Enbrel®) adalimumab (Humira®) infliximab (Remicade®) ustekinumab (Stelara®), secukinumab (Cosentyx®), brodalumab (Siliq®), guselkumab (Tremfya®), ixekizumab (Taltz®), tildrakizumab (Ilumya®), risankizumab (Skyrizi®), rituximab,	Not allowed during gap
live virus vaccinations	Not allowed during gap
other systemic immunomodulating treatments (e.g. corticosteroids[2], cyclophosphamide), tofacitinib (Xeljanz®), apremilast (Otezla®)	Must be stopped 4 weeks prior to Visit 1
Any investigational device or product	Not allowed during gap

[1] In case of worsening of the AD in the treatment period the use of a rescue medication is left at the discretion of the investigator.
[2]No restriction on inhaled corticosteroids to treat asthma or corticosteroid drops administered in the eye or ear.
[3]Low potency topical steroids and non-urea containing moisturizers are allowed.

Restricted medication is defined as the use of any drugs listed in the Table 4.2.2.1:1 for any reason with the exception of unstable or worsening of AD). If the restricted medication is taken during the trial, trial treatment discontinuation is not mandatory. The continuation of the treatment is left at the discretion of the investigator.

Rescue medication is defined as the use of highly potent topical corticosteroids, systemic immunomodulating treatments or biologics for the treatment of unstable or worsening of AD. The use of the rescue medication leads to the discontinuation of the trial treatment.

4.2.2.2 Restrictions on diet and life style

There are no restrictions on diet and life style however patients should avoid prolonged exposure to sunlight and artificial UV light.

4.2.2.3 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 for the duration of the trial and 16 weeks after the last study drug administration. A list of contraception methods meeting these criteria is also 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 (oral, intravaginal, transdermal).
- Progestogen-only hormonal birth control associated with inhibition of ovulation (oral, injectable, implantable).
- Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS).
- Bilateral Tubal occlusion (blocking of the fallopian tubes).
- Vasectomy of sexual partner (proven effective by documented absence of sperm on the ejaculation).
- Complete sexual abstinence (not to have male-female vaginal sex). This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

As monoclonal antibodies can be secreted in milk, women must stop nursing once they receive study drug and up to 16 weeks after the last study drug administration.

4.3 TREATMENT COMPLIANCE

Administration of the trial medication will be done in the study centre 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)[redacted]

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 very severe disease (0= clear,1 =almost clear, 2 = mild disease, 3 = moderate disease, 4= severe disease). The IGA scale uses clinical characteristics of erythema, infiltration, papulation, oozing and crusting as guidelines for the overall severity assessment [R18-2670].

[redacted]

[redacted]

5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:
- Adverse events (including drug-related AEs and AEs leading to discontinuation)
- 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
- Immunogenicity (ADA)

5.2.1 Physical examination

A complete physical examination will be performed at the visits as specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

A targeted physical examination will be performed at visits as specified in the Flow Chart. This includes vital sign assessment as well as an evaluation of the organ systems associated with AE(s) symptoms or laboratory abnormalities.

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

5.2.2 Vital signs

Vital signs will be performed pre-dose as well as within 1 hour post dose (Refer to Flow Chart). Vital signs include systolic and diastolic blood pressure, pulse rate (electronically or by palpation count for 1 minute) and body temperature. Vital signs will be measured after the patients has been sitting comfortably (resting) for at least 5 minutes The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3:1. For the sampling time points please see the Flow Chart.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.

Patients do not have to be fasted for the blood sampling for the safety laboratory.

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

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

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (Refer to Section 5.2.6.1.4) and the DILI Checklist provided in the ISF. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

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

Table 5.2.3:1 Safety laboratory tests

Category	Test Name
Haematology	Haematocrit Haemoglobin Red blood cell count (RBC) White blood cell count (WBC) Platelet count
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Manual differential WBC (if auto 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) Alanine transaminase (ALT) 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) Hepatitis B core Antibody (qualitative) Hepatitis B Virus (HBV)-DNA (quantitative)[2] QuantiFERON®-TB[3] Hepatitis C Antibodies (qualitative) HIV-1, and HIV-2 Antibody (qualitative)
Urine Pregnancy test[4] 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 (only if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin

[1] Refer to exclusion criteria Section 3.3.3 the Flow Chart and Section 6.2.1 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.
[3] Patients with suspected false positive or indeterminate QuantiFERON TB result may be re-tested once. A PPD skin test may be performed locally in case of an indeterminate QuantiFERON TB result.
[4] Urine pregnancy testing will be performed as indicated in the Flow Chart.
NOTE: See Section 4.2.1 and lab manual for lab procedures required for hypersensitivity and anaphylactic reactions.

5.2.4 Electrocardiogram

A central laboratory will not be used for ECG recording and evaluation.

The 12-lead ECGs must be administered by a qualified staff member and results will be recorded and reviewed prior to dosing as scheduled in the Flow Chart. Where possible, ECG measurements should precede blood sampling to avoid impact of sampling on the ECG results. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis.

Additional ECGs may be recorded for safety reasons. The 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 Visit 1) or as adverse events and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

All cases of malignancies that are detected during the trial will be reported as SAEs. Patients with a documented active or suspected malignancy (except for specific cancers) will be excluded from this trial per the exclusion criteria (Section 3.3.3).

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

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

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

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

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

5.2.6.1.2 Serious adverse event

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

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

For Japan only: the following events will be handled as “deemed serious for any other reason”. AEs which possibly lead to disability will be reported as SAEs.

5.2.6.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of 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 electronic data capture (eDC) system. A copy of the latest list of “Always Serious AEs” will be provided upon request. These events should always be reported as SAEs as described above.

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

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) 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 Section 5.2.6.2.2. Refer also to Section 1.4.2 and Section 4.2.1

The following are considered as AESIs:

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

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

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Systemic hypersensitivity reactions including anaphylactic reaction

Any suspicion of severe systemic hypersensitivity reaction and of any potential cases of anaphylaxis should be defined and assessed using the criteria discussed in the statement paper from Sampson HA (Appendix 10.1, 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].

5.2.6.1.5 Intensity (severity) of AEs

The intensity grading of AEs will be performed according to RCTC Version 2.0 developed by the [redacted] [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

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, 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.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

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

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 trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details 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 fax 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. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

5.2.6.2.3 Pregnancy

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.

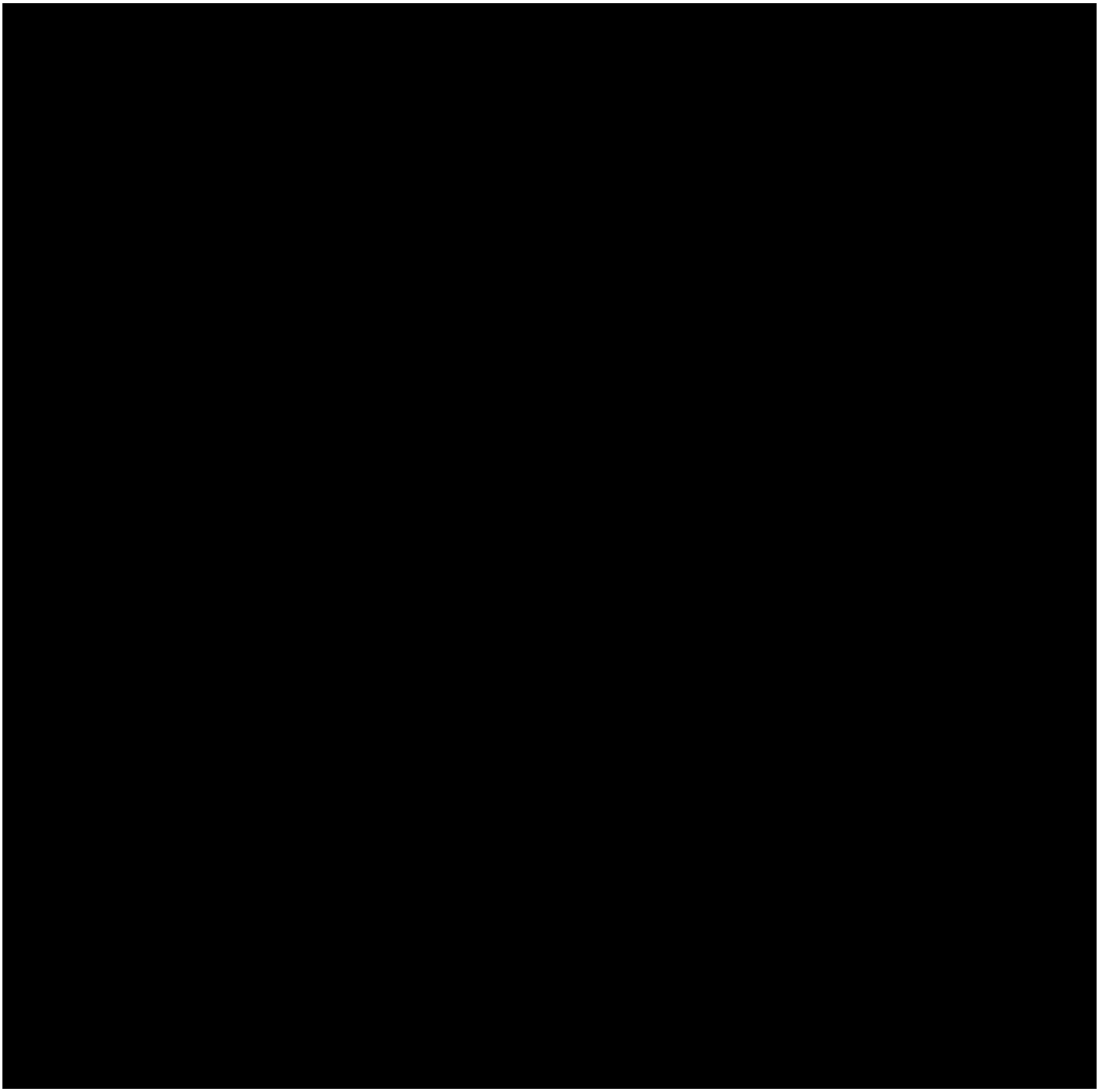
The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Studies (Part B).

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.

5.2.6.2.4 Exemptions to SAE reporting

For this study there are no exemptions to SAE reporting.



[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.5 BIOBANKING

N/A

5.6 OTHER ASSESSMENTS

N/A

5.7 APPROPRIATENESS OF MEASUREMENTS

The safety assessments are standard, are accepted for evaluation of safety and tolerability of a SC 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 biomarker parameters 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 AD 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 (V1).

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 and treatment interruptions are provided in Section 4.1.4.

Study measurements and assessments are scheduled to occur 'before' trial medication administration. For planned individual plasma concentration sampling times refer to the Flow Chart. 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 5.1 for explanations of the specified assessments and procedural details.

The patients' questionnaires [redacted] are to be completed by the patient him/herself, without any help from or interpretation by other people. [redacted].

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

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

[redacted]
3. IGA, EASI, SCORAD

6.2.1 Visit 1

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

Visit 1 should preferably be performed in one visit combined with EOS visit of the preceding BI 655130 parent trial. These duplicate procedures across the two studies are performed only once when the visit is combined. When these two visits across both studies does not occur on the same day then all procedures will need to be performed at V1 of this trial. Refer to the Flow Chart for procedures that are identical across the two visits.

If a patient performs the EOS visit in the parent study but a newly observed medical finding (for example) prohibits the patient to immediately enrol into this study, the patient can come back for Visit 1 at a later date per the opinion of the investigator. The sponsor should be immediately notified if Visit 1 of this trial cannot be performed on the same day as the EOS in the parent study.
The maximum gap for enrolling into this trial is 12 weeks after the EOS in 1368-0032.

Informed Consent
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. Study requirements, including the procedure for the follow-up of prematurely withdrawn patients, must be fully explained to the patient. The importance of staying in the study until completion of all requirements is to be emphasized.
Once consent is obtained, the patient is to be recorded on the enrolment log. The informed consent date will be reported in the eCRF.

IRT procedures and administration of study drug
Once consent is obtained an initial “enrolment call” must be made in the IRT system. At that time a patient number will be generated.

When confirmed at Visit 1 that the patient meets all criteria and can be administered study medication, a medication assignment call must be made in the IRT system in order to dispense the first dose of study medication. Medication assignment via the IRT system and administration of study drug should be the last activity at Visit 1.

Details of IRT procedures can be found in the IRT manual located in the ISF.

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

Medical History and Baseline Conditions:
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 Visit 1 will be recorded as medical and surgical history.

All ongoing AEs/SAEs at the end of the parent trial will be recorded on the Baseline Condition eCRF page of this 1368-0037 study.

Height and Weight
Height and Weight will be collected and reported in the eCRF per the Flow Chart.

Smoking Status
Smoking status will be collected at and reported in the eCRF per the Flow Chart.

Infection screening:
Infection testing will include tuberculosis, hepatitis B, hepatitis C, and HIV assessments (see Table 5.2.3:1). The results of the Infection Testing will not be available until after the patient receives the first dose at Visit 1. See Section 3.3.4.1 for Discontinuation Rules.
If there is less than 12 week gap from the EOS of the preceding trial to V1 of this trial, the Infection testing does not have to be repeated at Visit 1.

QuantiFERON TB testing

Patients with suspected false positive or indeterminate QuantiFERON TB result may have the test repeated once. If after repeat testing the QuantiFERON TB result is "indeterminate" A PPD skin test may be performed locally. A tuberculin skin test reaction ≥10mm (≥5mm if receiving ≥15mg/d prednisone or its equivalent) is considered positive.

Patients who now test positive for QuantiFERON TB test may continue and receive treatment in this study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis.

If presence of latent tuberculosis is established, patients can receive anti-tuberculosis treatment (according to local practice/guidelines) and continue receiving study medication.

Pregnancy Testing
Urine pregnancy testing for all woman of childbearing potential will be conducted on-site prior to every dosing and must be negative to receive study drug. A positive urine test must be confirmed with a serum pregnancy test at the central laboratory

Concomitant medication review:
Any concomitant treatment taken since the last visit of previous study will be recorded in the eCRF.

Review of inclusion/exclusion criteria:
Selection criteria will be reviewed carefully and patient eligibility confirmed prior to first dose.

Blood sampling
If EOS from the parent study and V1 from this study are performed on the same day, two lab kits will be required. The EOS lab kit from the parent study will be used. In addition a V1

lab kit from this trial will also need to be used as it contains labs not already included in the EOS from the previous parent trial. Details will be provided in the laboratory manual and the ISF.

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

6.2.2 Treatment period

After Visit 1, the patient will return for 51 additional visits during the treatment period. The duration between visits is 4 weeks. At every visit study drug will be administered.

If the patient completes this 4 year study, the last study drug administration will be at Visit 52 (EOT).

Drug administration and rules for early/late visits
It's important for the patient to adhere to the visit schedule per the Flow Chart. The visit schedule should always align with Visit 1.
The IRT system has been set up to make sure that a patient does not receive 2 doses of medication in less than a 14 day period.
In these scenarios, the patient should conduct the visit but skip the dose. The patient should be administered the dose at the next scheduled visit.

Pregnancy Testing
Urine pregnancy testing for all woman of childbearing potential will be conducted on-site prior to every dosing and must be negative to receive study drug. A positive urine test must be confirmed with a serum pregnancy test at the central laboratory.

See the Flow Chart for details of all procedures required at each visit.

Unscheduled visits
If a patient suspects that their AD is worsening in between the protocol specified scheduled visits, they should make an unscheduled visit and return to the clinic/site for assessment.
The patient may be called in for additional unscheduled visits due to safety reason at the discretion of the investigator or the sponsor, unless the patient has withdrawn his/her consent.
The patient may also contact the site due to safety reason for an unscheduled visit. The unscheduled visit may include additional collection of blood samples for safety reasons. The unscheduled visit may also include additional assessments deemed necessary by the investigator such as laboratory samples, ECGs, or other procedures which were missed at a previous visit. All unscheduled visits should be described (including the reason for the visit) and documented in the medical/source record, and in the eCRF.

6.2.3 End of Treatment and Trial Completion

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

For the comprehensive list of the trial procedures required at the EOT and the EOS visits please refer to Flow Chart.

The EOS visit must be performed 16 weeks after the date of last drug administration.

Early Treatment and Trial Discontinuation:
If trial treatment is discontinued prematurely prior to the planned Flow Chart EOT visit, every effort should be made to have the patient return and undergo the procedures for the EOT visit as well as the EOS visit 16 weeks after the last study drug administration as outlined in the Flow Chart.

Patients who are unable to physically return to the study site for the EOT and EOS visits should be contacted by the site by phone to collect information pertaining to adverse events and changes to concomitant therapy.

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 completing Visit 52 which is the EOT visit after receiving approximately 4 years of treatment

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This is an exploratory extension trial in patients with AD. It is designed as an open label study with one group of BI655130 150mg/mL (600mg once every four weeks).

The primary objective of this trial is to assess the long term safety and efficacy of treatment with BI 655130 in patients with AD who have completed and have responded to treatment in the parent study 1368-0032.

The primary endpoint is the number of patients with treatment emergent adverse events (AEs) at week 48. The efficacy will be assessed using secondary and further endpoints.

All analyses are planned to be descriptive in nature.

7.1 NULL AND ALTERNATIVE HYPOTHESES

No statistical testing is planned for this study. Only descriptive analyses are intended. Therefore, no statistical hypotheses are defined.

7.2 PLANNED ANALYSES

7.2.1 General considerations

The efficacy analyses will be performed for the Full Analysis Set (FAS) that includes all patients who entered the study, received at least one dose of treatment, had a baseline measurement, and at least one post-baseline measurement.

All safety analyses will be performed on patients who entered the study and received at least one dose of treatment during the trial. This set of patients is called Safety Analysis Set (SAF).

With regard to efficacy and safety endpoints “baseline” refers to:

1. Baseline for the parent trial – the measurement recorded at randomisation visit (Visit 2) of the parent trial (1368-0032). If the data at Visit 2 is missing, then the data from Visit 1 of the parent trial will be considered baseline.
2. Baseline for the extension trial – the last measurement before the BI655130 treatment intake in this extension trial.

Two separate analyses will be conducted – one including baseline from parent trial and the second including baseline form this extension trial.

Important deviations of the protocol will include key inclusion and exclusion deviations, incorrect medication taken, concomitant use of restricted medications, and any other deviations from the protocol deemed important by the study team.

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) of frequency tables (including patient frequencies and percentages) will be calculated where appropriate.

The statistical parameters will be provided for the following groups:

1. By treatment received in the parent trial (1368-0032):
    - Placebo followed by BI655130 treatment
    - Placebo followed by no BI655130 treatment
    - BI655130 followed by BI655130 treatment
    - BI655130 followed by no BI655130 treatment
    - Total
2. By the response achieved at week 16 of the parent trial (1368-0032):
    - Responders – patients who attained at least 75% reduction in EASI score at week 16 compared to baseline during the parent trial
    - Non-responders - patients who attained less than 75% reduction in EASI score at week 16 compared to baseline during the parent trial;
    - Total

7.2.2 Primary endpoint analyses

The primary endpoint is the number of patients with treatment emergent AEs at week 48 and will be a part of the safety analysis (as described in Section 7.2.5). The primary analysis will be descriptive and will result in frequency table presenting the numbers and percentages of patients with treatment emergent AEs displayed per group as defined in Section 7.2.1 and also by the following subgroups:

- Asian/Non-Asian
- Age groups: <=30 years old/>30 years old

The primary analysis will be performed on the SAF.

7.2.3 Secondary endpoint analyses

All secondary analyses are planned to be descriptive. For continuous endpoints (change form baseline in EASI score and in SCORAD), standard statistical parameters (including number of non-missing values, mean, SD, median, quartiles, minimum, and maximum) will be presented per group as defined in Section 7.2.1 and also by the following subgroups:

- Asian/Non-Asian
- Age groups: <=30 years old/>30 years old

For the EASI score, responder analyses will be performed. A patient is defined as EASI50 or EASI75 responder when percent change from baseline in EASI score is at least 50% or at least 75%, respectively. This results in binary variable with values of 1 (=responder) or 0 (=non-responder).

For binary endpoints (EASI50, EASI75, achieving at least a 2-grade reduction from baseline to clear (0) or almost clear (1) in IGA), frequency tables with numbers and percentages of patients will be used and display relevant categories in groups as defined in Section 7.2.1.

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, 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 Medical Dictionary for Drug Regulatory Activities (MedDRA).

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. Groups (defined in Section 7.2.1) 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 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.

[redacted]

7.2.7 Interim Analyses

In order to ensure the patient's safety during the trial, an external DMC, independent of the trial and project teams, will be set-up to review all available safety data as well as selected efficacy data at regular intervals following first-patient-in. A DMC SAP which describes the analyses required for assessment by the DMC will be produced and finalised prior to first patient included into the trial. Further details will be provided in a DMC charter.

There will not be an interim analysis from a statistical standpoint.
As the primary aim of this study is to collect long-term safety and efficacy data on the use of BI655130 in this population, multiple status reviews will be done over the approximate 4-year conduct phase of this trial to support, for example, regulatory interactions, CTA and MAA/BLA submissions, but also to provide important safety and efficacy information to the sponsor to guide further development of the compound, and to investigators via IB updates and publications. Status review analyses will be performed on demand and are not feasible to be pre-defined.

A CTR describing all data collected within this trial will be produced once the last patient in the trial has completed the final End-of-Study (EOS) visit.

7.3 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 or continuous efficacy evaluations, it is not planned to impute missing values.

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

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

For disease specific protein markers the following handling of data below or above the limit of quantification will be applied:

- Below limit of quantification (BLQ) data will be replaced by 0.5 times the lower limit of the quantification (LLOQ)
- Above limit of quantification (ALQ) data will be replaced by upper limit of quantification (ULOQ), if ULOQs are available. Otherwise, ALQ data will be excluded from the analysis.

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

7.4 RANDOMISATION

Given the single arm nature of the trial, no randomisation will be performed.
For packaging and labelling details, see Section 4.1.6.

7.5 DETERMINATION OF SAMPLE SIZE

This is an extension trial of the parent clinical trial 1368-0032 and given its descriptive nature, no sample size calculation has been performed. The sample size calculation for the parent trial can be found in the 1368-0032 CTP [c23806995-01].

Approximately 40 (but no more than 45) patients from the parent trial 1368-0032 who meet the entry criteria are planned for entry into this trial.

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

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

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

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

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

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 [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Copies of 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)
- Patient reported outcome forms and corresponding investigator assessment forms
- 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 Asociate (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 ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).
Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
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 Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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).

While Regular DMC meetings will be held at specified intervals. 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 will be specified in a charter. The DMC will maintain written records of all its meetings.

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 (CT Leader), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), 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 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. The central laboratory will also manage the collection, storage and shipment of samples to the bioanalytical labs used in this study. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

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10. APPENDICES

10.1 INSTRUCTIONS FOR USE

10.1.1 Clinical criteria for diagnosing anaphylaxis

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

PEF, Peak expiratory flow; BP, blood pressure.

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

11. DESCRIPTION OF GLOBAL AMENDMENT (S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		23 Mar 2020
EudraCT number **EU number**		NA
BI Trial number		1368-0037
BI Investigational Product(s)		BI 655130
Title of protocol		An open label extension study to assess the long term safety of treatment with BI 655130 administered subcutaneously in adult patients with moderate to severe atopic dermatitis

Global amendment due to urgent safety reasons	
Global amendment	X

Section to be changed		Flow chart footnote #2
Description of change		Administrative change to remove reference for completing procedures in the parent trial
Rationale for change		Clarification that procedures can be done as a combined visit (EOS/V1) as described throughout the protocol

Section to be changed		Flow chart footnote #12
Description of change		Hepatitis C and HIV assessment only, are to be completed for combined EOS/V1 visit
Rationale for change		Clarification that during a combined EOS/V1 visit only hepatitis C and HIV assessments are to be completed for this trial and the results of tuberculosis and hepatitis B testing will be used from the parent study

Section to be changed		Flow chart- End of Treatment and End of Study Visits
[redacted]		[redacted]

Section to be changed		3.3.1 Main diagnosis for trial entry
Description of change		Gap period of 16 weeks between IV infusion and first SC injection removed
Rationale for change		Sentence is not consistent with the parent trial amendment as there will be a 4 week period as described in the parent trial amendment

Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Reference to use of restricted medication in the parent trial removed
Rationale for change		The criteria for use of restricted medication through to EOS of parent trial is described in the parent trial protocol and will not be reiterated for this extension trial.

Section to be changed		4.2.2.1:1 Restricted medication table
Description of change		Administrative change to remove paragraph
Rationale for change		Explanation is already provided under section 4.2.2.1 and any reference to parent trial criteria is elaborated under the parent trial protocol

Section to be changed		4.2.2.1:1 Restricted medication table
Description of change		Column headings for medication or classes of medication in addition to washout period updated
Rationale for change		Administrative change for added clarity

Section to be changed		[redacted]
Description of change		
Rationale for change		

Section to be changed		[redacted]
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist	[redacted]	24 Mar 2020 15:11 CET
Approval-Therapeutic Area [redacted]		24 Mar 2020 16:56 CET
Approval-Clinical Project [redacted]		24 Mar 2020 21:09 CET
Approval-Team Member Medicine		25 Mar 2020 00:48 CET
Approval-Biostatistics		25 Mar 2020 16:57 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed