14 September 2023
EMA/453942/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ebglyss

International non-proprietary name: Lebrikizumab

Procedure No. EMEA/H/C/005894/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

(L)LOQ	(lower) imit of quantification
AD	atopic dermatitis
ADA	antidrug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADR	adverse drug reaction
AE	adverse event
AI	autoinjector
AI-PFP	autoinjector – pre-filled pen
ANCOVA	analysis of covariance
anti-ID	anti-idiotypic
AUC	area under the curve
BALF	bronchoalveolar lavage fluid
BMI	body mass index
BP	blood pressure
BSA	body surface area
Cavg,ss	average concentration at steady state
CDC	complement-dependent cytotoxicity
CDR	complementarity-determining region
CE-SDS	capillary electrophoresis sodium dodecyl sulfate
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary cells
CI	confidence interval
CL	vlearance
C_{max}	maximum observed serum concentration
Cmax,ss	maximum concentration at steady state
CMH	Cochran-Mantel-Haenszel
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CPP	critical process parameter
CQA	critical quality attribute
CSE	clinical summary of efficacy
CSR	clinical study report
CT	cycle threshold
Ctrough,ss	concentration before the next dose at steady state
DBL	database lock
DDI	drug-drug interactions
DILI	drug-induced liver injury
DLQI	dermatology life quality index
EASI	eczema area and severity index
EASI 50	50% decrease from Baseline in EASI
EASI 75	75% decrease from Baseline in EASI
EASI 90	90% decrease from Baseline in EASI
EC50	drug concentration that produces 50% of maximum effect (Emax)
ECLA	electrochemiluminescence assay
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
Emax	maximum effect
EOP	end of production
E-R	exposure-response
FDA	food and drug administration
GCP	good clinical practice
GD	gestation day
HCP	healthcare provider
HCP	host cell protein
HF	human factors
HFE	human factors engineering
HMWS	high molecular weight species
HR	hazard ratio
ICE	intercurrent event
IFU	instructions for use
IGA	investigator’s global assessment

IGA 0,1	IGA score of 0 or 1 with a 2-point or greater reduction from baseline
IgG	immunoglobulin G
IgG4	immunoglobulin G4
IL	interleukin
IL-13	interleukin-13
IL-13Rα1	IL-13 receptor alpha-1
IL-4Rα	IL4 receptor alpha
improvement	4-point or greater improvement in pruritus NRS, among participants with a baseline score of at least 4
IND	investigative new drug
IPF	idiopathic pulmonary fibrosis
IR	incidence rate
ISR	injection site reaction
ITT	intention-to-treat
IV	intravenous
JAK	Janus kinase
KD	equilibrium dissociation constant
KLH	keyhole limpet haemocyanin
LD	lactation day
LEB	lebrikizumab
Lilly	Eli Lilly and Company
LIVCA	limit for in vitro cell age
LLOQ	lower limit of quantification
LMWS	low molecular weight species
LTE	long-term extension
MAA	marketing authorisation application
mAb	monoclonal antibody
MACE	major adverse cardiovascular event
MCB	master cell bank
MCMC-MI	Markov chain Monte Carlo multiple imputation
MCV	meningococcal (Groups A, C, Y, and W-135) oligosaccharide diphtheria CRM197 conjugate vaccine
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
NHP	non-human primate
NLT	not less than
NMSC	non-melanoma skin cancer
NMT	not more than
NRS	numeric rating scale
NS0	murine myeloma cell line
PBO	placebo
PFS-NSD	prefilled syringe with needle safety device
PK	Pharmacokinetic(s)
PL	package leaflet
PND	Postnatal day
POEM	patient-oriented eczema measure
PPND	pre- and postnatal development
PRO	patient-reported outcome
PROMIS	patient-reported outcomes measurement information system
PRS	primary reference standard
Pruritus NRS 4-point	
PSB	primary seed bank
PT	preferred term
PY	patient-years
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
QRI	quick reference for injection
QXW	every x weeks
ROW	rest of world
RP-HPLC	reversed phase high performance liquid chromatography
RS	reference standard
SA	scientific advice
SAE	serious adverse event

SBL	Samsung BiologicsSC	subcutaneous
SCE	summary of clinical efficacy	
SCS	summary of clinical safety	
SD	standard deviation	
SD	standard deviation	
SFS	semi-finished syringe	
SmPC	summary of product characteristics	
SOC	system organ class	
SPR	surface plasmon resonance	
STAT6	Signal transducer and activator of transcription 6	
TCI	topical calcineurin inhibitor	
TCS	topical corticosteroids	
Tdap	diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed	
TE ADA	treatment-emergent antidrug antibody	
TEAE	treatment-emergent adverse event	
TGFβ1	transforming growth factor-β1	
TK	toxicokinetic	
TNX-650	lebrikizumab	
ULN	upper limit of normal	
ULOQ	upper limit of quantification	
VAS	visual analogue scale	
Vd	volume of distribution	
WCB	working cell bank	

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Almirall, S.A. submitted on 5 October 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Ebglyss, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication: Ebglyss is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years of age and older who are candidates for systemic therapy.

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0286/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0286/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. New active substance status

The applicant requested the active substance lebrikizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 January 2014	EMEA/H/SA/2699/1/2013/III	*Peter Kiely, Jens Reinhardt*
26 January 2017	EMEA/H/SA/2699/1/FU/1/2016/III	*Carin Bergquist, Peter Kiely*

The scientific advice pertained to the following non-clinical and clinical aspects:

- *Appropriateness of the non-clinical program*
- *Acceptability of the proposed doses, patient population, inclusion/exclusion criteria, trial size, use of the EASI score, treatment scheme, definitions of flare and rebound, assessment of skin infections, proposed safety assessment, inclusion of adolescents in adult trials, the proposed staggered approach for enrolment of different age groups*
- *The study design for WS39518 and WS39519, in particular the proposal for tapering of topical corticosteroids, the statistical plan, the re-randomisation proposal, handling of background TCS, allowance for transition to open-label lebrikizumab, and the study design for WS39520, in particular the statistical plan*
- *The proposed bridging strategy, and proposed plan to support patient self-administration and the acceptability of the proposed filing plan and labelling strategy, proposal to generate safety data.*

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Outi Mäki-Ikola Co-Rapporteur: Selma Arapovic Dzakula

The application was received by the EMA on	5 October 2022
The procedure started on	27 October 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	16 January 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	30 January 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	30 January 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 February 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 May 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all	23 June 2023

CHMP and PRAC members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 July 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	20 July 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	14 August 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	29 August 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	07 September 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ebglyss on	14 September 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	14 September 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Atopic dermatitis (AD) is a chronic and relapsing inflammatory disorder characterised by erythematous, pruritic, dry, scaly and often lichenified skin. Pruritus is a hallmark of AD and is responsible for much of the disease burden for patients and their families. Moderate to severe AD is associated with significant burden, impacting sleep, quality of life, and treatment needs.

2.1.2. Epidemiology

AD is the most common chronic inflammatory skin disease that is often diagnosed in early years in children, but it may also affect patients in their adult life. Global AD prevalence is increasing in all ages: in children up to 20%[1] , while in adults and elderly up to 10% [1,2,3]. In adolescents (≥12 to <18 years),

[1] Silverberg, J. I., et.al. (2021). Atopic dermatitis in the pediatric population: A cross-sectional, international epidemiologic study. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology, 126*(4), 417–428.e2. https://doi.org/10.1016/j.anai.2020.12.020

[2] Barbarot S, Auziere S, Gadkari A et al. Epidemiology of atopic dermatitis in adults: results from an international survey. Allergy 2018; 73: 1284– 1293

[3] Patruno C, Napolitano M, Argenziano G et al. Dupilumab therapy of atopic dermatitis of the elderly: a multicentre, real-life study. J Eur Acad Dermatol Venereol 2021; 35: 958–964

this prevalence is up to 16% worldwide[4]. Among patients with AD in the EU, the proportion with moderate to severe disease varies from 46% to 66% depending on the patient-reported measurement scale used[2].

2.1.3. Aetiology and pathogenesis

AD is a complex disease with an interplay between abnormal immune response, genetic impairment of skin barrier and environmental factors[5]. The immune response in AD is skewed towards T helper 2 (Th_2) cell-mediated pathways[6]. IL-13 is believed to be the central mediator that drives multiple aspects of the pathophysiology underlying the range of signs and symptoms of AD by promoting type 2 inflammation and mediating its effects on tissue, resulting in skin barrier dysfunction, itch, skin thickening, and propensity to infections[7].

2.1.4. Clinical presentation

AD is characterised by xerosis, erythematous crusted eruption (dermatosis), lichenification, and intense pruritus[8], which along with the distribution, chronicity, and history of skin lesions, form the basis for making the diagnosis. The clinical phenotype can vary depending on the age. In adolescents and adults (12-60 years), eczematous lesions prevalently affect head, neck and flexural areas, with xerosis, lichenification, and depigmentation[9].

2.1.5. Management

The goals of AD therapy are to reduce pruritus and establish persistent disease control that is sufficient to enable patients to be fully functional at home, work and school. These goals typically require a multistep approach with interventions that are aimed at avoiding relevant triggers, improving the skin barrier, normalizing the skin dysbiosis and reducing inflammation[10].

Topical therapies, e.g. moisturisers are the mainstay of therapy for patients with mild-to-moderate disease. Topical corticosteroids (TCS) are used as the first-line anti-inflammatory treatment and reduce disease recurrence when used intermittently. Use of low-potency TCS bears low risk, but inappropriate use of high-potency TCS can cause local side effect such as skin thinning, purpura, striae and dyspigmentation[10].

Topical calcineurin inhibitors (TCIs) tacrolimus and pimecrolimus are alternative topical immunomodulators for the treatment of AD. Currently per EMA recommendations, these medicines should be only used in patients over the age of 2 years with mild or moderate disease (in the case of pimecrolimus) and moderate to severe disease (in the case of tacrolimus), when treatment with topical corticosteroids should not or cannot be used[11].

Other treatment options include short-term phototherapy if disease cannot be controlled with topical therapies and oral glucocorticoids. Systemic non-biologic immunomodulatory therapies, e.g. ciclosporin, azathioprine, methotrexate and mycophenolate mofetil are also used[10]. Other treatments options for

[4] Abuabara K, Yu AM, Okhovat JP et al. The prevalence of atopic dermatitis beyond childhood: a systematic review and meta-analysis of longitudinal studies. Allergy 2018; 73: 696–704

[5] Patrick GJ, Archer NK, Miller LS. Which way do we go? Complex interactions in atopic dermatitis pathogenesis. J Invest Dermatol 2021; 141:274–284.

[6] Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016; 387:1109-1122.

[7] Rat narajah K, Le M, Muntyanu A, et al. Inhibition of IL-13: a new pathway for atopic dermatitis. J Cutan Med Surg. 2021; 25:315-328

[8] Bieber T. Atopic dermatitis. N Engl J Med. 2008; 358:1483-1494.

[9] Raimondo A and Lembo S. Atopic Dermatitis: Epidemiology and Clinical Phenotypes. Dermatol Pract Concept 2021; 11:e2021146

[10] Weidinger S, Beck L, Bieber T, et al. Atopic dermatitis. Nat Rev Dis Primers. 2018; 4:1.

[11] Elidel | European Medicines Agency (europa.eu)

moderate-to-severe AD include oral JAK inhibitors abrocitinib, baricitinib, upadacitinib. However, the use of JAK inhibitors has been associated with some serious side effects and should be used with caution[12].

Two biological therapies have been approved by EMA for moderate-to-severe disease: dupilumab in 2017 and tralokinumab in 2021. Dupilumab is a mAb against IL-4Rα that inhibits IL-4 signalling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signalling through the Type II receptor (IL-4Rα/IL-13Rα)[13]. Tralokinumab is a mAb against IL-13 that neutralises the biological activity of IL-13 by blocking its interaction with the IL-13Rα1/IL-4Rα receptor complex[14].

2.2. About the product

Lebrikizumab is an immunoglobin G4 (IgG4) monoclonal antibody (mAb) that binds with high affinity to soluble interleukin IL-13 and inhibits IL-13 signalling through the IL-4 receptor alpha (IL-4Rα)/IL-13 receptor alpha 1 (IL-13Rα1) pathway, thereby preventing the downstream effects of IL-13 with high selectivity. It blocks the binding of IL-13 to IL-4Rα, but does not block the binding of IL-13 to IL-13Rα1 or IL-13 receptor alpha 2 (IL-13Rα2).

ATC-code has not yet been assigned.

The proposed indication for lebrikizumab is as follows: "Lebrikizumab is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years of age and older who are candidates for systemic therapy". The summary of product characteristic (SmPC) also states that lebrikizumab can be used with or without topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI).

The proposed dose of lebrikizumab is an initial dose of 500 mg (two 250 mg injections) at week 0 and week 2, followed by 250 mg every other week administered as subcutaneous injection up to week 16. The recommended maintenance dose is 250 mg every fourth week.

2.3. Type of application and aspects on development

The application was submitted under the legal basis 8(3) of Directive 2001/83/EC which corresponds to a complete and independent application.

The applicant received EMA scientific advice on the preclinical and clinical development programme of lebrikizumab in the treatment of AD (see section 1.6. 'Scientific advice').

[12] Janus kinase inhibitors (JAKi) | European Medicines Agency (europa.eu)

[13] Dupixent | European Medicines Agency (europa.eu)

[14] Adtralza | European Medicines Agency (europa.eu)

2.4. Quality aspects

2.4.1. Introduction

Lebrikizumab, the active substance contained in Ebglyss, is a monoclonal antibody (MAb) based on a human immunoglobulin G4 (IgG4) framework, produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology.

Ebglyss is presented as a 250 mg/2 mL sterile solution for injection for subcutaneous administration at a concentration of 125 mg/mL. As described in section 6.5 of the SmPC there are two presentations:

- 2 mL solution in a 2.25 mL Type-1 clear glass pre-filled syringe with small round flange, with a 27 gauge special thin wall x 12.7 mm stacked stainless steel needle, closed with a laminated bromobutyl elastomeric plunger and a rigid needle shield and assembled in a passive safety device (further named 'PFS-NSD')
- 2 mL solution in a 2.25 mL Type-1 clear glass syringe in a pre-filled pen with extra-small round flange, with a 27 gauge special thin wall x 8 mm stacked stainless steel needle, and closed with a laminated bromobutyl elastomeric plunger and a rigid needle shield (further named 'autoinjector-pre-filled pen' or 'AI-PFP').

Other ingredients are histidine, glacial acetic acid, sucrose, polysorbate 20, water for injections.

2.4.2. Active Substance

2.4.2.1. General information

Lebrikizumab is a monoclonal antibody (MAb) based on a human immunoglobulin G4 (IgG4) framework containing light chain VL κ IV and heavy chain VHII subgroup sequences. The recombinant antibody is produced in Chinese Hamster Ovary (CHO) cells and consists of two heavy chains (445 amino acid residues each) and two light chains (218 amino acid residues each) with a relative molecular mass of approximately 145 kDa.

Mechanism of action is binding with high affinity to interleukin (IL)-13 and inhibiting IL-13 signalling through the IL-4 receptor alpha (IL-4Rα)/IL-13 receptor alpha 1 (IL-13Rα1) pathway, thereby blocking the downstream effects of IL-13 with high selectivity. Blockade of IL-13 signalling is expected to be of benefit in diseases in which IL-13 is a key contributor to the disease pathogenesis. Lebrikizumab does not prevent the binding of IL-13 to the IL-13 receptor alpha 2 (IL-13Rα2 or decoy receptor), which allows the internalisation of IL-13 into the cell.

An N-linked glycosylation site is present on Asn295 in each heavy chain. The predominant form of the fucosylated N-linked oligosaccharide of lebrikizumab is G0 (i.e. . 0 terminal galactose residues).

2.4.2.2. Manufacture, characterisation and process controls

The active substance is manufactured at Samsung Biologics Co., Ltd. (SBL), 300 Songdo-bio-daero, Yeonsu-gu, Incheon 21987, Republic of Korea. It was confirmed that the site involved in manufacture and quality control of the active substance operate in accordance with EU GMP.

Description of manufacturing process and process controls

The manufacturing process is based on a commonly used monoclonal production technology. Upstream process consists of several cell expansion steps and a harvest step. In the downstream process the harvested cell culture is purified using a series of purification and formulation steps.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Compendial raw materials are tested in accordance with the corresponding monograph, while specifications (including test methods) for non-compendial raw materials are presented. No human or animal derived materials are used in the active substance manufacturing process and acceptable documents have been provided for raw materials of biological origin used in the establishment of cell substrate.

The source and history of the CHO cell line used for active substance expression is stated. The expression construct is described in adequate detail. The applicant provided information on the process on the single-cell selection process of monoclonality. A two-tier cell bank system of master cell bank (MCB) and working cell bank (WCB) is used. Based to the provided results, the genetic stability for MCB and WCB is demonstrated for cells at and beyond the limit of cell age. Sufficient information is provided regarding testing of MCB and WCB and release of future WCBs.

An overview of the raw materials used in the manufacture of the active substance has been provided, with listing per unit operation. Specifications of raw materials have been also provided.

Control of critical steps and intermediates

A comprehensive overview of critical in-process controls and critical in-process tests performed throughout the lebrikizumab active substance manufacturing process is given. Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process. Actions taken if limits are exceeded are specified.

The lebrikizumab active substance manufacturing process does not produce isolated process intermediates for long-term storage. Each of the process intermediates are subject to short-term storage and have been evaluated for both physicochemical stability and microbiological control.

The microbiological testing strategy, consisting of bioburden and endotoxins testing, sufficiently supports the manufacturing process and hold times.

Process validation

The lebrikizumab active substance manufacturing process has been validated adequately. Consistency in production has been shown on three full scale commercial batches. All acceptance criteria for the critical operational parameters and likewise acceptance criteria for the in-process tests are fulfilled demonstrating that the manufacturing process consistently produces lebrikizumab active substance of reproducible quality that complies with the predetermined specification and in-process acceptance criteria. Shipping qualification studies were completed to verify that the lebrikizumab active substance can be transported from the active substance manufacturing site to the finished product manufacturing site, with no adverse impact on the product.

An extractable and leachable risk assessment regarding all contact materials used during the manufacturing process of active substance was provided.

Manufacturing process development

In course of development, changes were introduced to the active substance manufacturing process. The Applicant provided comparability studies which showed similarity between the material manufactured

across the used processes. CQA-based risk assessment was performed in order to establish the control strategy. Multiple studies were performed to understand the relationship between CQAs and the manufacturing process. Results of process characterisation and risk assessment studies were provided for each manufacturing step.

Characterisation

Characterisation results include determination of structure (primary, secondary, and higher-order structure), oligosaccharide structure (glycosylation site, oligosaccharide profiling and structural identification, sialic acid content), sulfhydryl groups and disulfide structure, isoform pattern and charge variants, isoelectric point, extinction coefficient, electrophoretic patterns, size variants, thermal stability, biological mechanism and immunological characterisation.

The primary structure of lebrikizumab including intact antibody and light and heavy chain structure is considered adequately determined using several techniques and confirm the expected sequence.

Various techniques were used to determine the N- and C-terminal sequences of the LC and HC.

The oligosaccharide structure was studied and the oligosaccharide profiling was considered sufficient.

Charge and size variants were analysed with variety of techniques and considered sufficient to cover different forms of charged and size variant versions.

Biological activity is characterised and controlled by a cell-based assay which measures the ability of lebrikizumab to bind to IL-13.

Fc effector functions studied demonstrated that no Fcγ receptor binding or C1q binding is detected. Thus, no ADCC or CDC activity is expected.

Product-related impurities/substances as well as process-related impurities have been identified. Impurities are characterised at sufficient level.

Control of mycoplasma and adventitious viruses are assessed.

Overall, the performed characterisation studies including identification of the impurities are considered relevant and cover a wide variety of physicochemical and biological characterisation studies.

2.4.2.3. Specification

The specifications for lebrikizumab active substance are based on the quality of lebrikizumab used in toxicological and clinical testing, the potential risk of the CQAs to the patient, the stability of lebrikizumab, the variability of the analytical methods, and ICH guidelines. The proposed release tests cover appearance, identity, quantity, purity/impurities, potency, general tests and microbial assurance. Overall, the set of quality attributes tested at release and at shelf-life can be considered acceptable.

Analytical methods

The analytical methods used have been adequately described. Non-compendial methods have been appropriately validated in accordance with ICH guidelines.

Compendial analytical procedures were verified and confirmed suitable for their intended use according to the current Ph.Eur. requirements.

Batch analysis

Batch analysis data of the active substance were provided. The results are within the specifications in place at the time of testing and confirm consistency of the manufacturing process.

Reference materials

A two-tiered reference standard (RS) program for lebrikizumab is in use which includes a primary reference standard (PRS) and a secondary/working reference standard (WRS). Used analytical methods are the same as those used for active substance or finished product batch release. The history and qualification of the reference standards used throughout development is described.

Container closure

Two container closure systems are used for the storage of the active substance: cryovessel and polymeric container. Sufficient results from extractable and leachables studies have been provided. However for the polymeric container, the on-going leachable studies continue to cover the proposed shelf-life of the active substance. The applicant is recommended to provide the results at the end of the shelf-life of the active substance when available **(REC)**.

2.4.2.4. Stability

Stability data are provided in support of a claimed shelf-life. The studies are conducted in accordance with the ICH Q5C and suitable study protocols are provided.

Data are provided for batches manufactured according to the commercial process and packaged in the two proposed container closure systems. All batches remained within specification over the course of the stability studies at the long term storage condition.

Accelerated and stress stability data was provided. In conclusion, the proposed drug substance shelf life is justified.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Ebglyss, or lebrikizumab injection, 250 mg/2 mL, is supplied as a sterile, non-pyrogenic parenteral solution for subcutaneous administration. The finished product is contained in a 2.25 mL, Type I glass syringe barrel with a laminated bromobutyl elastomeric plunger. The container closure system filled with product is referred to as the semi-finished syringe (SFS). The SFS is assembled with device components to form one of two integral medicinal products, that is, either the pre-filled syringe with needle safety device (PFS-NSD) or the autoinjector pre-filled pen (AI-PFP) presentation. The PFS-NSD is a needle-based injection system that enables the user to manually insert the needle and deliver the lebrikizumab finished product. The AI-PFP is a needle-based injection system that, when activated, automatically inserts the needle and delivers the lebrikizumab finished product.

All excipients (histidine, glacial acetic acid, sucrose, polysorbate 20, water for injections) are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. Standards. Excess volume is filled into each syringe to enable delivery of 2 mL in compliance with United States Pharmacopoeia (USP) general chapter <1151> pharmaceutical dosage forms.

The primary packaging is a 2.25 mL Type-1 clear glass pre-filled syringe with small round flange, with a 27 gauge special thin wall x 12.7 mm stacked stainless steel needle, closed with a laminated bromobutyl elastomeric plunger and a rigid needle shield, to be assembled in a passive safety device, or a 2.25 mL Type-1 clear glass syringe in an autoinjector pre-filled pen with extra-small round flange, with a 27 gauge special thin wall x 8 mm stacked stainless steel needle, and closed with a laminated bromobutyl elastomeric plunger and a rigid needle shield.

The material complies with Ph. Eur. requirements. The container closure systems meet the applicable requirements of the standard International Organization for Standardization (ISO) 11040-4: 2015, Prefilled syringes - Part 4: Glass Barrels for Injectables. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The finished presentations are medicinal products where the device part and the medicinal product form an integral product that is not reusable and where the action of the medicinal product is principal.

The SFS for PFS-NSD is assembled with commercially available syringe accessories to form the prefilled syringe with needle safety device (PFS-NSD).

The container closure studies have included analyses of extractables and leachables, photostability, safety, compatibility and performance. The applicant provided a Notified Body Opinion for the PFS-NSD container closure and delivery device, in accordance with Article 117 of the Medical Device Regulation, confirming full compliance with the General Safety and Performance Requirements (GSPRs).

The SFS for AI-PFP is assembled with components and subassemblies to form an autoinjector (also referred to as Pre-filled Pen). The autoinjector is a needle-based injection system (NIS) with automated functions. During the procedure, the applicant provided a Notified Body Opinion for the autoinjector container closure and delivery device, in accordance with Article 117 of the Medical Device Regulation confirming full compliance with the relevant GSPRs, this to respond to a major objection (MO).

Both presentations (PFS-NSD and AI-PFP) are supported by extensive studies for protection, light exposure, integrity and safety of container closure system materials, sterilisation, extractables and leachable studies, compatibility, biocompatibility, usability, stability, needle and needle shield performance and shipping/transportation studies.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The selected formulation is further supported by formulation development studies.

Sufficient process characterisation studies were performed for each unit operations to assess the robustness of the finished product manufacturing process conducted at laboratory, pilot and commercial scales.

Compatibility of lebrikizumab bulk product with the SFS for PFS-NSD and the SFS for AI-PFP has been demonstrated. Stability studies have been conducted to demonstrate product compatibility. A microbial hold time challenge study has been performed to evaluate the impact of hold times on microbial properties during active substance thaw and compounding. The provided data show that the hold times used for the proposed commercial process have no impact on microbial growth.

Based on the provided data the manufacturing process development is considered appropriately and sufficiently described.

2.4.3.2. Manufacture of the product and process controls

Lebrikizumab product in SFS is manufactured and further assembled to PFS-NSD and AI-PFP.

Industrias Farmacéuticas Almirall, S.A. Barcelona, Spain, is responsible for final EU release. It was confirmed that all sites involved in manufacture and quality control of the finished product operate in accordance with EU GMP.

The manufacturing process of the finished product consists of the following steps: thawing of active substance, transfer of active substance into compounding vessel, mixing, bioburden reduction filtration, sterile filtration, filling and plunger insertion, visual inspection and assembly.

The manufacturing process has been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls and processing time limits are adequate. The process validations include validation of manufacturing process steps for finished product filled into 2.25 mL syringes. Process validation has included process design, process performance qualification, continued process verification and quality system management of the control strategy. Besides process validation also equipment sterilisation, sterilising filter validation, aseptic process simulation and shipping validation were performed. The presented data demonstrate that the manufacturing process, in-process, and product controls are appropriate to provide consistent finished product.

2.4.3.3. Product specification

The release and shelf life specifications provided are based on the quality of lebrikizumab used in toxicological and clinical testing, the stability of lebrikizumab, the variability of the analytical methods used to analyse the finished product and ICH guidelines. These specifications assure control of the finished product quality and device functionality at release and during storage. Parameters tested include appearance, quantity, identity, purity/impurities, potency and general tests including those required for a sterile product and device specific tests.
The specifications for the prefilled syringe with needle safety device (PFS-NSD) include appropriate tests for this type of delivery device.: appearance (visual inspection), extractable volume (Ph.Eur.), activation force (compression force) and functionality (visual inspection).

The specifications for the autoinjector (AI-PFP) include appropriate tests: identity (RP-HPLC), dose accuracy (volume by weight), injection time (timing), visual/functional inspection (inspection).

Analytical methods

The analytical methods used have been adequately described. Non-compendial methods have been appropriately validated in accordance with ICH guidelines.

Compendial analytical procedures were verified and confirmed suitable for their intended use according to the current Ph.Eur. requirements.

Characterisation of impurities

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Studies comply with the expectations on ICH Guideline for Elemental Impurities Q3D. Based on the risk assessment, it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Batch analysis

Batch analysis data were provided for:

- Commercial scale batches of the semi-finished 2 mL SFS for PFS-NSD
- Assembled PFS-NSD process validation batches
- Commercial scale batches of the semi-finished 2 mL SFS for AI-PFP
- Assembled AI-PFP process validation batches

The results are within the specifications and confirm consistency of the manufacturing process.

In addition to this, batch analysis data for additional finished product batches have been presented, corresponding to all lebrikizumab clinical batches made to date including active substance batches and their corresponding finished product batches. The results are within the specifications that were in place at the time of testing.

Reference materials

The reference standards for finished product are the same as used for active substance testing.

Container closure system

Specifications, drawings with dimensions for each element of the packaging has been presented. Manufacturers of each component have been defined. The primary container closure components are received ready to use from the supplier. The primary product container is a sterilised 2.25 mL Type I glass syringe, with a sterilised elastomeric plunger inserted after product filling. Sterilisation sites have been presented in the dossier.

The lebrikizumab semi-finished syringe (SFS) is assembled with syringe accessories, a needle safety device, a plunger rod and an add-on finger flange to form the pre-filled syringe with needle safety device (PFS-NSD).

The lebrikizumab semi-finished syringe (SFS) is assembled with the autoinjector components and subassemblies to form the finished drug device combination product (AI-PFP).

The materials of construction for each syringe accessory are described in the dossier. The syringe accessories are not sterilised and are not in contact with lebrikizumab product.

2.4.3.4. Stability of the product

A shelf life of 3 years is claimed for the PFS-NSD, and 2 years for the AI-PFP, when stored at 2-8°C in the original package in order to protected from light. After removal from the refrigerator, Ebglyss must be used within 7 days (when stored up to 30°C).

Stability data up to 36 months at 2-8°C are provided to support the proposed shelf-life. The stability studies were in general performed in accordance with ICH Q5C.

The applicant has performed photostability studies which demonstrated that the finished product is sensitive to light exposure. Therefore, the finished product should be protected from light by secondary packaging.

The primary stability data and supporting stability studies at long term and accelerated conditions performed in accordance with ICH Q5C support a shelf-life of 36 months when stored at 2°C to 8°C for the PFS-NSD and a shelf-life of 24 months for the AI-PFP presentation when stored in the original carton protected from light at the long-term storage condition of 2°C to 8°C, with a patient use period of 7 days

stored up to 30°C. Studies supporting this patient use period was provided for PFS-NSD and AI-PFP presentations.

2.4.3.5. Adventitious agents

Viral safety evaluation have been conducted in accordance with ICH Q5A, as well as in other relevant guidelines. Appropriate testing has been conducted for cell banks and the unprocessed bulk harvest. The provided test results confirm the absence of adventitious agents in the cell banks. Viral clearance studies were performed using qualified scale-down models. The overall combined $\log_{10}$ reduction values for the orthogonal reduction unit operations can be considered satisfactory. The applicant's assessment and conclusion with regard to viral safety can be endorsed. No material of animal origin is used in the lebrikizumab manufacturing process and based on the provided data the TSE risk can be considered negligible.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. During the procedure, in response to a Major Objection, the applicant provided the notified body opinion for the AI-PFP, which confirms full compliance with the relevant GSPRs in Annex I of Regulation (EU) 2017/745. Overall, the active substance has been extensively characterised using state-of-art techniques. The set of quality attributes tested at release and at shelf-life can be considered acceptable. The risk assessment related to the exposure of active substance to the light during its processing, storage, and shipping was included in the dossier.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertains to the need to provide results of leachable studies on polymeric container at the end of the shelf-life of the active substance when available. This point is put forward and agreed as recommendation for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

The applicant is recommended to provide results of leachables studies on the polymeric container at the end of the shelf-life of the active substance (24 months at NMT -65°C) to support the final conclusion on leachables characterisation.

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical programme for lebrikizumab was conducted in accordance with the ICH guidelines S6(R1) and M3(R2). The pharmacology programme consisted of *in vitro* binding characterisation for IL-13, and its blockade of receptor formation and signalling, and *in vivo* study in airway inflammation model. No non-clinical efficacy studies were conducted in non-human primates (NHP), as sole pharmacologically relevant species. Safety pharmacology endpoints were evaluated in repeat-dose toxicity studies. Pharmacokinetic (PK) and toxicokinetic (TK) program consisted of assessments of lebrikizumab following single intravenous (IV) and SC dosing in cynomolgus monkeys and assessment of formation of anti-drug antibodies (ADA; anti-lebrikizumab antibodies). Toxicology program consisted of single and repeat-dose toxicity studies, fertility and embryofetal (EFD) development and pre- and postnatal development (PPND) studies in cynomolgus monkeys and *ex vivo* tissue cross-reactivity studies using cynomolgus monkey or human tissues. Carcinogenicity risk assessment was done by weight of evidence approach and no studies were conducted.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The primary pharmacodynamic studies focused on *in vitro* IL-13 binding, specificity and inhibition of IL-13 -mediated signalling.

Lebrikizumab is an IgG4 isotype mAb with modified Fc-region, which binds to human IL-13 with high affinity (31 pM) and neutralises the activity of IL-13. In addition to human IL-13, lebrikizumab binds to cynomolgus monkey IL-13 (with KD <0.67 pM), thus leaving NHPs as the sole pharmacologically relevant species. The accurate lebrikizumab binding affinity for cynomolgus monkey IL-13 could not be calculated due to slow off-rates being below the detection limits.

Lebrikizumab blocks the binding of IL-13 to IL-4Rα preventing heterodimerisation of IL-13Rα1/IL-4Rα, and thus inhibits the IL-13Rα1/IL-4Rα STAT-dependent signalling pathway. Lebrikizumab does not block the binding of IL-13 to IL-13Rα1 or IL-13Rα2.

Lebrikizumab inhibits IL-13-induced phosphorylation of STAT6, the primary downstream signalling mediator of the IL-13Rα1/IL-4Rα receptor complex. Lebrikizumab inhibits IL-13-induced proliferation of Hodgkin lymphoma L-1236 and HDLM-2 cell lines in a dose-dependent manner.

Lebrikizumab is a IgG4 Mab with modified Fc, which has moderate binding affinity to FcγRI, low binding ability to FcγRIIIa, FcγRIIa and to C1q, and thus has a low effector function potential.

In an *in vivo* C57BL/6 mouse airway inflammation model, lebrikizumab reduced human IL-13-induced inflammatory reactions; reduced recruitment of inflammatory cells, eosinophils, IL-13Rα2 expression in the lung and TGF- β1 levels in bronchoalveolar lavage fluid.

Serum IgE levels were measured retrospectively on the serum samples collected in toxicology study from healthy female cynomolgus monkeys dosed weekly with 0.05, 1 or 25 mg/kg lebrikizumab IV for 9-months (followed by 8-month recovery period). All animals had detectable IgE serum levels at all timepoints, but levels of IgE were variable between animals. In lebrikizumab-treated animals, approximately 25%−40% reduction of baseline corrected serum IgE levels were recorded. Maximum IgE reduction of 40% from pre-dose baseline levels was observed in the 25 mg/kg dose group on Day 29.

Collectively, the pharmacology data support that lebrikizumab is selective for IL-13, to which it binds with high affinity to block the formation of the IL-13Rα1/IL-4Rα receptor complex and thereby inhibits IL-13-induced phosphorylation of STAT6 and downstream signalling.

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were conducted.

2.5.2.3. Safety pharmacology programme

Safety pharmacology endpoints were incorporated within general repeat-dose toxicity and pre- and postnatal development and fertility studies of lebrikizumab in cynomolgus monkeys. Measurements were performed in compliance with ICH S6(R1) and S7A guidelines and according to GLP regulations. There were no indications of cardiovascular, respiratory, and central nervous system effects attributed to lebrikizumab in the toxicity studies. In addition, *in vitro* hERG ion channel current study was conducted, in which lebrikizumab induced no hERG inhibition at up to maximum concentration 6.0 mg/mL.

2.5.2.4. Pharmacodynamic drug interactions

No secondary pharmacodynamic drug interaction studies were conducted.

2.5.3. Pharmacokinetics

The single-dose pharmacokinetics (PK) of lebrikizumab was evaluated in rats and cynomolgus monkeys, and the repeat-dose toxicokinetics (TK) of lebrikizumab was evaluated in monkeys. In rats, PK parameters were evaluated after single SC administration of lebrikizumab derived from either Chinese hamster ovary (CHO) or murine myeloma (NS0) cells lines, and in cynomolgus monkeys after singe IV or repeated SC administration. TK was evaluated in monkeys as part of the repeat-dose toxicity studies after either IV or SC administration.

Methods of analysis

For the quantification of free lebrikizumab (TNX-650) or anti-TNX-650 antibodies in the cynomolgus monkey serum, an ELISA was used. The validation reports demonstrate that the assays were sensitive, selective and suitable for assessing the selected endpoints.

For assays S-1040 and S-1042, the FDA assay criteria were used. EU acceptance criteria (<15% or 20%) are stricter than the FDA criteria (<25%). Therefore, the EU criteria are not necessarily met. However, this is not considered as an issue in this data set.

Absorption

Single-dose PK studies were performed in male Sprague Dawley rats with 5 mg/kg SC dose of lebrikizumab and in cynomolgus monkeys with 1, 10 and 100 mg/kg IV dose of lebrikizumab. After a single IV administration, the C_{max} increased in a dose-proportional manner over the 100-fold dose range. The $AUC_{0\text{-}inf}$ was dose proportional over the 1 to 10 mg/kg dose levels but less than dose proportional at the 100 mg/kg. Clearance rates and volume of distribution were low (2.12 to 4.93 mL/day/kg and 59.0-85.0, respectively) and $T_{1/2}$ 9-25 days.

Repeat-dose TK studies were performed in male and female cynomolgus monkeys (weekly IV bolus or SC administration). The serum concentrations of lebrikizumab were analysed in the 6-week, 13-week and 9-month general toxicity studies and the serum peak concentrations and AUC values from the

13-week male fertility and 9-month female fertility studies. The dose levels 0.95 – 25 mg/kg bw were used in IV studies and 5-25 mg/kg in SC studies. With once weekly IV dosing, serum concentrations of lebrikizumab were dose-proportional and accumulation was low to moderate (about 4-fold). The clearance rates and volume of distribution were similar to the values collected from single-dose toxicity study. No sex differences were recorded. The TK data collected after SC administration was in line with the IV administration data. In the repeat-dose IV studies, treatment-emergent ADA were demonstrated in 2 monkeys (one at 1 mg/kg and one at 5 mg/kg dosing), and these animals were excluded from the analysis.

The TK data collected from IV administration DART-study with cynomolgus monkeys showed approximately 1.5-fold accumulation of lebrikizumab after repeated administration and T1/2 of approximately 19 days. 13 of 30 monkeys demonstrated treatment-emergent ADA (6 in the 0.05 mg/kg, 1 in the 1 mg/kg and 6 in the 25 mg/kg group). TK parameters were not estimated for 4/6 ADA-positive monkeys in the 0.05 mg/kg group due to the sample concentrations less than the LLOQ. The data collected from SC administration male fertility study showed was comparative to the DART-study with female monkeys. One monkey in the high dose group demonstrated treatment-emergent ADA.

Serum TK of lebrikizumab was investigated in pregnant cynomolgus monkeys (SC administration once weekly; 15-150 mg/kg). Samples were collected from dams and fetuses. Dose proportional exposure as well as Cmax and AUC was observed in all groups. The mean fetal exposure was approximately 0.3. Seven monkeys demonstrated treatment-emergent anti-lebrikizumab antibodies and were excluded from the analysis. The offspring with detectable ADAs corresponded to dams with ADAs.

No bioavailability studies were conducted.

The type and extent of exposure data and TK parameters varied between toxicology studies and therefore the comparison of the results from different studies is challenging. However, taking the data together, the observed results are in line and no TK differences between sex nor in fertility/DART studies were recorded.

ADA were observed in some of the studies with no clear association with sex or lebrikizumab concentration or administration route. The presence of ADAs did not seem to neutralise the effects of lebrikizumab; however, the neutralizing ADA assay was not performed to further investigate of ADAs had an effect to the efficacy of lebrikizumab as described in *EMA Guideline on immunogenicity assessment of monoclonal antibodies intended for in-vivo clinical use (EMA/CHMP/BMWP/86289/ 2010)*. The Applicant has provided data on effects of chronic administration of lebrikizumab on serum total IgE from Study 07-1706 to demonstrate sustained activity, however, given the uncertainties with the data, it can be considered only as supporting information.

Distribution

Formal tissue distribution and protein binding studies were not conducted with lebrikizumab.

Metabolism and excretion

No metabolism and excretion studies were conducted with lebrikizumab. No renal excretion of lebrikizumab is anticipated due to its molecular size.

Pharmacokinetic drug-interactions

Drug-drug interactions at the PK level are unlikely for biotechnology-derived substances as they do not metabolise via CYP P450 enzymes. It should be noted that the mechanism of action of lebrikizumab (cytokine secretion) may have an indirect effect on CYP450 activities.

The absence of these studies in animals is accepted, however, the pharmacokinetic drug-drug interactions (DDI) are assessed in the clinical AR.

Other Pharmacokinetic Studies

No other pharmacokinetic studies were conducted.

2.5.4. Toxicology

The toxicology program of lebrikizumab generally follows the principles given in ICH guideline S6 (R1) and ICH M3 (R2). Lebrikizumab binds only to human and cynomolgus monkey IL-13 target, thus leaving NHPs as a sole pharmacological relevant species to be used in toxicity testing.

Toxicology studies in cynomolgus monkeys were conducted using either CHO-cell-derived toxicology lots that were characterised using contemporary analytical methods (13-week male fertility and PPND), similar to CHO cell-derived clinical and commercial lots or using NS0 cell-derived toxicology lots that were characterised using older methods.

2.5.4.1. Single dose toxicity

There were no biological or toxicological differences between the individual animals and their pre-dose values. There were no apparent test article-related effects on measured clinical pathology parameters due to a single intravenous dose of lebrikizumab in cynomolgus monkeys. The highest IV dose 100 mg/kg was the maximal non-lethal dose.

2.5.4.2. Repeat dose toxicity

GLP-compliant repeat-dose studies of 6 weeks, 13 weeks and 9 months in duration were conducted in cynomolgus monkeys to evaluate the toxicity and TK of lebrikizumab. Monkeys of different ages and maturity (1 to 4.5 years) were used, and IV and SC routes of administration were evaluated. The highest dose across these studies was 25 mg/kg administered once weekly by bolus IV or SC injection and was both well tolerated and without adverse findings. There were no remarkable changes in peripheral blood immunophenotype (total lymphocytes, mature T cells, helper T cells, cytotoxic T cells, total B cells, NK cells, monocytes). At the 9-month necropsy, absolute and relative uterine weights were uniformly lower for lebrikizumab dose groups compared with the control group. No abnormalities of the uterus were noted microscopically at either the 3- or 9-month necropsy. There were no such differences in uterine weights in a subsequent 9-month IV administration study in mature female monkeys suggesting contribution of variability in relative sexual maturity to observed difference in uterine weights.

2.5.4.3. Genotoxicity

In accordance with ICH S6(R1) no genotoxicity studies were conducted with lebrikizumab.

2.5.4.4. Carcinogenicity

Carcinogenicity studies with lebrikizumab were not conducted. The Applicant used weight-of-evidence - based approach to assess the carcinogenicity risk of lebrikizumab. The structural and metabolic features of the mAb do not suggest potential for carcinogenicity. In repeat-dose toxicity studies in monkeys no evidence of carcinogenicity was observed. The totality of nonclinical and clinical evidence including other IL-13 inhibitors used for AD treatment does not suggest carcinogenicity risk of this group of compounds.

2.5.4.5. Reproductive and developmental toxicity

Fertility and early embryonic development

The main purpose of the male fertility study was to investigate the effects of lebrikizumab on spermatogenesis and fertility endpoints in sexually mature male monkeys during 13 weeks of dosing. This treatment period was sufficient to cover at least 1 full spermatogenic cycle including transit of sperm through the epididymis. Monkeys were 4 to 7 years of age at study start, and sexual maturity was confirmed by sperm evaluation. No effects on male reproductive endpoints were observed. Besides signs of reaction to injection in some animals there were no effects in several general toxicity endpoints that could be attributed to lebrikizumab. No ADA with effect on lebrikizumab exposure were observed.

The purpose of the female fertility study was to investigate the effects of lebrikizumab on menstrual cycling and related fertility endpoints in sexually mature female monkeys during 9 months of dosing. Monkeys were 4.8 to 9.3 years of age at study start, and sexual maturity was confirmed by evidence of menses and ovulation, assessed by vaginal swabs, and reproductive hormone cycling within the 4 months prior to dosing. No toxicity and no clear treatment-related effects on female reproductive endpoints were observed. One high dose group monkey developed serum polyclonal gammopathy of uncertain relationship to lebrikizumab. A subset of monkeys had microscopic tissue cysts present in the uterus, cervix, parathyroid, thyroid and/or thymus for which a possible relationship to lebrikizumab could not be excluded. None of the findings were considered adverse as such cysts do not result in clinical signs or other detectable abnormalities when they occur incidentally in the cynomolgus monkey. Cysts in other affected glands occurred either in lebrikizumab-treated animals only (parathyroid, thymus) or at a higher incidence compared with control animals (thyroid). At the end of the treatment-free period, thymic cysts were present with increased incidence in animals given lebrikizumab, while parathyroid and thyroid cysts were present in control and lebrikizumab-treated animals in a pattern suggesting an incidental effect.

Embryo-fetal development

The purpose of the embryo-fetal development study was to assess the potential effects of lebrikizumab on embryo-fetal development when administered to pregnant cynomolgus monkeys throughout the period of major organogenesis. Evaluated maternal parameters included serum chorionic gonadotrophic to confirm pregnancy, monitoring of pregnancy status by ultrasound, clinical chemistry, haematology, urinalysis, toxicokinetics and immunogenicity. Cesarean (C-) sections were performed on GD 100. Placental and fetal body weights and measurements were recorded. Fetuses underwent a standard teratological evaluation consisting of external, organ/visceral, and skeletal examinations, which included organ weights and long bone measurements. Lebrikizumab concentration in fetal cord blood was also measured. There was no maternal toxicity and no evidence of embryo-fetal toxicity or teratogenicity. Seven monkeys across the lebrikizumab treatment groups were ADA positive; however, only 2 animals, 1 in each of the low and high dose groups, had reduced serum concentrations consequently.

Prenatal and postnatal development, including maternal function

The purpose of the prenatal and postnatal study was to assess the potential effects of lebrikizumab on pre- and postnatal development in cynomolgus monkeys. Lebrikizumab was administered to pregnant animals throughout gestation and their infant offspring were evaluated through approximately 6 months of age. Throughout gestation, ultrasound was used to monitor pregnancy status, including fetal viability and growth. Evaluated maternal parameters also included clinical chemistry, haematology, urinalysis, serum concentrations of lebrikizumab, and immunogenicity throughout gestation and through to Lactation Day (LD) 180. Infants were evaluated from birth through Postnatal Day (PND) 180. In addition to general health, infants were evaluated for growth, morphological, functional, and neurobehavioral development. Evaluated infant parameters also included skeletal examinations on PND7, immunological

evaluations on PNDs 70 and 180, clinical chemistry and haematology, serum concentrations of lebrikizumab and immunogenicity, and ECGs. The overall rate of embryo-fetal loss, including abortions, embryo-fetal death, and stillbirths (18.75% [3/16], 12.5% [2/16], and 6.25% [1/16] in control, low, and high dose groups, respectively) was within the historical background information and rate for this species and at the Testing Facility. Among surviving infants, there were no treatment-related changes in physical or functional development parameters. there were no immune system changes, as evaluated by immunophenotype and T-cell-dependent antibody responses. At the terminal necropsy of infants, there were no gross findings and no organ weight, morphometric measurement, external, visceral or histopathology observations that were considered related to lebrikizumab.

2.5.4.6. Toxicokinetic data

Lebrikizumab produced variable incidences of treatment-emergent ADA across studies; presence of ADA was associated with reduced serum concentrations of lebrikizumab in some animals. Throughout the 6-week study, serum trough concentrations of lebrikizumab showed that exposure increased in a dose-proportional manner and accumulated about 4-fold across dose levels. Several animals had low levels of ADA with no appreciable impact on exposure. In a 9-month study one monkey in each of the low and mid dose groups had a positive ADA titre that impacted their serum lebrikizumab concentrations and AUC could not be determined for any dose. In 13-week study no lebrikizumab-treated monkey had a positive ADA titre. However, no AUC could be determined for male or female monkeys at dose levels of 5 and 25 mg/kg.

2.5.4.7. Local tolerance

Injection-site reactions were generally not observed across the lebrikizumab toxicology studies dosed either IV or SC. In the male fertility study, one high dose (25 mg/kg) group monkey had swelling in the area of SC dose administration for the majority of the dosing phase and a reaction to the injection could not be excluded. This clinical observation did not worsen with repeated dosing and was not associated with a histological correlate. Using modified Draize scoring and microscopic evaluation no dermal irritation was observed.

2.5.4.8. Other toxicity studies

Antigenicity

The repeat-dose general toxicity studies, fertility studies, EFD and PPND studies each contained direct immunogenicity assessment. Validated ELISA methods were used for measuring anti-drug antibodies to lebrikizumab. Immunogenicity was also indirectly assessed via analysis of lebrikizumab serum concentrations using an antigen-capture ELISA.

Immunotoxicity

Potential effects of lebrikizumab on the innate and humoral immune systems were evaluated in repeat-dose studies in monkeys by means of routine haematology, peripheral blood immunophenotyping (total lymphocytes, mature T cells, helper T cells, cytotoxic T cells, total B cells, NK cells, monocytes) and evaluation of lymphoid organs. There were no treatment-related adverse effects identified for these endpoints in any study. T-cell-dependent antibody (IgG and IgM) response to Keyhole limpet haemocyanin (KLH) immunisation was performed at about 6 months of age in the infant offspring of lebrikizumab-treated monkeys. No statistically significant differences were noted in response to KLH between the control group and lebrikizumab groups.

Studies on impurities

Toxicology studies were conducted using either CHO cell-derived toxicology lots that were characterised using contemporary analytical methods (male fertility; PPND) or using NS0 cell-derived toxicology lots that were characterised using older methods. Despite the differences in material source (NS0 versus CHO) and differences in analytical methods purity and impurity levels were generally similar across toxicology lots. The potential toxicity of lebrikizumab impurities was evaluated repeat-dose toxicology studies in cynomolgus monkeys. Specifications were justified to be acceptable by providing >1-fold margins of safety based on exposure at the NOAEL in repeat-dose toxicity studies compared with the exposure to maximal theoretical levels of impurities at the recommended clinical dose regimen and widest DS/DP specifications.

Exposure margins were calculated based Cmax and Cav,ss values at NOAEL (25 mg/kg IV QW) from 9-month chronic toxicity study and 9-month female fertility study. Exposure data from the female fertility study were used for exposure multiples given limited toxicokinetic data from the chronic toxicity study. Exposure multiples, which were based on the most conservative % impurity in toxicology study batches and the widest specifications across DS and DP identified, were calculated separately for purity, total HMWS, reduced purity, non-reduced purity, and total LMWS. In all cases, exposure multiples, based either on Cmax or Cav,ss, provided enough wide safety margins compared with the exposure to maximal theoretical levels of impurities at the recommended clinical dose regimen.

2.5.4.9 Other studies

Ex Vivo Tissue Cross-Reactivity

The tissue binding specificity of lebrikizumab was evaluated in a comprehensive panel of human and cynomolgus monkey tissues in separate studies. Lebrikizumab was applied to tissue cryosections (3 human and 2 monkey donors/tissue, donors/tissue, where available) at concentrations of 5 µg/mL (optimal concentration) or 40 µg/mL, based on prior method development. Lebrikizumab binding was assessed immunohistochemically using biotinylated lebrikizumab and a direct avidin-biotin complex immunoperoxidase staining procedure. No specific lebrikizumab staining was observed in any human or cynomolgus monkey tissues.

2.5.5. Ecotoxicity/environmental risk assessment

Lebrikizumab is a monoclonal antibody and it is classified as a protein. According to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00corr 2), proteins are included in products that are exempted from ERA. Due to its proteic nature and according to the abovementioned criteria of the EMA guideline, lebrikizumab is unlikely to result in a significant risk to the environment. Therefore, ecotoxicological studies are not required for lebrikizumab.

2.5.6. Discussion on non-clinical aspects

Pharmacology

Pharmacodynamics

The nonclinical pharmacology program of lebrikizumab is condensed but is considered adequate demonstrating the binding specificity to target IL-13 and principal mode of action. Lebrikizumab binds only to human and cynomolgus monkey IL-13 target, thus leaving NHPs as a sole pharmacologically

relevant species. No surrogates were developed and used in lebrikizumab nonclinical studies. The batches (PUR25081, PUR15846, 3D9-1) used in the primary pharmacology studies could not be tracked and this required further clarification. Upon CHMP's request, the applicant clarified, that batches were by large from small scale preclinical research batches (from one batch used in Studies S-1043 and S-1044, no information was trackable). The batches used in toxicology studies were trackable and not the development batches used in PD studies. Considering that the efficacy is demonstrated in the clinical trials, this issue is not pursued further by the CHMP.

In vitro studies show that lebrikizumab inhibits IL-13-induced phosphorylation of STAT6, the primary downstream signalling mediator of the IL-13Rα1/IL-4Rα receptor complex and inhibits IL-13-induced proliferation of Hodgkin lymphoma L-1236 and HDLM-2 cell lines in a dose-dependent manner. In these assays, lebrikizumab (10 ng/mL) clearly inhibited the IL-13 -induced proliferation of TF-1 cells, but the inhibition of IL-13-induced phosphorylation of STAT6 (the primary downstream signalling mediator of the IL-13Rα1/IL-4Rα receptor complex) was barely noticeable. However, the inhibition of primary downstream signalling of IL-13 was shown under the Quality data, where STAT6 signalling reflecting luciferase activity is used as a potency assay and is not pursued further from a non-clinical viewpoint. In conclusion, lebrikizumab binds with high affinity to soluble interleukin IL-13 and inhibits IL-13 signalling through the IL-4 receptor alpha (IL-4Rα)/IL-13 receptor alpha 1 (IL-13Rα1) pathway, thereby preventing the downstream effects of IL-13 with high selectivity.

Lebrikizumab is a IgG4 Mab with modified Fc, which has low binding ability to Fcγ receptors or components of the complement system and thus has a low effector function potential. No description was provided under the nonclinical pharmacodynamics regarding the Fc-modification, and no studies was included that characterise Fc-functions (or lack of them, being a IgG4). However, these studies were included under Quality module and demonstrated minimal binding affinity to FcγRIIIa, FcγRIIa and to C1q, and moderate binding affinity to FcγRI. No secondary pharmacodynamic studies were conducted, which is acceptable for a monoclonal antibody.

The only *in vivo* functionality study was conducted in C57BL/6 mouse airway inflammation model. No disease specific animal models for AD were used to verify *in vivo* functionality of lebrikizumab. Nevertheless, this issue is not pursued further as the AD and airway inflammation model share some similarities regarding the IL-13 / STAT6 signalling routes, and lack of binding to rodent target limits further the studies in rodents. In addition, serum IgE levels were measured retrospectively on the serum samples collected in toxicology study from healthy female cynomolgus monkeys dosed weekly with 0.05, 1 or 25 mg/kg lebrigizumab IV for 9-months (followed by 8-month recovery period). In lebrikizumab-treated animals, approximately 25%−40% reduction of baseline corrected serum IgE levels were recorded, with the greatest reduction noted at D29. Nevertheless, considering that the study was conducted in healthy animals whose baseline IgE levels are expected to be low and large inter-animal variation in IgE levels throughout the study, the clinical relevance and the translation of these findings to AD cannot be confirmed, however these data can be considered supportive.

Safety Pharmacology

There were no safety findings in CNS, respiratory and cardiovascular systems attributed to lebrikizumab.

Pharmacokinetics

The PK/TK program performed with lebrikizumab in Sprague Dawley rats and cynomolgus monkeys was considered acceptable demonstrating the absorption the lebrikizumab after single and repeat dose exposure. The bioanalytical method is considered to be adequate for the measurement of lebrikizumab from the serum of cynomolgus monkeys in PK and TK studies. The ELISA and ECLA assays for the measurement of anti-IL-13 antibodies from the serum of cynomolgus monkeys are acceptable. In line with ICH S6, no distribution, metabolism or excretion was studied. For assays S-1040 and S-1042, the

FDA assay criteria were used. EU acceptance criteria (<15% or 20%) are stricter than the FDA criteria (<25%). Therefore, the EU criteria are not necessarily met. However, this is not considered as an issue in this data set. The absence of other pharmacokinetic studies is accepted.

Toxicology

The Applicant states that the commonly used rodent species (mouse, rat) were not used since lebrikizumab does not bind to rat or mouse IL-13. However, no information about binding to non-rodent species such as the dog or pig IL-13 was given. It is understood that the nonclinical development program of lebrikizumab for the present MAA for AD was coordinated by the previous Sponsor for a different indication. However, considering the possible option to develop lebrikizumab for other indications in the future it is expected that the Applicant has studied these alternative species to assess replacement of monkeys in spirit of 3R principles.

The acute toxicity of lebrikizumab is low. There were no apparent test article-related effects on measured clinical pathology parameters due to a single intravenous dose of lebrikizumab in cynomolgus monkeys. The highest IV dose 100 mg/kg was the maximal non-lethal dose.

GLP-compliant repeat-dose studies of 6 weeks, 13 weeks and 9 months in duration were conducted in cynomolgus monkeys to evaluate the toxicity and TK of lebrikizumab. Monkeys of different ages and maturity (1 to 4.5 years) were used, and IV and SC routes of administration were evaluated. The highest dose across these studies was 25 mg/kg administered once weekly by bolus IV or SC injection and was both well tolerated and without adverse findings.

In humans, ocular disorders such as conjunctivitis and keratitis are quite frequently reported as adverse reactions with of IL-13 inhibitors including lebrikizumab. Conjunctivitis and keratitis were reported more frequently in patients treated with lebrikizumab (8.5 % and 0.6% respectively) compared to placebo in controlled clinical studies. Ophthalmological examinations did not suggest any ocular effects in long-term repeat-dose toxicity studies in healthy cynomolgus monkeys. Differences in conjunctivitis incidence across the different allergic diseases suggests that AD patients are predisposed to an increase in ocular disorders. In fact, these types of complications are well known in patients with severe AD (Akinlade et al. 2019). Long-term toxicity studies were conducted in healthy cynomolgus monkeys, which would have lacked this predisposition for ocular disorders. This aligns with the data that ocular effects were not observed in monkeys administered lebrikizumab.

No consistent haematological findings, no alteration (reduction or increase) in lymphocyte subsets, and no histopathologic changes in lymphoid organs could clearly be seen across the repeat-dose toxicity studies. However, some haematological parameters' changes (neutrophil increase, lymphocyte decrease) reached statistical significance following lebrikizumab treatment in males of 13-week (2.4-3.4 y old) and 9-month (2.5-4.5 y old) toxicity study, while no differences were seen in young males (1-2 y old) of the 6-week study and sexually mature monkeys (4-7 y old) in male fertility study. On the other hand, monocyte count and/or ratio was shown to be decreased on several occasions in dams of EFD and PPND study. It is well known that immune system function is age- and sex- dependent. While the e.g. immunophenotyping data for the offspring showed comparable means and standard deviations, the data for older animals were much more variable. The Applicant considered occasional numerical differences in haematology parameters, including some that were statistically significant, sporadic/incidental, transient, and/or of a magnitude of change that is commonly observed in laboratory-housed monkeys undergoing similar study procedures. These differences were considered not related to lebrikizumab treatment and not related to the age or gender of animals. Where differences were identified during the dosing phase of studies, they were inconsistent across the studies conducted, often were present already at pretest, did not achieve statistical significance at all time points included in a study, and were typically small changes and/or within laboratory historical control ranges. On the other hand, regarding the immunophenotyping data in offspring vs. in older animals, it is acknowledged that the variability may be

attributed to the age and sex differences as well as the differences in the physiology of individual animals. It can be concluded that the link between lebrikizumab and its potential effects on immune-related endpoints in healthy animals may be complex to establish and may be complicated by the differences in the physiology of individual animals.

Although IL-13 functions in immune response, assessments of immunotoxicity and immunomodulation in monkeys administered lebrikizumab identified no remarkable or consistent changes, even if applied in the dose as high as 25 mg/kg/week (claimed to saturate circulating IL-13 levels) producing the exposure multiple of 17-20x when compared to human C_{max}. The lebrikizumab toxicology studies were conducted using normal, healthy cynomolgus monkeys. Given the absence of disease, IL-13 is expected to be at low, constitutive levels and not upregulated in monkeys, which is in contrast to the diseased clinical population. Nevertheless, pharmacological action is evident by the effect of lebrikizumab on IgE pharmacodynamics in monkeys. It has been shown that autocrine IL-13 can drive IgE production from B cells and IL-13 receptor neutralisation can reduce IgE levels. Although IgE levels would have been lower in the normal monkey compared with a disease state-induced increase in IL-13, the site localised autocrine effect of IL-13 on B cells to drive IgE production would still have been inhibited by lebrikizumab. The Applicant states that immunophenotype and TDAR in monkeys have proven to be relatively insensitive or inconsistent for demonstrating desired pharmacology, whereas these immune system endpoints were included in the toxicology studies to assess the potential for exaggerated pharmacology (gross effects) that could be considered adverse, i.e., toxic. It is agreed that despite its limitations monkey is the only pharmacologically relevant model to characterise the potential toxicity of lebrikizumab.

No genotoxicity studies were conducted with lebrikizumab which is acceptable. Carcinogenicity studies with lebrikizumab were not conducted. To support the lack of carcinogenicity risk for lebrikizumab the Lebrikizumab Carcinogenicity Risk Assessment was provided. The totality of nonclinical and clinical evidence including other IL-13 inhibitors used for AD treatment does not suggest carcinogenicity risk of this group of compounds.

No significant findings were observed in reproductive and developmental toxicity studies in cynomolgus monkeys. In female fertility study a subset of monkeys had microscopic tissue cysts present in the uterus, cervix, parathyroid, thyroid and/or thymus for which a possible relationship to lebrikizumab could not be excluded. Cysts in other affected glands occurred either in lebrikizumab-treated animals only (parathyroid, thymus) or at a higher incidence compared with control animals (thyroid). At the end of the treatment-free period, thymic cysts were present with increased incidence in animals given lebrikizumab, while parathyroid and thyroid cysts were present in control and lebrikizumab-treated animals in a pattern suggesting an incidental effect. These cysts were interpreted as having an uncertain relationship with test article because a) cysts in thymus are a well-documented and frequent common background incidental finding in cynomolgus monkeys, b) thymi of sexually mature monkeys undergo age-related thymic involution, a physiological process where the thymus progressively undergoes various changes including loss of lymphocytes and presence of epithelial remnants, often with a cystic appearance, c) the historical control data for cysts and involution in thymus in the age-matched control female and male cynomolgus monkeys from the conducting facility show that while the overall incidence of cysts in thymi in females and males are 3.89% and 9.73%, respectively, the individual studies can have incidences as high as 50% and 80%, respectively. Further, when combined with the finding of thymic involution, which might encompass cystic changes, the overall combined incidence is 12.8% and 28.8%, with individual studies having incidences as high as 75% and 100%, respectively and d) Cysts in thymus were not present in the 9-month repeat dose toxicology study with 3-month interim sacrifice and the 13-week repeat-dose toxicity and local tolerability study in both sexes in comparable doses groups that used sexually immature/peripubertal monkeys. Cysts in thymus were not considered adverse regardless of test article-relatedness because cysts in thymus did not result in clinical signs and/or other

pathological changes or abnormalities that adversely affected the quality of life of these animals and because in most tissues, occasional presence of cysts is not considered adverse especially in thymus where there is little to no functional significance in adult animals.

Several deviations from ICH S6(R1) were noted in this procedure: the longest repeat dose toxicity study conducted with monkeys was 9 months and also included 4 animals/sex/group. Increasing group sizes or study durations is not required and will generally not generate more informative data than the standard 6 month 3/sex/group, control+3 design.

In addition, the applicant conducted fertility studies in males and females. A FEED study in NHP for mAbs is unusual and a rationale for this study remains unclear, particularly since no untoward effects were noted in the pivotal RDT studies. An EFD study is also unusual since IgG transfer is extremely limited in the 1st and 2nd trimester. However, retrospective discussion on these deviations from regulatory guidelines is not pursued.

In a 9-month study one monkey in each of the low and mid-dose groups had a positive ADA titre that impacted their serum lebrikizumab concentrations and AUC could not be determined for any dose. In 13-week study no lebrikizumab-treated monkey had a positive ADA titre. However, no AUC could be determined for male or female monkeys at dose levels of 5 and 25 mg/kg. The incidences of ADA positive responses were much higher in DART studies, when compared with general repeat-dose toxicity studies. The assay formats, ADA positive criteria, and drug tolerance within the assays could account for the differences in ADA positive responses in DART studies compared to the general repeat dose toxicity studies. Overall, lebrikizumab exposures were generally dose-proportional in the various toxicity studies. While ADA analysis demonstrated a low to moderate rate of ADA detection, toxicokinetic determinations demonstrated continued exposure in most animals.

Validated ELISA methods were used for measuring anti-drug antibodies to lebrikizumab. Immunogenicity was also indirectly assessed via analysis of lebrikizumab serum concentrations using an antigen-capture ELISA. The applicant's conclusion that in most cases the presence of ADA appeared not to impact lebrikizumab exposure in monkeys is not fully endorsed. However, it is generally accepted that immunogenicity of therapeutic proteins in animals (NHPs and other species) is not predictive of the immunogenicity in human.

Potential effects of lebrikizumab on the innate and humoral immune systems were evaluated in repeat-dose studies in monkeys by means of routine haematology, peripheral blood immunophenotyping (total lymphocytes, mature T cells, helper T cells, cytotoxic T cells, total B cells, NK cells, monocytes) and evaluation of lymphoid organs. There were no treatment-related adverse effects identified for these endpoints in any study. T-cell-dependent antibody (IgG and IgM) response to keyhole limpet haemocyanin (KLH) immunisation was performed at about 6 months of age in the infant offspring of lebrikizumab-treated monkeys. No statistically significant differences were noted in response to KLH between the control group and lebrikizumab groups.

Specifications of impurities in DS and DP are considered as toxicologically qualified.

No specific lebrikizumab staining was observed in any human or cynomolgus monkey tissues suggesting high specificity for IL-13.

The results of the toxicity studies are reflected in Section 5.3 of the SmPC "Preclinical safety data".

Environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, lebrikizumab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

In conclusion, the applicant provided a comprehensive evaluation of pharmacologic, pharmacokinetic and toxicologic properties of lebrikizumab which supports the intended clinical use. Relevant information has been included in SmPC section 5.3.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 1: Efficacy and Safety Studies

Study Identifier; Phase	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status as of this report date; Type of Report
GS29735 (ARBAN)/ J2T-DM-KGAH; Phase 2;	To evaluate the safety of lebrikizumab used as monotherapy compared with topical corticosteroids alone in patients with persistent moderate-to-severe AD that is inadequately controlled with TCS	Randomised, open-label study of lebrikizumab monotherapy in adult patients (18-75 years of age) with persistent moderate-to-severe AD, inadequately controlled by TCS.	Lebrikizumab: 3 SC injections (3 doses of 125 mg/mL lebrikizumab, one Q4W) TCS: self-applied by patients during run-in period (Days -14 to -1) and treatment period (Day 1 to Week 12): 2 times per day to active skin lesions, and during safety follow-up period (Weeks 13 to 20): self-applied to active skin lesions as decided by the patient and study investigator	**Randomised**: 55 patients Lebrikizumab 125 mg Q4W: 28 patients TCS: 27 patients **Completed:** 43 patients Lebrikizumab 125 mg Q4W: 23 patients TCS: 20 patients	Patients with persistent moderate-to-severe AD	12-week treatment period	Completed; Full CSR
GS29250 (TREBLE)/ J2T-DM-KGAG[a]; Phase 2;	To evaluate the efficacy of lebrikizumab used as adjunctive therapy with TCS, compared with TCS in patients with persistent moderate-to-severe AD	Randomised, double-blind, placebo-controlled study of lebrikizumab in patients with persistent moderate-to-severe AD that is inadequately controlled by TCS.	**Group 1**: Lebrikizumab 250 mg SC single dose (Day 1) followed by 2 placebo doses (Weeks 4 and 8) for a total of 3 doses + TCS **Group 2:** lebrikizumab 125 mg SC single dose (Day 1) followed by 2 placebo doses	**Randomised**: 212 patients Lebrikizumab 250 mg single-dose group+TCS: 53 patients Lebrikizumab 125 mg single-dose group+TCS: 53 patients Lebrikizumab 125 mg Q4W group+TCS: 52 patients Placebo Q4W group+TCS: 54 patients **Completed**: 197 patients Lebrikizumab 250 mg single-dose	Patients with persistent moderate-to-severe AD	12-week treatment period	Completed; Full CSR

			(Weeks 4 and 8) for a total of 3 doses + TCS **Group 3**: lebrikizumab 125 mg SC Q4W for a total of 3 doses + TCS **Group 4**: placebo SC Q4W for a total of 3 doses + TCS	group+TCS: 53 patients Lebrikizumab 125 mg single-dose group+TCS: 49 patients Lebrikizumab 125 mg Q4W group+TCS: 48 patients Placebo Q4W group+TCS: 47 patients			
DRM06-AD01/ J2T-DM-KGAF; Phase 2b;	• To evaluate the safety and efficacy of lebrikizumab compared with placebo in patients with moderate-to-severe AD. • To evaluate the dose-response of lebrikizumab in patients with moderate-to-severe AD.	Randomised, double-blind, placebo-controlled, dose-ranging trial.	**Group 1**: Baseline loading dose of lebrikizumab 250 mg, followed by lebrikizumab 125 mg Q4W **Group 2:** Baseline loading dose of lebrikizumab 500 mg, followed by lebrikizumab 250 mg Q4W **Group 3:** Baseline and Week 2 loading doses of lebrikizumab 500 mg, followed by lebrikizumab 250 mg Q2W **Group 4:** Placebo Q2W	**Randomised**: 280 patients Lebrikizumab 125 mg Q4W (with a loading dose of 250 mg): 73 patients Lebrikizumab 250 mg Q4W (with a loading dose of 500 mg): 80 patients Lebrikizumab 250 mg Q2W (with a loading dose of 500 mg given at baseline and Week 2): 75 patients Placebo Q2W: 52 patients **Completed**: 201 patients Lebrikizumab 125 mg Q4W (with a loading dose of 250 mg): 58 patients Lebrikizumab 250 mg Q4W (with a loading dose of 500 mg): 62 patients Lebrikizumab 250 mg Q2W (with a loading dose of 500 mg given at baseline and Week 2): 58 patients Placebo Q2W: 23 patients	Patients with moderate-to-severe AD	16-week treatment period	Completed; Full CSR
DRM06-AD04/ J2T-DM-KGAB (ADvocate 1); Phase 3;	To evaluate the safety and efficacy of lebrikizumab compared with placebo in adult and adolescent (≥12 to <18 years and weigh at least	Randomised, double blind, placebo-controlled monotherapy trial.	**Induction Period:** randomised 2:1 to: • Lebrikizumab: 500 mg lebrikizumab at baseline and Week 2 (loading dose; 2 PFS-	**Enrolled:** 424 patients Induction Period: • Lebrikizumab 250mg Q2W: 283 • Placebo: 141	Patients with moderate-to-severe AD	16-week induction period 36-week maintenance period	Completed; Full CSR

	40 kg) patients with moderate-to-severe AD.		NSD) and 250 mg Q2W through Week 14 • Placebo: 4 mL (2 PFS-NSD) at baseline and Week 2 and 2 mL Q2W through Week 14 **Maintenance Period:** • randomised 2:2:1 to: Lebrikizumab 250 mg Q2W through Week 50 • Lebrikizumab 250 mg Q4W: through Week 50 • Placebo Q2W **Escape arm:** lebrikizumab 250 mg as open-label treatment Q2W through Week 52				
DRM06-AD05/ J2T-DM-KGAC (ADvocate 2); Phase 3;	To evaluate the safety and efficacy of lebrikizumab compared with placebo in adult and adolescent (≥12 to <18 years and weigh at least 40 kg) patients with moderate-to-severe AD.	Randomised, double blind, placebo-controlled monotherapy trial.	**Induction Period:** randomised as 2:1 to: • Lebrikizumab: 500 mg lebrikizumab at baseline and Week 2 (loading dose; 2 PFS-NSD) and 250 mg Q2W through Week 14 • Placebo: 4 mL (2 PFS-NSD) at baseline and Week 2 and 2 mL Q2W through Week 14 **Maintenance Period:** • randomised 2:2:1 to: Lebrikizumab 250 mg Q2W through Week 50 • Lebrikizumab 250 mg Q4W through Week 50 • Placebo Q2W **Escape arm:** • lebrikizumab 250 mg as open-label treatment Q2W through Week 52	**Enrolled:** 445 patients Induction Period: • Lebrikizumab 250mg Q2W: 295 • Placebo: 150	Patients with moderate-to-severe AD	16-week induction period 36-week maintenance period	Completed; Full CSR
DRM06-AD06/ J2T-DM-KGAD (ADhere); Phase 3;	To evaluate the safety and efficacy of lebrikizumab when used in combination with TCS	Randomised, double blind, placebo-controlled TCS combination therapy trial.	**Lebrikizumab 250 mg Q2W + TCS**: 500 mg lebrikizumab administered at baseline and Week 2 (loading	**Randomised**: 228 patients Lebrikizumab 250 mg Q2W: 145 patients Placebo: 66 patients	Patients with moderate-to-severe AD	16-week treatment period	Completed; Full CSR

	treatment compared with placebo, in adult and adolescent (12 to <18 years and weigh at least 40 kg) patients with moderate-to-severe AD.		dose) and 250 mg given Q2W through Week 14. TCS treatment was initiated at baseline and applied PRN. **Placebo + TCS**: 4 mL (2 PFS-NSD) administered at baseline and Week 2 and 2 mL given Q2W through Week 14. TCS treatment was initiated at baseline and applied PRN.	**Completed**: 192 patients Lebrikizumab 250 mg Q2W: 134 patients Placebo: 58 patients			
DRM06-AD07/ J2T-DM-KGAA (ADjoin); Phase 3;	To assess the long-term safety and efficacy of lebrikizumab in adult and adolescent (12 to <18 years and weigh at least 40 kg) patients with moderate-to-severe AD.	A long-term extension study	Two treatment regimens: 250 mg lebrikizumab, administered Q2W and 250 mg lebrikizumab, administered Q4W.	Sample size is dependent on the number of patients who enter from a parent study (approximately 900 patients) + approximately 100 patients from the addendum.	Patients with moderate-to-severe AD	100 weeks	Ongoing, Abbreviated CSR
DRM06-AD17/ J2T-DM-KGAE (ADore); Phase 3;	To evaluate the safety and efficacy of lebrikizumab in adolescent patients (12 to <18 years and weigh at least 40 kg) with moderate-to-severe AD.	Open-label, single-arm study	**Lebrikizumab 250 mg Q2W**: 500mg lebrikizumab administered at baseline and Week 2 (loading dose) and 250 mg given Q2W through Week 50	**Enrolled**: 206 patients.	Adolescent patients (12 to <18 years and weigh at least 40 kg) with moderate-to-severe AD	52-week treatment period	Complete; Full CSR
DRM06-AD18/ J2T-DM-KGAK (ADopt-VA); Phase 3;	To compare the sero-responses to the Tdap and MCVbetween lebrikizumab-treated and placebo-treated participants with moderate-to-severe AD.	Phase 3, randomised, double-blind, placebo-controlled, parallel-group trial.	**Lebrikizumab 250 mg Q2W**: subcutaneous injection at Baseline and Week 2: 500-mg loading dose Weeks 4-14: 250 mg Q2W	**Enrolled**: 442 patients.	Adult patients with moderate-to-severe AD	16-week treatment period	Complete; Full CSR
J2T-JE-KGAL, Phase 3	To test the hypothesis that lebrikizumab 250 mg Q2W or lebrikizumab 250 mg Q4W is superior to placebo in reducing signs and symptoms of AD at Week 16 in Japanese participants with moderate-to-severe AD when used in combination with TCS treatment.	Randomised, double-blind, placebo-controlled, parallel-group TCS combination study,	**Induction Period** randomised in a 3:2:2 ratio to Group 1: Lebrikizumab 250 mg Q2W SC (loading dose of 500 mg given at baseline and Week 2) + TCS Group 2: Lebrikizumab 250 mg Q4W SC (loading dose of 500 mg given at baseline) + TCS Group 3: Placebo SC + TCS **Maintenance period**	**Planned**: approximately 280 patients	Japanese patients with moderate-to-severe AD	16-week treatment period 52 week maintenance period	Complete;

			Group 1: responders re-randomised in a 1:1 ratio to lebrikizumab 250 mg Q2W SC + TCS or lebrikizumab 250 mg Q4W SC + TCS Group 2: Lebrikizumab 250 mg Q4W SC + TCS Group 3: Placebo SC + TCS				
J2T-AP-KGBQ	To evaluate the efficacy of lebrikizumab compared with placebo in patients not adequately controlled with cyclosporine or for whom cyclosporine is not medically advisable up to Week 16.	Randomised, double-blind, placebo-controlled, parallel-group study.	**Induction Period** either 250 mg lebrikizumab (loading dose of 500 mg given at baseline and Week 2) or placebo through SC injection Q2W **Maintenance Period** Patients having achieved EASI 75: lebrikizumab 250 mg Q4W Patients not having achieved EASI 75: lebrikizumab 250 mg given Q2W	**Planned**: approximately 312 patients	Patients with moderate-to-severe AD	Up to 52 weeks	Ongoing

Abbreviations: AD = atopic dermatitis; CSR = clinical study report; EASI 75 = 75% reduction from baseline in Eczema Area and Severity Index; MCV = meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GlaxoSmithKline); PFS-NSD = prefilled syringe with needle safety device; PRN = as needed; Q2W= every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; TCS = topical corticosteroid; Tdap = tetanus, diphtheria, and pertussis.

a This study investigated changes in blood biomarkers in patients that received lebrikizumab.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The applicant presented pharmacokinetic (PK) data in support of the application collected in 6 phase 1 studies in healthy volunteers, 1 phase 1 study in patients with mild asthma, 3 phase 2 studies in patients with AD, and 4 completed phase 3 studies in patients with AD (KGAB, KGAC, KGAD, and KGAE).

Anti-drug antibodies (ADAs) did not have clinically relevant effect on exposure to lebrikizumab, see Clinical safety – Immunological events of this report.

Bioanalytical methods

Serum lebrikizumab concentration

ELISA based method was developed and validated for the quantification of lebrikizumab concentrations in human serum. The initial validated assay was used in one clinical study (KGBB).

Subsequently, the ELISA method was validated for precision, accuracy, selectivity, and short-term stability and used in studies KGAZ, KGBA and KGBF.

Thereafter, the ELISA method was validated for method selectivity in atopic dermatitis, IP fibrosis and COPD. This method was used in studies KGAG, KGAH, and KGAY. The validation did not meet FDA current guidelines and the method was partially further validated in terms of accuracy, precision, matrix selectivity, bench top stability at ambient room temperature, and freeze/thaw stability. The revalidated ELISA-assay was in principle validated according to ICH M10 Bioanalytical method validation guideline. It was used in clinical studies KGAA, KGAB, KGAC, KGAD, KGAE, KGAF, KGAM and KGBG.

Anti-drug antibody and neutralising antibody assays

Both, developed ELISA based assays to characterise anti-drug antibodies (ADAs) and neutralising antibodies (NAbs) against lebrikizumab included the validation in atopic dermatitis serum and to other disease indications. Later, both assays were validated for parameters for the AD disease state.

For phase 3 AD studies Eli Lilly developed an immunogenicity assay to screen and to characterise the neutralizing ability of ADAs against lebrikizumab. The validation report was provided.

The ELISA based ADA and NAb methods used in phase 1 and 2 studies were acceptable in terms of precision, selectivity, and stability but their sensitivity and drug tolerance was clearly lower compared to the method used in phase 3 AD studies. Screening, confirmatory, titration and neutralizing cut points of the method were acceptable.

Population PK analysis

PK of lebrikizumab in adult and adolescent (12 to <18 years of age weighing ≥40 kg) subjects was characterised using population PK analysis. The dataset included lebrikizumab concentrations from 11 studies (four Phase 1 studies with dense PK sampling in healthy volunteers: KGAZ, KGAY, KGAM, and KGBA, and seven Phase 2 and 3 studies in patients with AD with sparse PK sampling: KGAG, KGAH, KGAF, KGAB, KGAC, KGAD, and KGAE). Intravenous administration was used in only one small study (KGBA; see below for more information on study KGBA).

The initial PK dataset contained 8050 postbaseline observations from 2015 participants. A total of 1190 observations were excluded from the source data to form the final analysis dataset. The most common reasons for exclusion were samples from placebo-treated subjects (n=977) and postbaseline

samples below the limit of quantitation from lebrikizumab-treated subjects (n=122). The final dataset contained 6860 measurable observations from 1607 participants (healthy subjects, n=281; adult patients with AD, n=1022; adolescent patients with AD, n=304). The age distribution for adolescent patients was evenly distributed across 12 to <18 years of age. Approximately 20% and 2% of subjects had mildly (eGFR 60-89 mL/min) and moderately (eGFR 30-59 mL/min) impaired renal function, respectively. The SC injection site locations most frequently used were arm and abdomen (51% and 37%, respectively), with thigh and multiple sites being less frequently used for dosing.

The base model was based on a published lebrikizumab population PK model in healthy subjects and patients with asthma. It was a 2-compartment model with first-order absorption and linear elimination parameterised in terms of bioavailability (F), first order absorption rate constant (ka), clearance, (CL), central and peripheral volume of distribution (V2 and V3), and intercompartmental clearance (Q). Body weight based allometric exponents were included as fixed values of 0.8 on CL and Q, and 1.0 on V2 and V3. Interindividual variability (IIV) terms were included on ka, CL, V2, and F parameters, with omega blocks on CL-ka and ka-V2 terms and a logit transformation on F to restrict the estimate of bioavailability to between 0 and 1. Residual unexplained variability (RUV) was incorporated using a proportional and additive error structure. The goodness-of-fit (GOF) plots and pcVPC plots indicated that the base model adequately described the observed data.

An assessment of prespecified covariate effects (including injection location) was conducted using the SCM procedure in PsN (forward inclusion $p<0.01$, backward elimination $p<0.001$). Body weight was formally tested on ka only because it was already included in the base model on clearance and volume parameters. Immunogenicity (ADA) was not tested as a covariate since the Week 52 data from the phase 3 studies were not available at the time of the population PK analysis. In the SCM, a total of 9 covariate effects were found to be statistically significant. These covariates were on CL (age, eGFR, and race), V2 (age, age category, disease state, and sex), and ka (disease state, race) parameters. These 9 covariates were then evaluated stepwise to assess model diagnostics and to determine if these covariates reduced their respective OMEGA variance by at least 10%, as prespecified in the analysis plan. Because these covariates did not result in notable improvements in parameter estimates, visible improvements in GOF plots, or reduction in variance of ≥10%, they were considered not significant and were not retained in the final model. Forest plots and simulations (provided upon request) supported the conclusion that age, gender, race, eGFR, and disease state (AD vs. healthy subjects) had no clinically relevant effect on exposure to lebrikizumab. Hence, the base model and the final model were the same. The model parameters are summarised in Table 2. Estimated interindividual variability (IIV) was relatively low (around 24%) for CL and V2 after body weight was used as covariate for these parameters, but for ka and F the estimated IIV was moderate to high (45% and 119%, respectively). ETA-shrinkage for CL, ka, V2, and F were moderate to high: 24%, 48%, 45%, and 37%, respectively. The mean (SD) elimination half-life was 24.5 (5.4) days.

Table 2: Pharmacokinetic and Covariate Parameters in Population PK Model.

Model Parameter (Unit)	Population Estimate (%SEE)	Interindividual Variability %CV[a] (%SEE)	95% Confidence Interval from Bootstrap Analysis
ka (1/day)	0.303 (22.9)	45.1 (14.1)	(0.249-0.355)
F	0.861 (6)	119 (33.3)	(0.805-0.915)
CL (L/day)	0.154 (6.62)	24.7 (9)	(0.144-0.165)
V2 (L)	3.86 (10.6)	23.6 (38.1)	(3.31-4.36)
Q (L/day)	0.524 (19.1)	-	(0.320-0.687)
V3 (L)	1.28 (47.9)	-	(0.730-1.92)
Covariates effects			
Covariate for body weight on CL[b]	0.8 FIX	-	-
Covariate for body weight on V2[c]	1 FIX	-	-
Covariate for body weight on Q[d]	0.8 FIX	-	-
Covariate for body weight on V2[e]	1 FIX	-	-
Variance			
Covariance for CL-ka[f]	-	-0.057 (56.7)	-
Covariance for ka-V2[f]	-	-0.0384 (145)	-
Residual error[g]			
Proportional	0.0342 (7.22)		(0.0300-0.0384)
Additive (µg/mL)	0.00307 (44)		(0.00120-0.00762)

CL = clearance after IV administration; CV = coefficient of variation; F = bioavailability; FIX = fixed; ka = absorption rate constant; Q = intercompartmental clearance, SEE = standard error of estimate; V2 = central volume of distribution; V3 = peripheral volume of distribution.

a %CV = (SQRT(e^(OMEGA(N))−1))*100%.

b CL = population CL*(WTE/70)$^{0.8}$, where WTE is body weight at study entry and 70 is median body weight.

c V2 = population V2*(WTE/70)^{1}, where WTE is body weight at study entry and 70 is median body weight.

d Q = population Q*(WTE/70)$^{0.8}$, where WTE is body weight at study entry and 70 is median body weight.

e V3 = population V3*(WTE/70)^{1}, where WTE is body weight at study entry and 70 is median body weight.

f Covariance between ω^2.

g Reported as σ^2.

Absorption and bioavailability

Absorption and bioavailability of lebrikizumab was characterised in healthy volunteers.

Bioavailability of lebrikizumab was evaluated in one study (KGBA). It was a phase I, randomised, single-dose, open-label, parallel group study in healthy volunteers conducted at one study site in the Hawaii in 2008.

Twenty of the 22 enrolled subjects (11 subjects/group, 12 males and 10 females, age 18 to 49 years, weight 39.9 to 96.8 kg) completed the study, while 2 subjects withdrew from the study (both from SC group). Each subject received a single dose of lebrikizumab (1 mg/kg) administered by SC injection or IV bolus infusion on day 1. Blood samples were taken on day 1 at pre-dose and 30 min post-dose and at days 2, 4, 8, 11, 15, 22, 36, 57, 78 and 92, and at early termination as applicable. The initial lebrikizumab concentration dataset contained several anomalous values (e.g., measurable predose concentrations and very low concentrations compared with other subjects at the same timepoint). A subset of anomalous data that was considered most critical to the estimation of PK parameters was re-assayed (a total of 18 samples; most results of the re-assays were markedly different than the initially reported values). Other anomalous data were excluded from the PK analysis; they included but were not

limited to one subject who had high pre-dose concentration confirmed in re-assay (the subject was excluded from PK analysis) and three subjects with embedded zero concentration values (the embedded zero values were excluded from PK analysis).

The reported exposure parameters and SC bioavailability results are presented in Table 3. After a subcutaneous dose of 250 mg lebrikizumab, peak serum concentrations were achieved approximately 7 to 8 days post dose. The absolute bioavailability was estimated at 86% based on a population PK analysis.

Table 3: Lebrikizumab Exposure Parameters and Statistical Analysis (SC Injection relative to IV Infusion) – Study KGBA.

Parameter (Units)	SC injection (Group 2)		IV Infusion (Group 1)		SC/IV (Ratio of Geometric Means, %)[c]	90% CI[d]
	N[a]	LS means[b]	N[a]	LS means[b]		
AUC_{0-t} (ng∘hr/mL)	11	6229081	10	7797469	79.89	66.23, 96.36
$AUC_{0-\infty}$ (ng∘hr/mL)	9	7275319	10	8534570	85.25	69.51, 104.54
Cmax (ng/mL)	11	8506	10	19836	42.88	37.35, 49.23

a In Group 1 (IV infusion), 1 participant was excluded from PK analysis due to anomalous predose value. One participant from Group 1 (IV infusion) and 2 participants from Group 2 (SC injection) were not included for assessment of bioavailability based on $AUC_{0-\infty}$ values due to difficulties in estimating the terminal elimination.
b Geometric means calculated by transforming the natural log means back to the linear scale.
c Ratio of parameter means (expressed as a percent), transformed back to the linear scale.
d 90% CI for ratio of parameter means (expressed as a percent), transformed back to the linear scale.

PK similarity between pre-filled syringe with needle safety device (PFS-NSD) and autoinjector (AI) was evaluated in study KGBG. It was a phase 1, multi-site, randomised, parallel-design, open-label, 2-arm, single-dose study conducted in 4 study sites in the USA in 2021-2022.

Eligible subjects were stratified into 1 of 3 weight categories (less than 70.0 kg, 70.0 to 80.0 kg, greater than 80.0 kg), randomised 1:1 to delivery device (either PFS-NSD [reference] or AI [test]), and sub-randomised 1:1:1 to injection site (arm, thigh, or abdomen). A total of 242 subjects were randomised. One subject was identified as a screen failure after the randomisation and did not receive the study drug. Two-hundred and forty-one subjects ((PFS-NSD = 122, AI = 119; 104 men and 137 women; aged 21 to 65 years, weights 48.3 to 116.5 kg) received one dose of study treatment per the study design. Six subjects prematurely discontinued from the study resulting in 235 participants that completed the study; three discontinued subjects were included in assessment of C_{max}. PK blood samples were taken at pre-dose and days 3, 5, 8, 11, 15, 22, 29, 43, 57, 71, 85, and 99.

The statistical analysis showed that 2-ml (125 mg/ml) lebrikizumab AI had comparable PK with 2-mL (125 mg/mL) lebrikizumab PFS-NSD (reference) as the 90% CIs of the geometric least squares means ratios for lebrikizumab AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were all completely contained within the pre-specified confidence limits of 0.80 and 1.25 (Table 4). Based on a comparison of descriptive statistics, injection-site location did not appear to impact lebrikizumab systemic exposure (AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}) for either device.

Table 4: Statistical Analysis of the PK Parameters of Lebrikizumab (Study KGBG)

Parameter	Treatment	n	Geometric LS Mean	Ratio of Geometric LS Mean (Test:Reference) (90% CI)
AUC(0-t) (μg·day/mL)	2-mL (125 mg/mL) lebrikizumab PFS-NSD (Reference)	117	1262	1.09 (1.03, 1.14)
	2-mL (125 mg/mL) lebrikizumab AI (Test)	117	1370	
AUC(0-∞) (μg·day/mL)	2-mL (125 mg/mL) lebrikizumab PFS-NSD (Reference)	106	1357	1.07 (1.02, 1.14)
	2-mL (125 mg/mL) lebrikizumab AI (Test)	100	1458	
C_{max} (μg/mL)	2-mL (125 mg/mL) lebrikizumab PFS-NSD (Reference)	120	38.6	1.09 (1.03, 1.16)
	2-mL (125 mg/mL) lebrikizumab AI (Test)	118	42.2	

PK similarity following administration of 2 x 1 mL SC injections or a single 2 mL SC injection was evaluated in study KGAM. It was a phase 1, single-centre, randomised, 2-arm, parallel group study conducted in one study site in the USA in 2018-2019. Study drug was administered in the abdomen, upper arm, or thigh. If the subject was to receive two 1-mL injections, the injections were to be given one after the other in the same body region and same body side (both in the left arm, both in the right abdomen, etc.); the two injections were to be ≥10 cm from one another.

Subjects were stratified by albumin level (<4.3 mg/dL, ≥4.3 mg/dL) at screening then randomised 1:1. A total of 41 subjects (19 males and 22 females) were randomised and 38 subjects completed the study. PK blood samples were collected at baseline (pre-dose), and on days 2, 4, 6, 8, 11, 15, 29, 43, 57, 71, 85 and 99.

The statistical analysis (Table 5) showed that the exposure parameters (AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}) were comparable, although similarity was not formally demonstrated for $AUC_{0-\infty}$ and C_{max} because the upper and lower limits of 90% CIs, respectively, were outside the pre-specified confidence limit (0.80 to 1.25).

Table 5: Statistical Analysis of the PK Parameters of Lebrikizumab (Study KGAM)

Parameter (Units)	Lebrikizumab Two 1-mL Injections		Lebrikizumab One 2-mL Injection		Least Square GMR (90% CI)
	N	Geometric Means (CV%)	N	Geometric Means (CV%)	
AUC_{0-t} (day·ng/mL)	18	1460000 (19.8)	20	1510000 (24.2)	1.03 (0.91 – 1.16)
$AUC_{0-\infty}$ (day·ng/mL)	7	1530000 (30.4)	8	1560000 (24.1)	1.02 (0.80 – 1.30)
C_{max} (ng/mL)	19	47900 (49.4)	20	42500 (21.2)	0.89 (0.73 – 1.08)

Comparable PK and exposure (AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}) parameters between a 125 mg/mL formulation of lebrikizumab administered SC by a needle and syringe and a 37.5 mg/mL formulation of lebrikizumab administered SC by a pre-filled syringe with needle safety device (PFS-NSD) was demonstrated in study KGAY. Detailed information is omitted because the 37.5 mg/mL formulation was terminated for development and used only in this study.

Distribution and elimination

The central and peripheral volume of distribution estimates for a typical subject (weight 70 kg) were 3.86 L and 1.28 L, respectively, in the population PK analysis. This indicates a total volume of distribution at steady state of 5.14 L. Body weight based allometric exponents were included in the population PK

model as fixed value of 1.0 on the central and peripheral Vd, indicating larger Vd in subjects with higher body weight. Similar results were reported in individual clinical pharmacology studies using noncompartmental analysis. Binding to plasma proteins and distribution to erythrocytes has not been investigated.

No studies on metabolism and excretion of lebrikizumab were conducted. In the population PK analysis, the CL for a typical subject was 0.154 L/day and mean elimination half-life was approximately 24.5 days (SD 5.4 days). Body weight based allometric exponents were included in the population PK model as fixed value of 0.8 on clearance parameters, indicating higher clearance in subjects with higher body weight. Similar results were reported in individual clinical pharmacology studies using noncompartmental analysis.

Dose proportionality and time dependencies

Study KGBB was a randomised, double-blind, placebo-controlled, dose-escalation study in healthy volunteers. The objectives were to determine the safety, tolerability, and PK of lebrikizumab in healthy subjects. The study was conducted in 2006-2007 at one clinical study site in the USA. Five dose cohorts of 8 subjects each received single IV bolus infusion of lebrikizumab (6 subjects) or placebo (2 subjects) as a bolus infusion. Lebrikizumab doses were 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, and 5.0 mg/kg. The early phosphate formulation was used in the study. Blood samples for PK were collected at predose (Day 1), and 15 minutes and 1, 2, 4, and 24 hours, and on Days 3, 5, 8, 15, 22, 29, 36, 43, 57, 78, and 92 postdose.

The time-concentration curve for one subject (randomised to lebrikizumab 0.3 mg/kg) was indicative of SC dosing, and this subject's data were excluded from the PK analysis. The PK parameters by dose group are summarised in Table 6. Lebrikizumab C_{max} and AUC increased in approximately dose-proportional manner across the 0.1- to 5.0-mg/kg dose range used in this study.

Table 6: Lebrikizumab Mean (SD) PK Parameters by Dose (Study KGBB)

Parameter (Units)	0.1 mg/kg, N=6	0.3 mg/kg, N=5	1.0 mg/kg, N=6	3.0 mg/kg, N=6	5.0 mg/kg, N=6
C_{max} (ng/mL)	2788 (289)	9070 (871)	30675 (7721)	92300 (15507)	142433 (20538)
AUC0-last (day·ng/mL)	51423 (5040)	204090 (19645)	575111 (48160)	1766282 (578161)	3158958 (616744)
AUC0-∞ (day·ng/mL)	55561 (6517)	227809 (21131)	621196 (54902)	1927488 (672053)	3491756 (761033)
C_{max} / Dose (kg/mL)	0.028 (0.003)	0.030 (0.003)	0.031 (0.008)	0.031 (0.005)	0.028 (0.003)
AUC0-∞ / Dose (day·kg/mL)	0.556 (0.065)	0.759 (0.070)	0.621 (0.055)	0.642 (0.224)	0.698 (0.152)
$t_{½}$ (day)	25.1 (3.3)	28.8 (2.6)	25.0 (3.8)	23.3 (6.8)	27.2 (3.6)

$AUC_{0\text{-last}}$ = area under the concentration-time curve determined using all time points at which measurable drug concentration were observed; **$AUC_{0\text{-}\infty}$** = area under the concentration-time curve extrapolated to infinity; **C_{max}** = maximum observed serum concentration; **SD** = standard deviation; **$t_{½}$** = terminal elimination half-life.

Study KGBF was a randomised, double-blind, placebo-controlled, dose escalation study that evaluated the safety, tolerability, PK, and immunogenicity of four IV doses (0.3 mg/kg, 1.0 mg/kg, and 3.0 mg/kg) of lebrikizumab administered Q4W in patients with mild, intermittent asthma. The primary objective was to evaluate the safety and tolerability of multiple doses of lebrikizumab in patients; the secondary objective was to characterise the PK and immunogenicity. The study was conducted in 2007-2009 at seven study sites in the USA. The early phosphate formulation was used in the study. Blood samples for PK were collected at predose and 30 minutes post dose on study drug administration Days 0, 28, 56, and 84. In addition, PK samples were collected on Days 1, 3, 7, 14, 85, 91, 112, 140, 168, and 196.

Of the 37 patients randomised to lebrikizumab, 33 completed the study and were included in the PK population. The PK parameters by dose group are summarised in Table 7. Following multiple (4) doses, lebrikizumab C_{max} and AUC increased in a dose-proportional manner and clearance was similar across the 0.3- to 3.0-mg/kg dose range used in this study.

Table 7: Lebrikizumab Mean (SD) PK Parameters by Dose following Multiple-dose Administration (Study KGBF)

Parameter (Units)	0.3 mg/kg, N=10	1.0 mg/kg, N=12	3.0 mg/kg, N=11
Cmax (µg/mL)	13.5 (7.01)	40.6 (6.71)	99.9 (22.0)
AUC0-∞ (day·µg/mL)	748 (140)	2340 (496)	6560 (1470)
Clearance (mL/day/kg)	1.65 (0.270)	1.78 (0.399)	1.92 (0.462)
Terminal half-life (day)	22.4 (3.84)	21.7 (3.82)	25.2 (9.36)
Vss (mL/kg)	117 (17.3)	116 (25.7)	132 (28.7)

AUC0-∞ = area under the serum concentration-time curve extrapolated to infinity; **Cmax** = maximum observed serum concentration; **SD** = standard deviation; **Vss** = volume of distribution at steady state.

Study KGAZ was a randomised, double-blind, placebo-controlled, parallel group study that evaluated the safety, tolerability, and PK following single SC dose administration of lebrikizumab in healthy Japanese and Caucasian subjects. The primary objective was to investigate the safety, tolerability, and PK of SC lebrikizumab in Japanese subjects, and the secondary objective was to compare the safety, tolerability, and PK between healthy Japanese and Caucasian subjects. The study was conducted in 2011-2012 at one study site in Hawaii. The commercial formulation was used in the study. Blood samples for PK were collected at predose, 4 and 12 hours postdose on Day 1, and on Days 2, 5, 8, 15, 29, 50, 71, 99, and Day 120 (or early termination).

A total of 21 Japanese and 21 Caucasian participants were randomly assigned to lebrikizumab (7 Japanese and 7 Caucasian to each lebrikizumab dose group). Two Caucasian subjects randomised to 125 mg lebrikizumab withdrew from the study, one of them had sufficiently PK observations and was included in the PK analyses.

The PK parameters are presented in **Table 8**. In Japanese subjects, dose normalised Cmax and AUC values were comparable and the CL/F was similar across the 125- to 375-mg dose range used in this study. In Caucasian subjects, dose normalised AUC0-inf values were comparable, but dose normalised Cmax and AUC0-t were increased in the 375 mg dose qroup. Statistical analysis using the power model to assess dose proportionality showed that the slope estimate (90% CI) was 1.08 (0.85, 1.32), 0.99 (0.79, 1.19), and 0.98 (0.77, 1.18) in Japanese subjects and 1.39 (1.25, 1.53), 1.17 (1.01, 1.32), and 1.13 (0.97, 1.29) for Caucasian subjects for Cmax, AUC0-t, and AUC0-∞ adjusted for weight, respectively.

Table 8: Lebrikizumab Mean (SD) PK Parameters by Dose (Study KGBZ)

	Japanese			Caucasian		
Parameter (Units)	**125 mg, N=7**	**250 mg, N=7**	**375 mg, N=7**	**125 mg, N=6**	**250 mg, N=7**	**375 mg, N=7**
Cmax (µg/mL)	15.3 (4.37)	29.0 (7.99)	47.2 (8.28)	14.2 (3.85)	27.9 (8.74)	61.0 (11.9)
DN Cmax (µg/mL/mg)	0.122 (0.0350)	0.116 (0.0319)	0.126 (0.0221)	0.114 (0.0308)	0.112 (0.0350)	0.163 (0.0317)
AUC0-t (µg·day/mL)	622 (125)	1180 (306)	1760 (294)	733 (218)	1260 (438)	2430 (465)
DN AUC0-t (µg·day/mL/mg)	4.97 (1.00)	4.70 (1.23)	4.69 (0.784)	5.86 (1.74)	5.04 (1.75)	6.47 (1.24)
AUC0-∞ (µg·day/mL)	643 (134)	1210 (324)	1790 (297)	802 (245)	1300 (462)	2550 (507)
DN AUC0-∞ (µg·day/mL/mg)	5.15 (1.07)	4.86 (1.30)	4.78 (0.792)	6.42 (1.96)	5.22 (1.85)	6.81 (1.35)
tmax (day)[a]	4.00 (1.00, 14.0)	6.00 (4.00, 14.0)	6.96 (6.94, 7.95)	7.00 (4.00, 14.0)	6.00 (4.00, 14.0)	6.98 (3.98,7.19)
CL/F (mL/day/kg)	3.37 (0.628)	3.43 (1.36)	3.12 (0.344)	2.52 (0.509)	2.78 (0.869)	2.20 (0.133)
$t_{1/2}$ (day)	23.1 (2.48)	21.3 (5.61)	20.4 (1.61)	31.6 (2.99)	22.2 (3.37)	28.3 (5.06)
Vz/F (mL/kg)	112 (22.7)	98.0 (14.2)	91.1 (8.55)	115 (23.6)	86.9 (20.0)	90.0 (17.4)

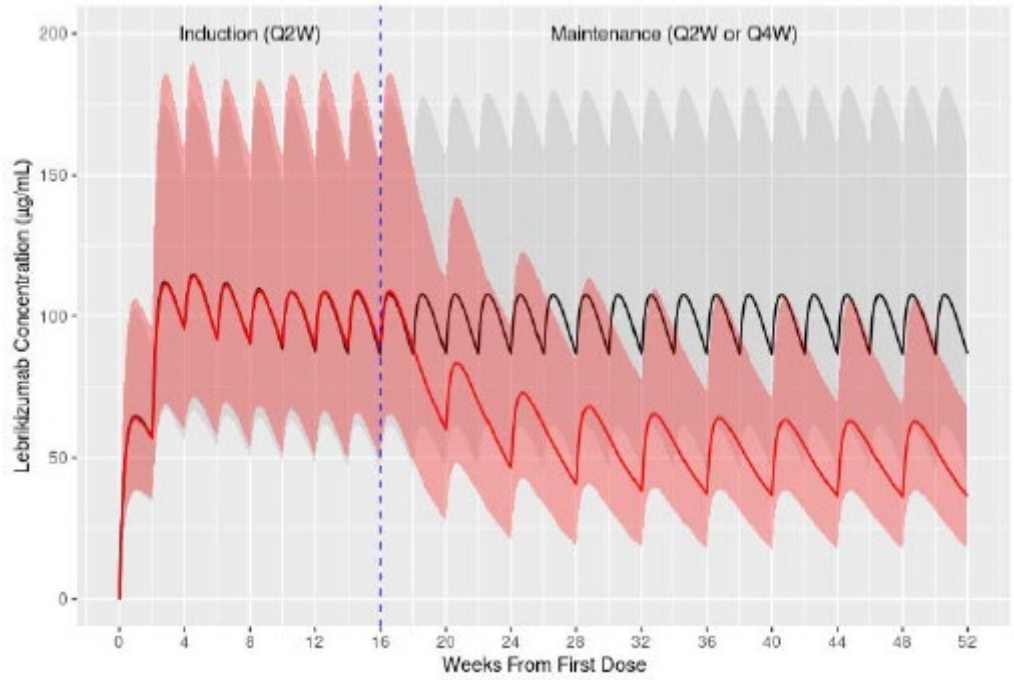
AUC0-∞ = area under the concentration-time curve extrapolated to infinity; **AUC0-t** = area under the concentration-time curve from time 0 to the last measurable concentration; **Cmax** = maximum observed serum concentration; **CL/F** = apparent clearance after SC administration; **DN** = dose normalised; **SD** = standard deviation; **t1/2** = terminal elimination half-life; **tmax** = time of maximum observed serum concentration; **Vz/F** = apparent volume of distribution at the terminal phase after SC administration.

Dedicated time dependency studies were not conducted. No indication of time-dependent clearance was found in the population PK analysis.

PK in target population

The proposed dosing regimen, which was used in the pivotal phase 3 studies, consists of an induction phase (500 mg SC at weeks 0 and 2, followed by 250 mg SC Q2W up to week 16), followed by a maintenance phase (250 mg SC Q4W). Exposure to lebrikizumab will be highest during the induction phase and, based on simulations using the final population PK model, the steady state average concentration ($C_{avg,ss}$) will be approximately 50% lower during the maintenance phase compared with the induction phase (Figure 1 and Table 9).

Figure 1: Virtual patient simulations to 52 weeks: Loading/induction doses up to Week 16, then lebrikizumab 250 mg Q2W versus 250 mg Q4W in maintenance period.



Q2W = every 2 weeks; **Q4W** = every 4 weeks.
[a] Simulated patients received 500 mg loading doses at Weeks 0 and 2, followed by 250 mg Q2W dosing until Week 16. At Week 16, 1 group remained on 250 mg Q2W and 1 group reduced their dose to 250 mg Q4W for remainder of maintenance period to Week 52.
N = 500 participants for each dose group in maintenance period. Lines represent medians and shaded areas represent 5th and 95th percentiles of simulated values at each time point.

Table 9: Observed and Simulated Lebrikizumab Concentrations Following Phase 3 Dosing Regimens, Reported as Median (5th Percentile, 95th Percentile).

Dosing Regimen	**500 mg Loading Dose at Weeks 0 and 2, 250 mg Q2W Weeks 4 to 16, and 250 mg Q2W or 250 mg Q4W Starting at Week 16**			
Population	**Observed data: Phase 3 Study Participants (N = 796)**	**Simulations of 500 Virtual Participants Based on Body Weight Distribution of Phase 3 Adolescent and Adult Participants**		
PK Parameter	**250 mg Q2W Week 16**	**250 mg Q2W Week 16**	**250 mg Q2W Week 52**	**250 mg Q4W Week 52**
$C_{max,ss}$ (µg/mL)	NA	109 (61.6-177)	108 (61.7-182)	62.6 (38.2-106)
$C_{avg,ss}$ (µg/mL)	NA	100 (56.3-167)	99.9 (56.1-175)	51.1 (29.4-86.5)
$C_{trough,ss}$ (µg/mL)	94.4 (32.6-152)	86.4 (46.4-153)	86.6 (46.0-159)	36.1 (17.6-67.9)

Cavg,ss = average concentration over a dosing interval at steady state; **Cmax,ss** = maximum concentration over a dosing interval at steady state; **Ctrough,ss** = minimum concentration over a dosing interval at steady state;
NA = not applicable; **Q2W** = every 2 weeks; **Q4W** = every 4 weeks.

Following the 500 mg loading doses at week 0 and week 2, steady-state serum concentrations were achieved with the first 250 mg Q2W dose at week 4.Based on a population pharmacokinetic (PK) analysis, the predicted steady-state trough concentrations (Ctrough,ss) following lebrikizumab 250 mg Q2W and Q4W subcutaneous dosing in patients with atopic dermatitis (median and 5th - 95th percentile) were 87 (46-159) µg/mL and 36 (18-68) µg/mL, respectively.

Special populations

Dedicated studies in special populations were not conducted. Potential effects of intrinsic factors [including age, weight, gender, race, markers of renal and hepatic function, and disease state (patients with AD vs healthy subjects)] on PK parameters were tested in population PK analysis.

Exposure is inversely correlated with body weight (Figure 2 and Table 10). Interindividual variability in observed serum lebrikizumab levels can be partly, but not entirely, attributed to differences in body weight.

Figure 2: Observed lebrikizumab Week 16 predose concentrations by baseline body weight: all Phase 3 participants (adults and adolescents).

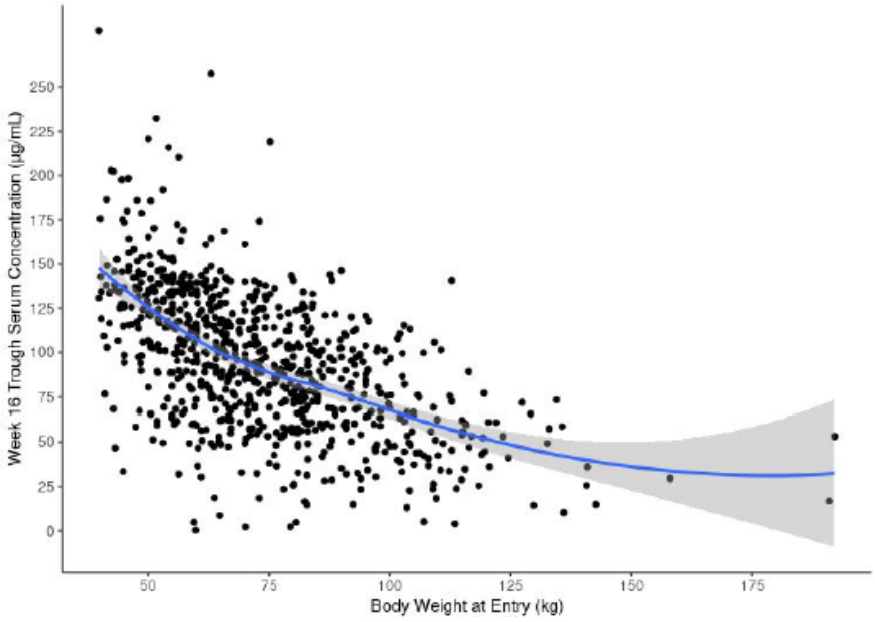


Table 10: Simulated Lebrikizumab Exposure Parameters at Week 52 by Regimen and Weight Category.

Simulations of 500 Virtual Participants in Each Maintenance Period Regimen Based on Body Weight Distributions of Phase 3 Adolescent and Adult Participants. Concentrations Are Expressed as Median (5^{th}, 95^{th})						
Dosing Regimen	**500 mg Loading Dose at Weeks 0 and 2, 250 mg Q2W from Weeks 4 to 16, and 250 mg Q2W or 250 mg Q4W Starting at Week 16**					
Maintenance Regimen	**Q2W**			**Q4W**		
Body Weight Category	**<60 kg**	**60-100 kg**	**>100 kg**	**<60 kg**	**60-100 kg**	**>100 kg**
N (%) [a]	130 (26)	317 (63)	53 (11)	151 (30)	293 (59)	56 (11)
$C_{max,ss}$ (µg/mL)	142 (97.2-217)	104 (64.8-156)	70.1 (49.2-96.5)	80.3 (57.3-127)	58.7 (39.9-90.3)	43.6 (29.7-58.7)
$C_{avg,ss}$ (µg/mL)	132 (86.2-206)	96.8 (57.8-148)	64.1 (44.6-91.5)	64.0 (39.6-107)	47.7 (29.9-77.6)	36.4 (23.3-51.0)
$C_{trough,ss}$ (µg/mL)	117 (67.9-188)	83.8 (48.3-133)	56.3 (35.7-84.0)	43.0 (22.2-81.8)	33.8 (17.3-61.0)	25.4 (14.8-40.7)

[a] The number and percentage of participants in each body weight category of the 500 simulated participants in each maintenance period regimen.
Cavg,ss = average concentration over a dosing interval at steady state; **Cmax,ss** = maximum concentration over a dosing interval at steady state; **Ctrough,ss** = minimum concentration over a dosing interval at steady state; **N** = number of participants; **Q2W** = every 2 weeks; **Q4W** = every 4 weeks.

The predicted mean steady state exposure in adolescents (12 to <18 years of age weighing ≥40 kg) with AD was approximately 20% higher compared with adults, which was attributed to the lower body weight distribution in adolescents.

Age (range: 12 to 93 years), gender, race, and markers of renal and hepatic function were considered not to have meaningful effect on PK. The number of 65-74 years old, 75-84 years old, and ≥85 years old subjects in the PK dataset were 71, 17, and 3, respectively.

Pharmacokinetic interaction studies

No formal studies have been conducted to examine the effect of lebrikizumab on the PK of other drugs. Monoclonal antibodies are not anticipated to directly impact the PK of other drugs. Published literature (Davis et al. 2018) indicates that blockade of the IL-4α receptor (thus blocking IL-13 activity) was not associated with changes in CYP3A, CYP2C19, CYP2C9, CYP1A2, or CYP2D6 activity following 4 weeks of treatment in patients with AD. Based on these data, it is unlikely that lebrikizumab (an anti-IL-13 mAb) will have an effect on the PK of other drugs due to potential drug-disease interactions.

2.6.2.2. Pharmacodynamics

Mechanism of action

Lebrikizumab is an immunoglobulin (IgG4) monoclonal antibody that binds with high affinity to interleukin (IL)-13 and selectively inhibits IL-13 signalling through the IL-4 receptor alpha (IL-4Rα)/ IL-13 receptor alpha 1 (IL-13Rα1) heterodimer, thereby inhibiting the downstream effects of IL-13. Inhibition of IL-13 signalling is expected to be of benefit in diseases in which IL-13 is a key contributor to the disease pathogenesis. Lebrikizumab does not prevent the binding of IL-13 to the IL-13 receptor alpha 2 (IL-13Rα2 or decoy receptor), which allows the internalisation of IL-13 into the cell.

Primary and Secondary pharmacology

Limited pharmacodynamic data were collected in the clinical program, mainly clinical efficacy endpoints were used in the proof-of-concept and dose finding studies. PD biomarker data were not evaluated in phase 3 studies in patients with AD.

Study KGAG was a preliminary Phase 2 study to evaluate the efficacy of lebrikizumab plus TCS vs. TCS alone in moderate to severe AD. A total of 212 patients were randomised 1:1:1:1, 209 of whom received study drug (and TCS) as follows: lebrikizumab 250 mg SC single-dose, lebrikizumab 125 mg SC single-dose, lebrikizumab 125 mg SC at weeks 0, 4, and 8, placebo. The 12-week treatment period was followed by an 8-week safety follow-up period. Changes in candidate biomarkers in patients with AD [serum periostin, IgE, CCL-13 (monocyte chemotactic protein-4), CCL-18 (pulmonary and activation-regulated chemokine), and peripheral blood eosinophils] were evaluated as an exploratory objective in the study.

Lebrikizumab (combined with TCS) decreased the levels of CCL-13, CCL-18, and periostin compared to placebo (TCS only). Median reduction from baseline (%) to week 1 was 25.7-33.2% and 52.3-58.4%, for CCL-13 and CCL-18, respectively, in the lebrikizumab arms compared to 3.4% and 12.1% in the placebo arm (Table 11). The percent reductions from baseline were generally sustained through the 12-week treatment period in the lebrikizumab arms. Median reduction from baseline (%) to week 1 was 8.3-10.6% for periostin in the lebrikizumab arms compared to 1.4% in the placebo arm. Serum periostin levels continued to gradually decline during the study in all lebrikizumab treatment arms (Table 11).

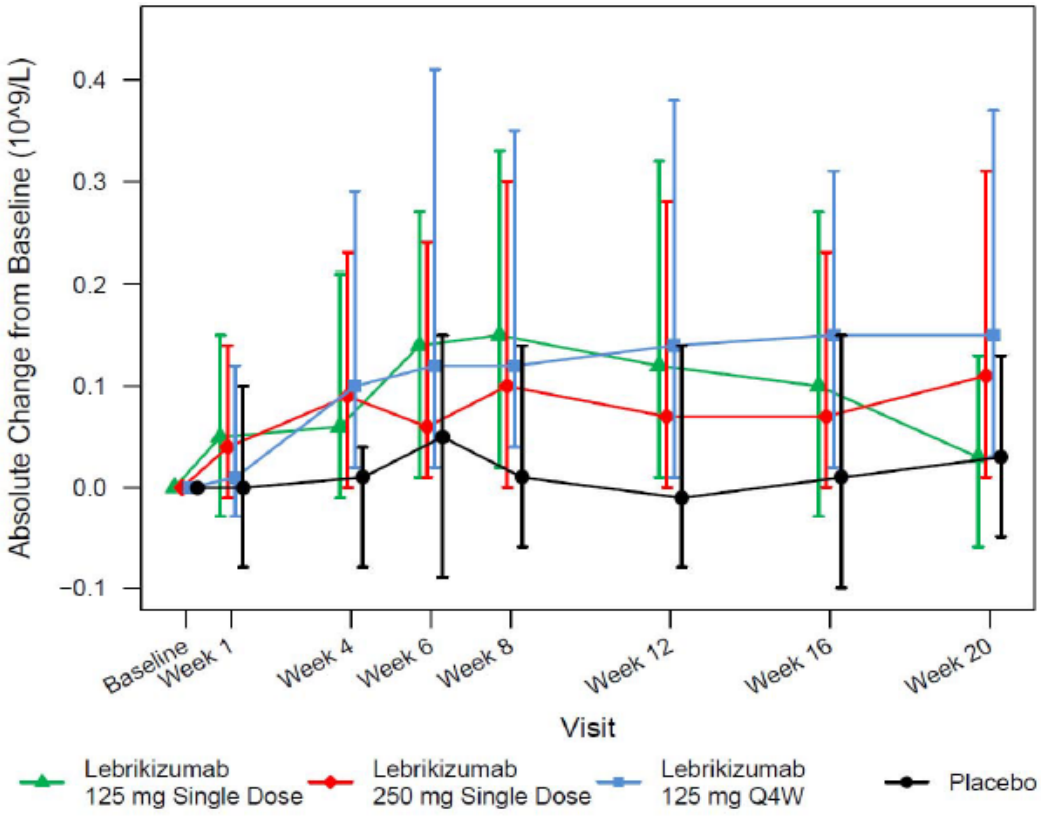
Peripheral blood eosinophils tended to increase above baseline levels in lebrikizumab-treated patients (Figure 3). Between-subject variability in serum IgE levels was high. Overall, a gradual reduction in median serum total IgE occurred in both the placebo and lebrikizumab arms during the treatment phase, with the decline continuing throughout the safety follow-up period. At the end of the safety follow-up period (Week 20), the median decrease in IgE levels from baseline was 28.7%, 37.3%, 40.0% and 25.6% in lebrikizumab 250 mg single dose, 125 mg single dose, 125 mg Q4W and placebo arms, respectively.

Overall, the responses were comparable in each lebrikizumab dose groups, i.e., no dose-response was observed for these PD biomarkers.

Table 11: Serum CCL-13, CCL-18, and Periostin Median Concentrations (Study KGAG).

	250 mg SC single dose	125 mg SC single dose	125 mg SC at weeks 0, 4, and 8	Placebo
CCL-13 (ng/l)				
Baseline	240.4	272.2	280.0	243.0
Week 1	169.1	186.7	189.9	235.1
Week 4	158.2	178.5	193.5	226.6
Week 12	145.2	192.7	181.9	229.0
Week 20	154.5	192.9	154.4	219.4
CCL-18 (ng/ml)				
Baseline	214.7	260.5	232.1	250.4
Week 1	90.3	118.4	118.7	234.4
Week 4	73.0	86.4	91.5	171.1
Week 12	79.1	100.0	83.7	160.9
Week 20	106.1	114.7	82.0	155.4
Periostin (ng/ml)				
Baseline	67.6	61.1	64.2	66.6
Week 1	64.2	55.6	54.6	68.5
Week 4	58.9	58.5	55.3	68.2
Week 12	54.2	54.6	50.1	64.9
Week 20	57.8	58.1	47.3	67.0

Figure 3: Median (Q1-Q3) absolute change from baseline in eosinophils over 20 weeks (Study KGAG).



The effect of lebrikizumab on serum PD biomarkers was also evaluated in randomised, placebo-controlled, double-blind phase 3 studies KGAN and KGAO in patients with asthma. In these two studies, serum levels of CCL-13, CCL-17, periostin, and IgE decreased in patients treated with lebrikizumab.

Lebrikizumab induced no hERG inhibition *in vitro* at test concentrations up to 6.0 mg/mL, which is markedly higher than clinical exposure (Table 9).

Relationship between plasma concentration and effect

Exposure-response (E-R) model was developed including efficacy data (EASI) up to Week 16 from 5 randomised, double-blind, placebo-controlled Phase 2 and Phase 3 trials in patients with AD: KGAF, KGAG (data up to week 12), KGAB, KGAC and KGAD.

A placebo model was developed first. Exploratory graphical analyses indicated response to placebo and use of topical corticosteroids (TCS) appeared to improve the response, as expected. The placebo response was described by an indirect effect model, including a TCS effect on K_{out} and study effects (Phase 2 vs Phase 3) on baseline EASI. Other structures (direct effect, asymptotic, linear model) were explored, but indirect effect was most predictive (lowest OFV). The logit fractional placebo effect was found to be most stable and was used in all models.

Lebrikizumab treatment data were added to the placebo model using the individual EBEs from the population PK model. Treatment effect, linear, E_{max} and sigmoidal E_{max} drug effect models were evaluated; the inhibitory E_{max} model provided the best fit. The TCS effect on K_{out} was re-evaluated with

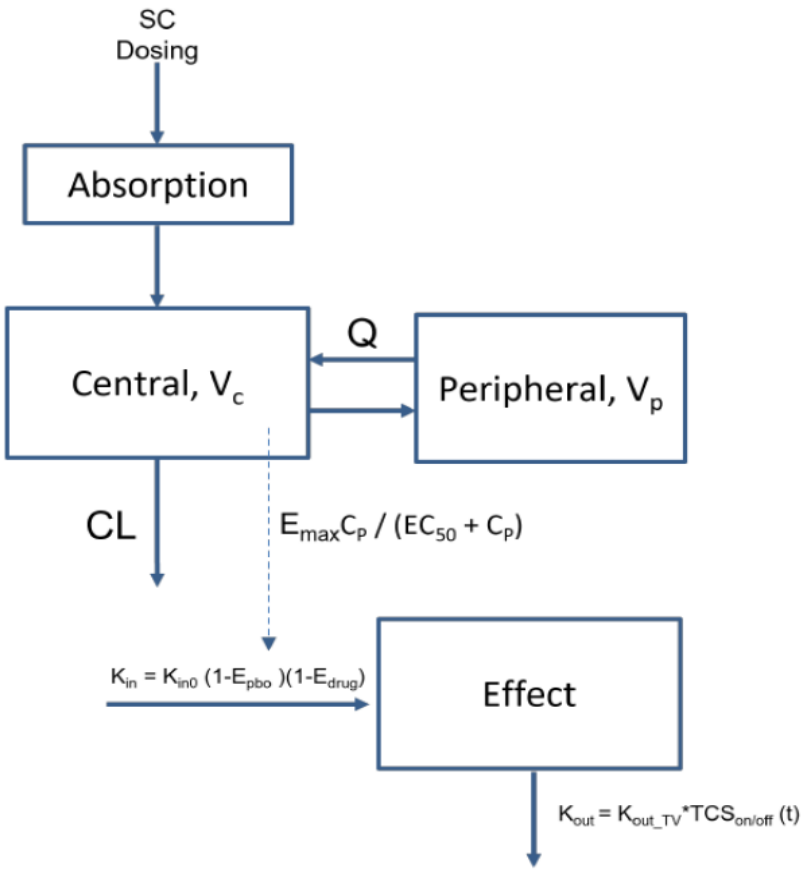
the addition of lebrikizumab-treated patients. A time-varying effect was added to the model (ΔOFV -13.7), then rewritten by expanding the TCS effect on K_{out} described in the placebo model.

Different implementations of random effects models were also assessed. The off-diagonal block from the placebo model was removed and rearranged to include correlation between the individual estimated EASI baseline and placebo effect, which improved model fit. Switching IIV from E_{max} to EC_{50} provided a lower condition number. Lastly, allowing estimation of K_{out} showed strong improvement in the model fit. This final structural model was carried forward for the evaluation of patient covariate effects.

Covariates of interest were explored graphically. Potential trends in continuous body weight were seen versus K_{out} and EC_{50}. Age and body weight were tested as covariates on E_{max} and EC_{50} but were not found to be significant. Study effect on estimated population baseline EASI score was re-evaluated as a covariate effect. With the addition of the treatment data, the study effect was re-stratified into three groups: KGAG (mean baseline 25.4), KGAF and KGAD (mean baseline 26.8), KGAB and KGAC (mean baseline 29.0). This adjustment in the baseline effect was significant and allowed the model to more accurately identify responders relative to each group.

The final model comprised an indirect effect, including a time varying TCS effect on K_{out} and study effects on baseline EASI (Figure 4 and Table 12).

Figure 4: The final exposure-response model for lebrikizumab in atopic dermatitis. Effect compartment represents the EASI score.



CL = clearance after IV administration; **C_p** = drug concentration; **EC_{50}** = drug concentration that produces 50% of maximum effect; **E_{drug}** = drug effect; **E_{max}** = maximum effect; **E_{pbo}** = placebo effect; **K_{in}** = zero-order constant for production of response; K_{out} = first-order rate constant for loss of response; **Q** = intercompartmental clearance; **SC** = subcutaneous; **TCS** = topical corticosteroid; **V_c** = volume of distribution of central compartment; **V_p** = volume of distribution of peripheral compartment.

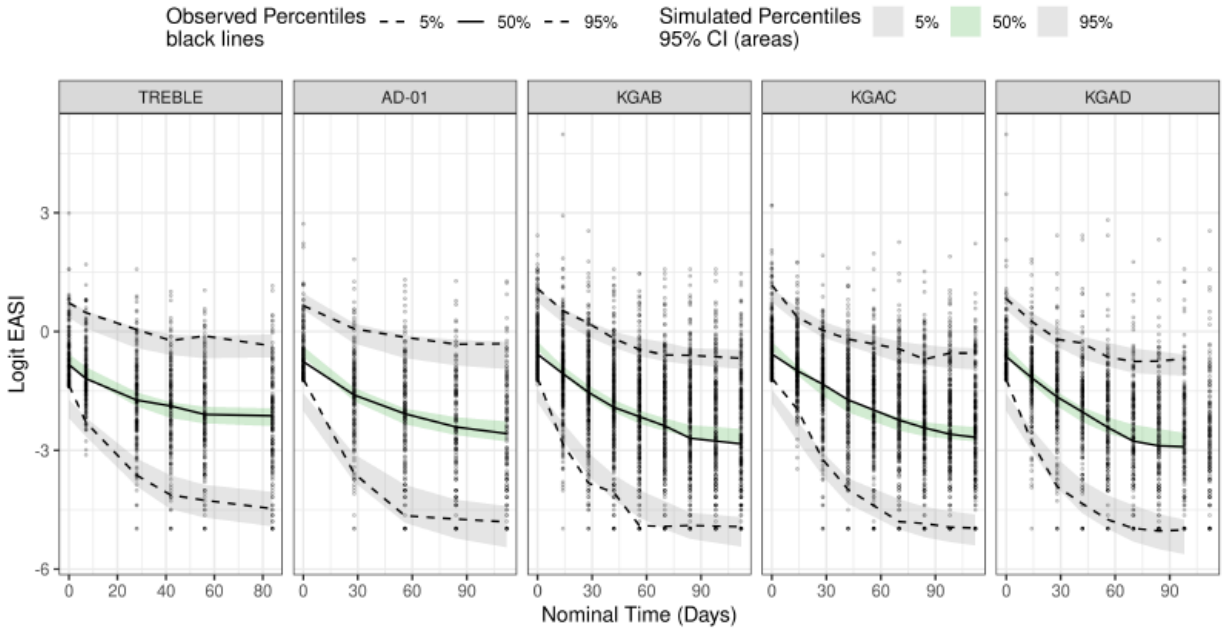
Table 12: Parameter Estimates of the Final Exposure-Response Model

Param	Alias	Estimate	Relative SE (%)	95% CI
θ_1	Baseline EASI (KGAG)	23.9	3.1	(22.4 - 25.3)
θ_2	Baseline EASI (KGAF,KGAD)	26.8	1.9	(25.8 - 27.8)
θ_3	Kout (1/d)	0.0523	.....	(0.0489 - 0.0559)
θ_4	Placebo Effect (Fixed)	0.702	.....	.....
θ_5	TCS on Kout (unitless multiplier)	1.08	.....	(1.06 - 1.10)
θ_6	sigmaE	0.468	.....	(0.463 - 0.474)
θ_7	Emax	0.831	.....	(0.761 - 0.883)
θ_8	EC50 (ug/mL)	16.5	.....	(9.84 - 27.6)
θ_9	Baseline EASI (KGAB,KGAC)	29.5	0.5	(29.3 - 29.8)
$\omega_{1.1}$	ω^2_{E0}	1.74	8.4	(1.45 - 2.03)
$\omega_{2.1}$	$\omega^2_{E0,Kout}$	-0.0599	82.5	(-0.157 - 0.0370)
$\omega_{2.2}$	ω^2_{kout}	0.340	8.2	(0.285 - 0.395)
$\omega_{3.2}$	$\omega^2_{kout,Epbo}$	0.0860	81.8	(-0.0519 - 0.224)
$\omega_{3.3}$	ω^2_{Epbo}	2.46	7.9	(2.08 - 2.84)
$\omega_{5.5}$	ω^2_{EC50}	4.96	32.2	(1.83 - 8.09)

Parameter values for the final PK-PD model. **EASI:** Eczema Area and Severity Index; **TCS:** topical corticosteroid; **E0:** individual baseline EASI estimate; **Epbo:** placebo effect; **sigmaE:** individual variability on baseline; ω^2_X: variance of the IIV of parameter X, IIV is derived from variance according to $\sqrt{\omega^2_X} \cdot 100$. $\omega^2_{X,Y}$: covariance of the IIV of parameters X and Y.

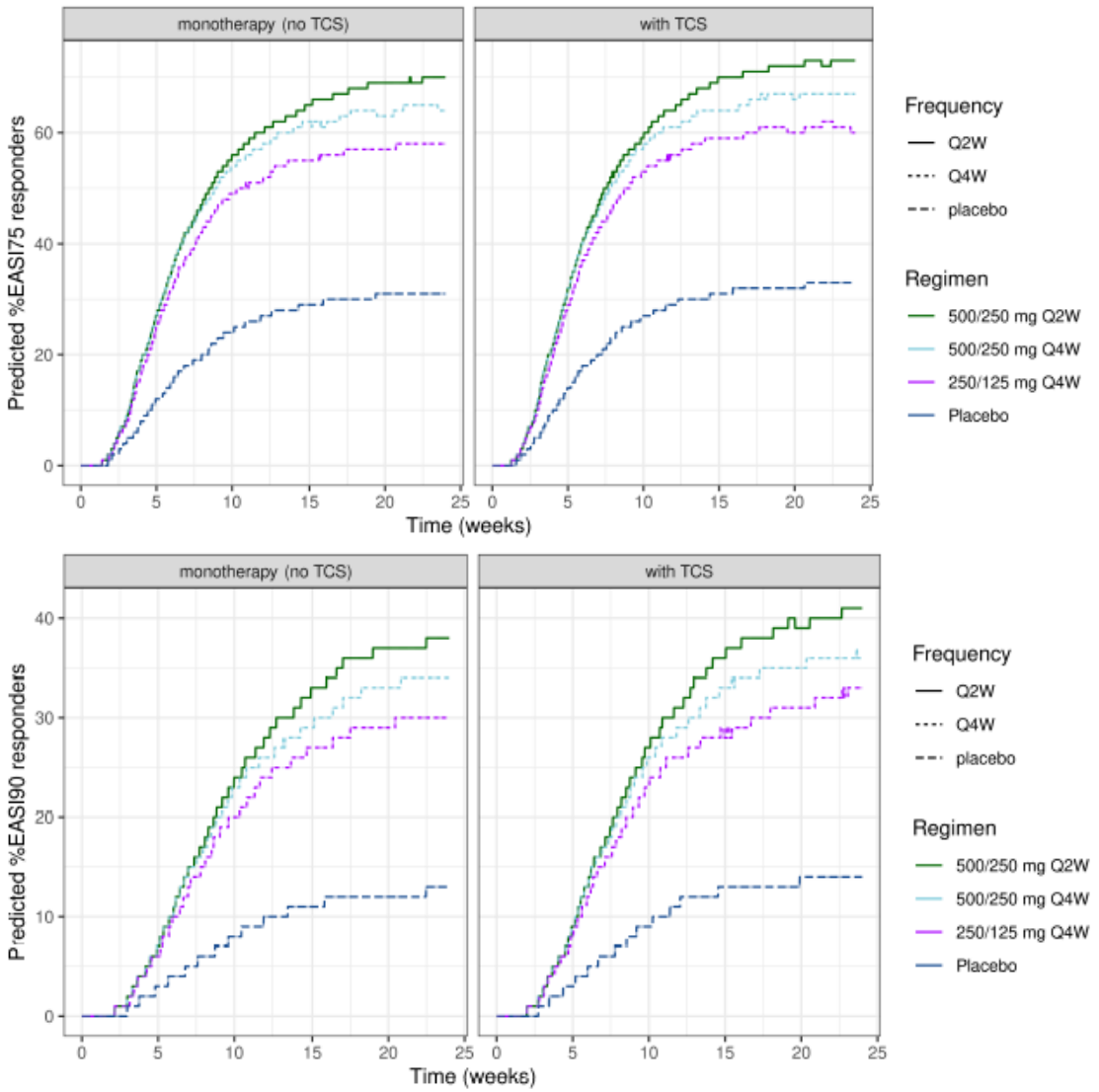
Shrinkage in ETA1 (estimated individual baseline, E0), ETA2 (K_{out}), ETA3 (E_{pbo}), and ETA4 (EC_{50}) were 12.9%, 32.1%, 24.9% and 53.6%, respectively. Due to high shrinkage values the model evaluation and predictive performance relied mostly on VPC. Logit-transformed EASI scores were reasonably well described by the final model, with good agreement between predicted and observed data through week 12 (KGAG) and week 16 (all other studies) (Figure 5). The percentage change from baseline (%CFB) EASI score was reasonably well described for those with typical (median) and good (95th percentile) response but the model underpredicted the response for those with poor response (5th percentile).

Figure 5: Prediction-corrected VPC of EASI Score over Time by Study.



A response curve over time for patients with and without TCS is provided in Figure 6 for the prediction of percentage of patients achieving EASI-75 and EASI-90 response. The phase 3 dose regimen shows the highest predicted proportion of patients achieving reduction in EASI scores, compared to the lower phase 2 dose regimens (single loading dose of 500 mg or 250 mg followed by 250 mg Q4W or 125 mg Q4W).

Figure 6: Predicted percent of EASI-75 (Top) and EASI-90 (Bottom) responders over time by dose.



Regimen refers to the loading dose followed by the treatment regimen. **500/250 mg Q2W:** two loading doses of 500 mg Q2W followed by 250 mg Q2W; **500/250 mg Q4W:** single loading dose of 500 mg followed by 250 mg Q4W; **250/125 mg Q2W:** single loading dose of 250 mg followed by 125 mg Q4W.

2.6.3. Discussion on clinical pharmacology

Bioanalytical methods

Serum lebrikizumab concentrations

The ELISA method was validated For performance of calibration standards, precision, accuracy, selectivity, and short-term stability of the assay were acceptable. The Genentech method was used in studies KGAZ, KGBA, and KGBF. Bioanalysis of lebrikizumab samples in these clinical studies met precision and accuracy acceptance criteria and the performance of calibration standards was acceptable.

Subsequently, the ELISA assay was validated according to ICH M10 Bioanalytical method validation guideline. The partial re-validation was done with different lebrikizumab batch than the validation and these methods were shown to be comparable. The revalidated method showed acceptable accuracy,

precision, selectivity, stability and parallelism and was used in clinical studies KGAA, KGAB, KGAC, KGAD, KGAE, KGAF, KGAM and KGBG. The bioanalytical reports of these clinical studies indicated that the sample analysis was reliable within the given accuracy and precision ranges. The reasons for repeat analysis were acceptable and the required criteria for incurred method analysis was met.

ADA and NAb

In phase 1 and 2 studies, ELISA based methods were utilised to characterise ADAs and NAbs against lebrikizumab. For phase 3 clinical trials Eli Lilly developed an immunogenicity assay for the detection of ADAs and NAbs in the healthy and AD serum samples.

The original ELISA based ADA and NAb methods were acceptable in terms of precision, selectivity, and stability but their sensitivity and drug tolerance was lower compared to the immunogenicity assay method. Therefore, it is difficult to compare the prevalence and incidence of ADAs and NAbs in phase 1 and 2 vs. phase 3 studies. Assessment of the ADA/NAb assays is focused on the immunogenicity assay method that was used in the pivotal studies in target population. Screening, confirmatory, titration and neutralizing cut points immunogenicity assay method were determined in an acceptable manner. ADA/NAb bioanalytical reports for studies KGAA, KGAB, KGAC, KGAD and KGAE were provided and were within the given accuracy and precision ranges.

PD biomarkers

Candidate PD biomarkers were determined in two phase 2 AD studies, one of which was a small open-label study, and two asthma studies. No validation reports for the PD biomarker bioanalytical methods were provided in the dossier. This is not pursued because the candidate PD biomarker data are not considered essential for the application.

Bioanalytical methods used in clinical study KGAK

In clinical study KGAK two bioanalytical methods for the determination of bactericidal antibody (SBA) against Neisseria meningitidis serogroup C and tetanus Toxoid IgG in human serum were utilised. SBA method was validated in terms of precision, accuracy, linearity, specificity and stability (ambient temperature and freeze/thaw) and was considered acceptable. Only high-level summary of the validation results for anti-tetanus Toxoid IgG Enzyme Immunoassay method was provided but according to the summary the validation seems to be appropriate. The bioanalytical report of clinical study KGAK regarding SBA was provided but only contained information about control performance which, however, seems to be acceptable. The Applicant committed to provide the final bioanalytical report for tetanus toxoid IgG by the end of November 2023.

Population PK analysis

The dataset included in the original population PK analysis includes only data from Induction period (up to week 16) and not from maintenance period of the phase 3 studies. The Applicant provided updated population PK analysis with data from maintenance period (from weeks 16 to 52) included; the majority of the new data were trough concentrations at steady state. The model estimates from the original and the updated datasets parameters were similar and had overlapping 95% CI.

The model development strategy was generally appropriate; the fixed allometric exponent (0.8) for clearance parameters differs slightly from the more commonly used exponent 0.75, but it is unlikely that this would significantly affect the parameter estimates and applicability of the model. Most of the THETA parameters were estimated with good precision (low standard error of estimate) but ETA shrinkage values were high (24% to 48%), probably due to sparse sampling in majority of subjects and low number of subjects with IV administration. The pcVPC plots indicated that the base model adequately described the observed data.

Only linear (dose-independent) CL was tested in model development. This is acceptable because the model adequately described the observed data and non-compartmental analyses of several studies indicated that clearance of lebrikizumab is similar over the investigated dose range.

The estimate for SC bioavailability (0.861, or 86.1%) is larger than that usually reported for mAbs (typically ~60-70%) and the interindividual variability of the estimate was high (CV% of 119). This estimate is based on little data following IV administration, which are from one study (KGBA). Supplementary information was provided upon request, including additional PK data following IV administration in patients with asthma. These data supported the initial estimate for SC bioavailability.

A total of 9 covariates were statistically significant in the SCM but not considered relevant based on the definitions pre-specified in the analysis plan (age, eGFR, and race on CL; age, age category, disease state, and sex on V2; disease state and race on ka. Forest plots and simulations (supplementary information provided upon request) supported the conclusion that age, gender, race, eGFR, and disease state (AD vs. healthy subjects) had no clinically relevant effect on exposure to lebrikizumab.

Absorption and bioavailability

Four studies (KGBA, KGAY, KGAM, and KGBG) in healthy subjects were carried out to evaluate bioavailability of lebrikizumab after SC administration and PK similarity of different formulations or devices. The general problem in these studies was that the study sampling periods were too short to optimal characterise the whole PK profile, and the PK sampling could have been more frequent around the t_{max}.

In study KGBA the PK of lebrikizumab following SC and IV administration was evaluated, and the absolute SC bioavailability was estimated. According to the clinical study report there were numerous anomalous values in lebrikizumab concentrations, which were attributed to suspected problems with the bioanalytical assay. Supplementary information was provided upon request, including sensitivity analysis for study KGBA and additional PK data following IV administration in patients with asthma. These data supported the initial estimate for SC bioavailability.

PK similarity was established between the PFS-NSD and the AI devices in study KGBG. The geometric means for the primary PK parameters (i.e., C_{max}, $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$) were slightly higher with AI than with PFS-NSD and the 90% CIs were above 1 (not including the unity in the range). The differences are not considered clinically relevant.

The KGAM study showed overall comparable total exposure (AUC) of 250 mg doses administered by 2 injections x 1 mL and a single injection of 2 mL. The geometric mean C_{max} was 11% lower following the single injection of 2 mL, suggesting that absorption is slightly more rapid following 2 separate injections. Results of study KGAM have no impact on the benefit/risk profile because both applied drug products (PFS-NSD and AI) contain 250 mg of lebrikizumab in 2 mL solution (125 mg/mL, which is administered as a single injection. This method of administration was used in the pivotal phase 3 studies.

In study KGAY, the studied histidine formulations 37.5 mg/mL by a PFS-NSD and 125 mg/mL by a needle and syringe were shown to have similar PK. Results of study KGAY have little significance because the 37.5 mg/mL formulation was terminated for development and used only in this study.

The proposed method of administration (section 4.2 of the SmPC) is SC injection into the thigh, abdomen, or upper arm. This is acceptable; results of the population PK analysis and study KGBG indicate that no clinically meaningful difference in exposure is expected between the three injection sites. This has been adequately reflected in SmPC section 5.2.

Distribution and elimination

The PK of lebrikizumab in adult and adolescent populations was characterised using population PK analysis. The estimated total volume of distribution and clearance for a 70-kg subject at steady state were 5.14 L and 0.154 L/day, respectively, and the estimated mean elimination half-life was approximately 24.5 days (SD 5.4 days). Comparable values were reported in individual clinical pharmacology studies using noncompartmental analysis. These values are similar to those reported for several mAb drug products.

Metabolism and excretion pathways, binding to plasma proteins, and distribution to erythrocytes were not investigated. This is acceptable because lebrikizumab is a large protein.

Dose proportionality and time dependencies

Formal statistical assessment of dose proportionality was not conducted in studies KGBB and KGBF, but dose normalised AUC values suggested no meaningful deviation from dose proportionality in these studies. In study KGAZ, statistical analysis to assess dose proportionality was conducted using the power model for exposure parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ adjusted for weight). In Japanese subjects, the 90% CI of the slope estimate of each parameter contained 1.0 indicating dose proportionality, whereas in Caucasian subjects the slope estimate (90% CI) was 1.39 (1.25, 1.53), 1.17 (1.01, 1.32), and 1.13 (0.97, 1.29) for weight-adjusted C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively, indicating slightly more than dose proportional increase in exposure, especially for C_{max}. In addition, sparse PK sampling data from studies KGAF and KGAG indicated dose proportionality (data shown in Clinical AR). The dose was not tested as a covariate on PK parameters in population PK analysis and time-dependent clearance was not evaluated, but linear clearance adequately described the observed data. Based on the overall data, the Applicant's conclusion of dose proportional PK is acceptable. This information has been adequately reflected in SmPC section 5.2.

PK in target population

The proposed dose regimen (induction phase: 500 mg SC at weeks 0 and 2 followed by 250 mg SC Q2W up to week 16, followed by maintenance phase 250 mg SC Q4W), was used in the pivotal phase 3 studies; a more frequent maintenance phase regimen (250 mg Q2W) was also tested in them. Using the proposed regimen, exposure to lebrikizumab is highest during the first 16 weeks and the steady state average concentration ($C_{avg,ss}$) is approximately 50% lower during the maintenance phase compared with the induction phase.

Special populations

Dedicated studies in special populations (e.g., patients with impaired renal and hepatic function) were not conducted, which is acceptable because lebrikizumab is a large protein and is not expected to undergo significant renal or hepatic elimination. Potential effects of intrinsic factors [including age, weight, gender, race, markers of renal and hepatic function, and disease state (patients with AD vs healthy subjects)] on PK parameters were tested in population PK analysis. Exposure is inversely correlated with body weight. The predicted mean steady state exposure in adolescents (12 to <18 years of age weighing ≥40 kg) with AD was approximately 20% higher compared with adults, which can be attributed to the lower body weight distribution in adolescents. The Applicant did not yet have clinical data on PK, efficacy, and safety of lebrikizumab in subjects weighing < 40 kg. The other aforementioned subject characteristics were considered not to have meaningful effect on PK in the population PK analysis. Based on the population PK analysis, dose adjustment in special populations is not warranted. These issues are reflected in sections 4.1 and 4.2 of the SmPC.

PK drug interactions

Monoclonal antibodies are not anticipated to directly impact the PK of other drugs. Published literature indicate that blockade of the IL-4α receptor (thus blocking IL-13 activity) was not associated with changes in CYP3A, CYP2C19, CYP2C9, CYP1A2, or CYP2D6 activity in patients with AD. Hence, PK drug interactions are not expected for lebrikizumab in the target population and the corresponding information in section 4.5 of the SmPC is acceptable.

Pharmacodynamics

Pharmacodynamic endpoints have limited value for the current application. Nevertheless, they do provide some limited evidence that the use of lebrikizumab can modulate the IL-13 pathway. Mainly clinical efficacy endpoints were used in the proof-of-concept and dose finding studies.

Changes in candidate biomarkers in patients with AD [serum periostin, IgE, CCL-13 (monocyte chemotactic protein-4), CCL-18 (pulmonary and activation-regulated chemokine), and peripheral blood eosinophils] were evaluated as an exploratory objective in one randomised double-blind phase 2 study (KGAG). The results indicated that treatment with lebrikizumab (plus TCS) was associated with decreased CCL-13, CCL-18, and periostin levels, and increased peripheral blood eosinophils compared with placebo (plus TCS). Serum IgE levels decreased similarly in lebrikizumab- and placebo-treated patients. No dose-response association was observed for any of the biomarkers (lebrikizumab 125 mg single dose vs. 250 mg single dose vs. 125 mg three doses Q4W). In addition, PD biomarker data including CCL-17 were evaluated in patients with asthma in two phase 3 studies (KGAN and KGAO). Overall, the results indicate that treatment with lebrikizumab was associated with decreased levels of serum periostin, CCL-13, CCL-17, CCL-18, and IgE, although the between-subject variability was very high for IgE.

During the assessment, the Applicant provided the results of a randomised, double-blind, placebo-controlled study to assess the impact of lebrikizumab on vaccine immune responses in adult patients with moderate-to-severe AD [Study J2T-MC-KGAK (KGAK)]. The vaccines used in the study were Tdap (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed; Sanofi), and MCV (Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine; GlaxoSmithKline). The results are reflected in section 4.5 of the SmPC.

An exposure-response (E-R) analysis was conducted by the Applicant. The dataset included efficacy data (observed EASI) up to Week 16 from 5 randomised, double-blind, placebo-controlled Phase 2 and Phase 3 trials: KGAF, KGAG (data up to week 12), KGAB, KGAC and KGAD. Exposure was based on individual empirical Bayesian estimates from a population PK model. Approximately 10.0% (n=131) of subjects in the dataset were adolescents (12 to <18 years of age). Because the proposed posology was investigated in the pivotal phase 3 trials, the E-R model is considered as supportive information. Model development was overall acceptable, although some details were not sufficiently presented. The E-R model was built using up to 16 weeks efficacy data (i.e., induction phase), and it was able to adequately describe the EASI response from week 0 to week 16. However, supplementary information provided during the assessment indicated that the E-R model could not accurately describe the observed clinical efficacy from week 16 to week 52 in studies KGAB and KGAC. Given the low impact of the E-R model for the marketing authorisation application these issues are not further pursued by the CHMP.

2.6.4. Conclusions on clinical pharmacology

The PK profile of lebrikizumab has been adequately characterised although it relies mostly on population PK analysis. The final proposed dosing regimen is acceptable. Appropriate information relevant for the prescribers and patients has been included in the SmPC and package leaflet.

2.6.5. Clinical efficacy

The pivotal Phase 3 studies in AD are shown in Table 13.

Table 13: Pivotal Phase 3 Studies in AD

	Study KGAB		Study KGAC		Study KGAD
N	424		427		211
Participants	Adults and adolescents[a]		Adults and adolescents[a]		Adults and adolescents[a]
Monotherapy or combination	Monotherapy		Monotherapy		Combination w/ TCS
Treatment periods	Induction (0-16W)	Maintenance (16-52W)	Induction (0-16W)	Maintenance (16-52W)	Induction (0-16W)
Treatment	• PBO Q2W • LEB 250mgQ2W[b]	• PBO Q2W • LEB 250mg Q2W[c] • LEB 250mg Q4W[c]	• PBO Q2W • LEB 250mg Q2W[b]	• PBO Q2W • LEB 250mg Q2W[c] • LEB 250mg Q4W[c]	• PBO Q2W +TCS • LEB 250mg Q2W[b] + TCS
Randomization ratio	1:2	1:2:2[d]	1:2	1:2:2[d]	1:2
Location of study	Australia, Canada, Estonia, France, Latvia, Lithuanian, Poland, Spain, South Korea, US		Bulgaria, Canada, Germany, Mexico, Singapore, Taiwan, Ukraine, US		Canada, Germany, Poland, US
Study status	Completed		Completed		Completed

Abbreviations: EASI 75 = at least 75% improvement from Baseline in Eczema Area and Severity Index score; IGA = Investigator's Global Assessment; LEB = lebrikizumab; N = number of participants included in efficacy analyses; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; TCS = topical corticosteroid; US = United States; W = week; w/ = with.

a Adults (≥18 years); Adolescents (12 to <18 years weighing ≥40 kg)

b Participants randomly assigned to lebrikizumab 250 mg Q2W at Baseline received 500-mg loading doses at Week 0 and Week 2.

c Participants who received placebo during the first 16 weeks of the study and who were rerandomized to lebrikizumab treatment, received loading doses of 500 mg at Weeks 16 and 18 if randomized to the LEB 250 mg Q2W arm, or at only Week 16 if randomized to the 250 mg Q4W arm.

d Only participants who achieved an IGA of 0 or 1 or EASI 75 at Week 16 and did not use rescue treatment before Week 16 were rerandomized at the start of the maintenance phase. All other participants were treated with LEB 250 mg Q2W during the maintenance phase.

2.6.5.1. Dose response study

The selection of doses into the pivotal Phase 3 studies was based on Phase 2b dose-ranging study KGAF. The study included patients ≥18 years with chronic AD that had been present for ≥1 year. Patients had moderate-to-severe AD, defined by EASI score ≥16, an IGA score ≥3, and ≥10% BSA of AD involvement. Patients were to have a history of inadequate response to treatment with topical medications or determination that topical treatments were medically inadvisable.

The patients participated in the study up to a maximum of approximately 36 weeks, including screening period (up to approximately 4 weeks), a treatment period (baseline through Week 16), and a follow-up period (through Week 32).

Altogether 280 patients were enrolled; 73, 80, and 75 patients to the lebrikizumab 125 mg Q4W (with 250 mg loading dose at week 0), 250 mg Q4W (with 500 mg loading dose at week 0), and 250 mg Q2W (with 500 mg loading dose at weeks 0 and 2) groups, respectively, and 52 patients to the placebo group.

All 280 randomised patients were included in the mITT population defined as all randomised patients who received at least 1 dose of study drug. The primary and key secondary endpoints are shown in Table 14.

Table 14: Primary and Key Secondary Endpoints for Study KGAF at Week 16

	PBO N = 52	LEB 125mg Q4W N = 73	LEB 250mg Q4W N = 80	LEB 250mg Q2W N = 75
Loading dose		**250mg W0**	**500mg W0**	**500mg W0 + W2**
Primary Endpoint: EASI percentage change from Baseline at Week 16				
LS Mean (LSSD)[a, b]	-41.1 (56.5)	-62.3 (37.3)	-69.2 (38.3)	-72.1 (37.2)
p-Value vs. placebo[a]		.0165	.0022	.0005
Proportion of participants with IGA 0,1 and ≥2-point reduction from Baseline to Week 16				
Participants with response (%)[b]	15.3	26.6	33.7	44.6
p-Value vs. placebo[c]		.1917	.0392	.0023
Proportion of participants with EASI 75 at Week 16				
Participants with response (%)[b]	24.3	43.3	56.1	60.6
p-Value vs. placebo[c]		.061	.0021	.0005
Proportion of participants with EASI 90 at Week 16				
Participants with response (%)[b]	11.4	26.1	36.1	44.0
p-Value vs. placebo[c]		.0800	.0062	.0006
Proportion of participants with Pruritus NRS 4-point or greater improvement from Baseline to Week 16				
Participants with response n/N (%)	6/22 (27.3)	23/55 (41.8)	27/57 (47.4)	35/50 (70.0)
p-Value vs. placebo[d]		.2371	.1067	.0008

Abbreviations: ANCOVA = analysis of covariance; EASI = Eczema Area and Severity Index; EASI 75 = 75% reduction from Baseline in EASI; EASI 90 = 90% reduction from Baseline in EASI; IGA = Investigator's Global Assessment; IGA 0,1 = IGA score of 0 or 1, with a 2-point or greater reduction from Baseline; LEB = lebrikizumab; LS = least square; LSSD = least square standard deviation; MCMC = Markov Chain Monte Carlo; N = number of participants in the analysis population; n = number of participants in the specified category; NRS = numeric rating scale; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.

[a] LS mean, SD, contrast p-values from an ANCOVA with a factor of treatment group and corresponding baseline EASI as a covariate. Values were adjusted for multiple imputation.

[b] Missing values were imputed using MCMC multiple imputation. For categorical endpoints, participants with a missing baseline value were not included in the analyses.

[c] p-Value from pairwise Cochran-Mantel-Haenszel tests. Values were adjusted for multiple imputations.

[d] p-Value from pairwise Cochran-Mantel-Haenszel tests. No imputations were made for missing data.

In terms of lebrikizumab doses in the pivotal studies, the data from the 16-week Phase 2b study KGAF supported selection of the lebrikizumab 250 mg Q2W (with the 500 mg loading doses at weeks 0 and week 2) as the induction dose (weeks 0-16) for the Phase 3 studies.

2.6.5.2. Main studies

KGAB and KGAC studies had an identical title: "a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of lebrikizumab in patients with moderate-to-severe atopic dermatitis"

KGAD was titled: "a randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of lebrikizumab when used in combination with topical corticosteroid treatment in patients with moderate-to severe atopic dermatitis"

KGAB and KGAC studies had identical design and therefore the studies are described together.

Methods

KGAB and KGAC studies

KGAB and KGAC studies were randomised, double-blind, placebo-controlled, parallel-group studies designed to confirm the safety and efficacy of lebrikizumab in adults and adolescents (12 to less than 18 years of age that weighted at least 40 kg) with moderate-to-severe AD.

Both studies had a screening period 30 to 7 days before the baseline visit (day 1) and a 16-week **induction treatment period** followed by a 36-week long-term **maintenance treatment period** up to 52 weeks of total treatment. Patients who terminated early from the study or did not enroll in the long-term extension study (KGAA), underwent a follow-up visit approximately 12 weeks after the last study drug injection.

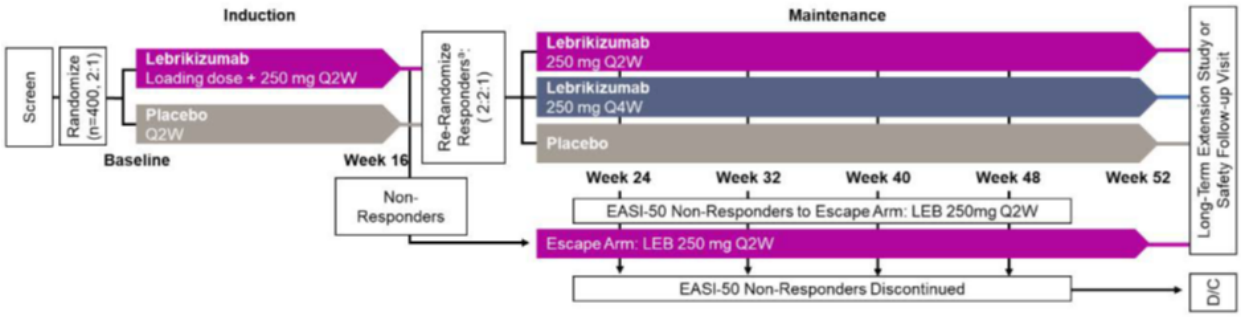
During the 16-week induction period, the patients were randomised (2:1) to receive lebrikizumab 250 mg Q2W (loading dose of 500 mg given at baseline and week 2) or placebo Q2W. Patients considered to have responded to treatment were defined as having an IGA score of 0 or 1, or at least a 75% reduction in EASI (EASI 75 from baseline to Week 16, and not receiving any rescue treatment during the induction period). After completion of the Week 16 visit, patients who responded to the lebrikizumab treatment were randomly reassigned (2:2:1) to lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W or placebo.

Patients who did not achieve an IGA of 0 or 1 nor an EASI 75 at Week 16 or who received topical or systemic rescue therapy between baseline to Week 16 were assigned to an **Escape Arm** and received open-label lebrikizumab 250 mg Q2W through Week 52. Patients who had received placebo during Induction Period initiated lebrikizumab 250 mg Q2W after loading doses.

Following re-randomisation at Week 16, patients not maintaining an EASI 50 response at Weeks 24, 32, 40, or 48 were assigned to an Escape Arm and received open-label lebrikizumab 250 mg Q2W through Week 52.

Patients who did not achieve an EASI 50 response in the Escape Arm after 8 weeks of treatment were terminated from the study.

Figure 7: Study design of KGAB and KGAC studies



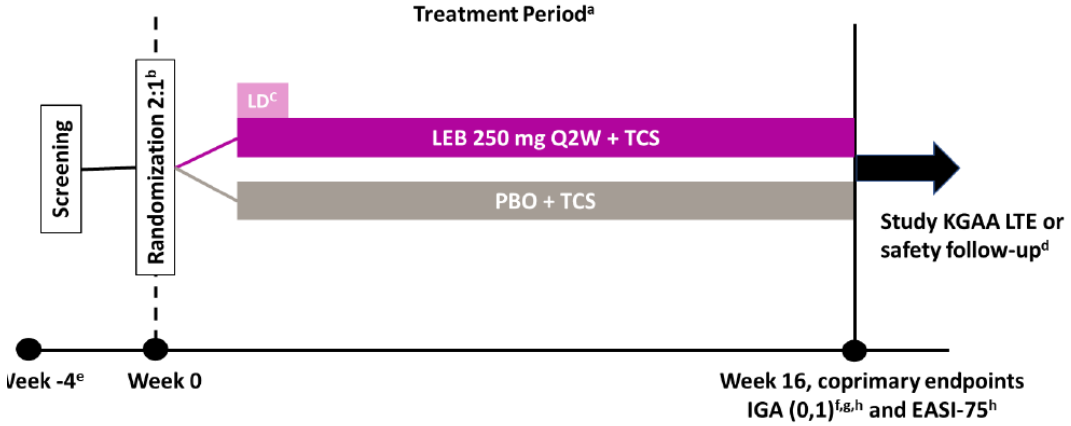
Abbreviations: D/C = discontinue; EASI = Eczema Area and Severity Index; EASI 50 = 50% reduction in EASI; LEB = lebrikizumab; n = number of participants; Q2W = every 2 weeks; Q4W = every 4 weeks.

KGAD study

KGAD study was a randomised, double blind, placebo-controlled, parallel-group study designed to evaluate the safety and efficacy of lebrikizumab + TCS compared with placebo + TCS in adults and adolescents (12 to less than 18 years of age that weighted at least 40 kg) with moderate-to-severe AD.

The study had a screening period 30 to 7 days before the baseline visit (day 1) and 16-week treatment period. After completion of the Week 16 visit, patients were offered the option to continue treatment in a separate long-term extension study (KGAA). Patients who terminated early or chose not to enter the long-term extension study, underwent a safety follow-up approximately 12 weeks after the last study drug injection.

Figure 8: Study design of KGAD study



Abbreviations: AD = atopic dermatitis; EASI= Eczema Area and Severity Index; EASI 75 = 75% reduction in EASI; IGA = Investigator's Global Assessment; LD = loading dose ; LEB = lebrikizumab; LTE = long-term extension; PBO = placebo; TCS = topical corticosteroid.

[a] Use of TCS was required at baseline but could be used, tapered, stopped, and resumed as needed after that.

[b] A total of 228 participants with moderate-to-severe AD, including 53 adolescent participants.

[c] 500 mg loading dose at W0 and W2.

[d] Participants who completed Study KGAD had the option to enroll in Study KGAA long-term extension. Otherwise, participants entered a safety follow-up period for 12 weeks after their last dose.

[e] ≤30-day screening period.

[f] IGA (0,1) with ≥2-point improvement from baseline.

[g] FDA primary endpoint.

[h] EMA co-primary endpoint.

Study Participants

KGAB and KGAC studies

The study population consisted of adult and adolescent patients with moderate-to-severe AD who had inadequate response to treatment with topical medications or for whom topical treatment was otherwise medically inadvisable.

The eligibility criteria for the KGAB and KGAC studies were identical.

Inclusion criteria

Patients were to meet all the following criteria to be eligible for the study:

1. Adults and adolescents (≥12 to <18 years of age and weighing ≥40 kg).

2. Chronic AD (according to American Academy of Dermatology Consensus Criteria) that has been present for ≥1 year before the screening visit.
3. Eczema Area and Severity Index (EASI) score ≥16 at the baseline visit.
4. Investigator Global Assessment (IGA) score ≥3 (scale of 0 to 4) at the baseline visit.
5. ≥10% body surface area (BSA) of AD involvement at the baseline visit.
6. History of inadequate response to treatment with topical medications; or determination that topical treatments are otherwise medically inadvisable.
7. Apply a stable dose of non-medicated topical moisturiser at least twice daily for ≥7 days prior to the baseline visit.
8. Completed electronic diary entries for pruritus and sleep-loss for a minimum of 4 of 7 days preceding randomisation.
9. Willing and able to comply with all clinic visits and study-related procedures and questionnaires.
10. For women of childbearing potential: agree to remain abstinent (refrain from heterosexual intercourse) or use a highly effective contraceptive method during the treatment period and for at least 18 weeks after the last dose of lebrikizumab or placebo.
11. Male patients must agree to use an effective barrier method of contraception during the study and for a minimum of 18 weeks following the last dose of study drug if sexually active with a female of child bearing potential
12. Provide signed informed consent/assent.

Exclusion criteria

Patients meeting any of the criteria below were to be excluded from the study:

1. Participation in a prior lebrikizumab clinical study.
2. History of anaphylaxis as defined by the Sampson criteria (Sampson, 2006).
3. Treatment with topical corticosteroids, calcineurin inhibitors or phosphodiesterase-4 inhibitors such as crisaborole within 1 week prior to the baseline visit.
4. Prior treatment with dupilumab or tralokinumab.
5. Treatment with any of the following agents within 4 weeks prior to the baseline visit:
    a. Immunosuppressive/immunomodulating drugs (e.g., systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.)
    b. Phototherapy and photochemotherapy (PUVA) for AD.
6. Treatment with the following prior to the baseline visit:
    a. An investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer.
    b. B Cell-depleting biologics, including rituximab, within 6 months.
    c. Other biologics within 5 half-lives (if known) or 16 weeks, whichever is longer.
7. Use of prescription moisturisers within 7 days of the baseline visit.

8. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit.

9. Treatment with a live (attenuated) vaccine within 12 weeks of the baseline visit or planned during the study.

10. Uncontrolled chronic disease that might require bursts of oral corticosteroids, e.g., comorbid severe uncontrolled asthma (defined by an ACQ-5 score ≥1.5 or a history of ≥2 asthma exacerbations within the last 12 months requiring systemic [oral and/or parenteral] corticosteroid treatment or hospitalisation for > 24 hours).

11. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit.

    NOTE: patients may be rescreened after infection resolves.

12. Evidence of active acute or chronic hepatitis (as defined by the Department of Health & Human Services Centers for Disease Control and Prevention) or known liver cirrhosis.

13. Diagnosed active endoparasitic infections or at high risk of these infections.

14. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g., tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, and aspergillosis) despite infection resolution: or unusually frequent, recurrent, or prolonged infections, per the Investigator's judgment.

15. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening.

16. In the Investigator's opinion, any clinically significant laboratory results from the chemistry, haematology or urinalysis tests obtained at the screening visit.

17. Presence of skin comorbidities that may interfere with study assessments.

18. History of malignancy, including mycosis fungoides, within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.

19. Severe concomitant illness(es) that in the Investigator's judgment would adversely affect the patient's participation in the study. Any other medical or psychological condition that in the opinion of the Investigator may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient because of his/her participation in this clinical trial, may make patient's participation unreliable, or may interfere with study assessments.

20. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study.

KGAD study

The eligibility criteria for the KGAD study were identical to the criteria in the KGAB and KGAC studies (see above), except for the following:

- Concerning the inclusion criteria "History of inadequate response to treatment with topical medications; or determination that topical treatments are otherwise medically inadvisable", the wording "or determination that topical treatments are otherwise medically inadvisable" was removed, as TCS use was required in the study (per Amendment 1, dated 13 May 2020).

- Whereas patients with prior treatment with dupilumab or tralokinumab were excluded from the KGAB and KGAC studies (exclusion criteria no. 4), patients with prior dupilumab treatment could enroll into the KGAD study after appropriate washout (patients with prior treatment with dupilumab within 8 weeks were to be excluded).
- Patients that had had an important side effect to TCS (e.g., intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and systemic effects), as assessed by the investigator or treating physician that would prevent further use, were to be excluded, as TCS was required in the study (criterion added per Amendment 1, dated 13 May 2020).

Treatments

In each of the pivotal studies (KGAB, KGAC and KGAD), the study drug (lebrikizumab and placebo) was supplied as a sterile prefilled syringe with a preassembled needle safety device. Each prefilled syringe was intended for a single 2-mL dose (250 mg) administered subcutaneously.

KGAB and KGAC studies

The treatment schemes in the KGAB and KGAC studies were identical.

Induction period

During the 16-week induction period, the patients received lebrikizumab 250 mg Q2W (loading dose of 500 mg given at baseline and week 2) or placebo Q2W. All study drug injections were administered in the clinic.

Use of rescue therapy in the Induction Period

Use of topical or systemic treatments for AD was prohibited during the induction period, unless used as a rescue therapy. Patients who experienced intolerable AD symptoms and required rescue treatment could be started on topical treatments, such as TCS, and still continue study drug, but were then assigned to the **Escape Arm** at Week 16. If patients required systemic rescue treatments, such as oral corticosteroids, phototherapy, and cyclosporine, study drug was discontinued, though patients could enter the escape arm after a washout period equal to 5 or more half-lives of the medication.

Maintenance Period

During the 36-week maintenance period, the patients were assigned to either **maintenance blinded period** or **maintenance escape period** based on their response to treatment during the induction period. Because treatments were administered between visits as well as at visits, patients were trained and instructed to self-administer study drug at home.

Maintenance Blinded Period

After completion of the Week-16 visit, patients who completed the induction period and achieved an IGA 0,1 or EASI 75 response, without the use of rescue therapy, entered the maintenance blinded period and received lebrikizumab 250 mg Q2W, lebrikizumab 250 mg Q4W or placebo. Responders who received placebo during the first 16 weeks of study and who were randomised to lebrikizumab arms, received a loading dose of lebrikizumab of either 500 mg at week 16 or 500 mg given at week 16 and 18 based on the active treatment group assigned in the maintenance period.

Maintenance Escape Period

The maintenance escape period included patients who achieved neither IGA 0,1 nor EASI 75 at Week 16, received topical or systemic rescue therapy from baseline to week 16, or did not maintain an EASI 50 response at Week 24, 32, 40, or 48 following rerandomisation to the maintenance blinded period.

All patients received open-label lebrikizumab 250 mg Q2W through week 52.

Patients in the Escape Arm received blinded loading doses based on their prior treatment assignment:

- Patients assigned to the lebrikizumab treatment group in the Induction Period who then entered the Escape Arm received 2 injections at Week 16 and Week 18, i.e. 1 lebrikizumab injection (250 mg) and 1 placebo injection.
- Patients assigned to the placebo treatment group in the Induction Period who then entered the Escape Arm received 2 lebrikizumab injections (500 mg) at Week 16 and Week 18
- Patients who did not achieve an EASI 50 response after 8 weeks of treatment were terminated from the study.

Use of rescue therapy in the Maintenance Period

Intermittent use of topical rescue medications for AD was permitted. Patients who required short-term systemic treatment for symptoms of AD were assessed on a case-by-case basis and discussed with the medical monitor prior to initiating treatment.

Topical moisturiser

All patients were to use nonmedicated topical moisturiser daily during the 7 days preceding randomisation and throughout the study.

KGAD study

Treatment period

During the 16-week treatment period, the patients received lebrikizumab 250 mg Q2W (loading dose of 500 mg given at baseline and week 2) + TCS or placebo Q2W + TCS.

Concomitant topical treatment

All patients were instructed to use TCS for AD symptoms starting at the Baseline visit (Day 1). Patients were provided with a mid-potency TCS (triamcinolone acetonide 0.1% cream) and a low potency TCS (hydrocortisone 1% cream) for use on sensitive skin areas. Patients were allowed to taper or stop TCS use as needed. If AD lesions returned or a patient experienced AD exacerbation, TCS treatment could be resumed at the patient's discretion. Low potency TCI use was permitted for use on sensitive areas only, but they were not supplied by the study site. All use of TCS and TCI was recorded daily by the patient using an electronic diary.

Rescue treatment

Add-on rescue therapies were permitted when a patient experienced clinical worsening of symptoms that were intolerable, including high potency TCS or systemic treatments, such as oral corticosteroids, phototherapy, and cyclosporin. Study drug was discontinued for patients receiving systemic rescue treatment, but patients were still required to attend all study visits and be assessed for safety and efficacy according to the schedule of events, even when rescue medication was initiated.

Topical moisturiser

All patients were to use nonmedicated topical moisturiser daily during the 7 days preceding randomisation. Nonmedicated moisturisers were to be used during the study. The patient could continue her/his current over-the-counter moisturiser regimen, if approved by the Investigator.

Objectives

KGAB and KGAC studies

KGAB and KGAC were identical studies in design, with the objective to evaluate the safety and efficacy of lebrikizumab compared with placebo in patients with moderate-to-severe AD.

KGAD study

The objective of the KGAD study was to evaluate the safety and efficacy of lebrikizumab in combination with TCS compared with placebo in patients with moderate-to-severe AD.

Outcomes/endpoints

KGAB and KGAC studies

Primary endpoint

Co-primary endpoint:

- Percentage of patients with an IGA score of 0 or 1 and a reduction ≥2 points from baseline to Week 16.
- Percentage of patients achieving EASI-75 (≥75% reduction from Baseline in EASI score) at Week 16

Key secondary endpoints specific for induction period

- Percentage of patients achieving EASI-90 at Week 16
- Percentage of patients achieving EASI-90 at Week 4
- Percentage change in EASI score from Baseline to Week 16
- Percentage change in Pruritus NRS score from Baseline to Week 16
- Percentage of patients with a Pruritus NRS of ≥4-points at Baseline who achieve a ≥4-point reduction from Baseline to Week 16
- Percentage of patients with a Pruritus NRS of ≥4-points at Baseline who achieve a ≥4-point reduction from Baseline to Week 4
- Percentage of patients with a Pruritus NRS of ≥4-points at Baseline who achieve a ≥4-point reduction from Baseline to Week 2
- Change from baseline in DLQI total score at Week 16
- Percentage of patients with a DLQI total score of ≥4-points at Baseline who achieve a ≥4-point improvement from baseline to Week 16
- Change from Baseline in Sleep-loss score at Week 16
- Percentage of patients with a Sleep-loss score ≥2 points at Baseline who achieve a ≥2 points reduction from Baseline at Week 16

Key secondary endpoints specific for maintenance period

- Percentage of patients from those re-randomised having achieved EASI-75 at Week 16 who continue to exhibit EASI-75 at Week 52 (EASI-75 calculated relative to baseline EASI score)
- Percentage of patients from those re-randomised having achieved IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 16 who continue to exhibit an IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 52
- Percentage of patients from those with a Pruritus NRS of ≥4-points at baseline re-randomised having achieved ≥4-point reduction from baseline at Week 16 who continue to exhibit ≥4-point reduction from baseline at Week 52

- Percentage change in EASI score from Baseline at Week 52 in the subset of patients who were re-randomised at Week 16

KGAD study

Primary endpoint

Co-primary endpoint was identical to the KGAB and KGAC studies:

- Percentage of patients with an IGA score of 0 or 1 and a reduction ≥2 points from baseline to Week 16.
- Percentage of patients achieving EASI-75 (≥75% reduction from Baseline in EASI score) at Week 16

Key secondary endpoints

- Percentage of patients achieving EASI-90 at Week 16
- Percentage change in Pruritus NRS score from Baseline to Week 16
- Percentage of patients with a Pruritus NRS of ≥4-points at Baseline who achieve a ≥4-point reduction from Baseline to Week 16
- Percentage change in EASI score from Baseline to Week 16
- Change from baseline in DLQI at Week 16
- Percentage of patients with a DLQI total score of ≥4-points at baseline who achieve ≥4-point improvement in DLQI from baseline to Week 16
- Change from Baseline in Sleep-loss score at Week 16
- Percentage of patients with a Pruritus NRS score of ≥4 points at Baseline who achieve both EASI-75 and a ≥4-point reduction in NRS score from Baseline at Week 16

Sample size

KGAB and KGAC studies

In the Phase 2b dose-range finding study (KGAF), the proportion of patients who achieved an IGA score of 0 or 1 at Week 16 using the rescue medication non-response sensitivity analysis was approximately 34.7% for lebrikizumab 250 mg Q2W versus 7.7% for placebo, and the proportion of patients who achieved an EASI-75 at Week 16 using the rescue medication non-response sensitivity analysis was approximately 48.0% for lebrikizumab 250 mg Q2W versus 11.5% for placebo. A sample size of 96 for lebrikizumab 250 mg Q2W versus 48 for placebo had more than 95% power to detect a statistically significant difference based on a two-group continuity corrected chi-square test with a two-sided significance level of 0.05 for each of the co-primary endpoints, which imply and overall power of at least 90%. However, to ensure sufficient safety information was collected and to ensure sufficient responders for the Maintenance Period, the sample size was increased to 400 in total with a randomisation ratio of 2:1 lebrikizumab:placebo.

KGAD study

Approximately 225 patients were to be randomised at a 2:1 ratio to lebrikizumab or placebo (150 patients:75 patients). The assumed IGA score of 0 or 1 at Week 16 response rates were 38% for lebrikizumab 250 mg Q2W and 13% for placebo. The assumed EASI 75 response rate at Week 16 response rates were 58% for lebrikizumab 250 mg Q2W and 20% for placebo. The assumptions for lebrikizumab were based on the dose-range finding Phase 2b study (KGAF), the proportion of patients

who achieved an IGA score of 0 or 1 and proportion of patients who achieved EASI75 response at Week 16 using the rescue medication non-response sensitivity analysis, adjusting for the allowed use of TCS/TCI. The placebo response rates were based on the review of historical TCS clinical studies in atopic dermatitis. This study had power >95% for testing superiority of lebrikizumab to placebo based on a two-sided Fisher's exact test with alpha of 0.05.

Randomisation and blinding (masking)

KGAB, KGAC and KGAD studies

All patients were randomly allocated to receive the study treatment using an electronic data capture (EDC) system at the Baseline visit. The allocation to treatment was prospectively stratified by geographic region (US versus EU versus rest of world), age (adolescent patients 12 to <18 years versus adults ≥18 years) and disease severity (IGA 3 versus 4). At the Baseline visit (Day 1), once a patient was considered eligible to participate in the study, demographic and stratification information was entered into the EDC system to receive a medication number assigning a kit to a patient.

During the Maintenance Period in KGAB and KGAC studies, the EDC was used to re-randomise a patient to a maintenance treatment based on the IGA or EASI score at Week 16 and rescue therapy usage during induction period.

The Sponsor or designee, the Investigator, study-site personnel, and the patient were blinded to treatment assignment. The integrity of the clinical study was to be maintained by observing the treatment blind. If knowledge of a patient's treatment assignment was required for the patient's clinical care and/or safety, the Investigator consulted with the Sponsor's medical monitor prior to breaking the blind.

Placebo solution was identical in appearance and content to the active solution except for lebrikizumab. All study drug (lebrikizumab and placebo) were supplied as a sterile PFS-NSD. Each pre-filled syringe was used to deliver a single 2-mL dose (250 mg) administered subcutaneously.

Appropriate combination of active and placebo injections was given to maintain blinding.

Statistical methods

Induction Treatment Periods in Studies KGAB, KGAC, and KGAD

Primary and supportive estimands for Induction Periods

Three types of prespecified estimands were used to address different clinical questions of interest and ICEs for the Induction Period. Two types of ICEs were considered for the Induction Period, including initiation of rescue medication, as defined for the individual study, and permanent treatment discontinuation. All estimands of the Induction Period were defined for the patient population as defined by the protocol inclusion or exclusion criteria. The primary estimand was a hybrid estimand combining composite strategy and hypothetical strategy to handle ICEs depending on their causes. The primary estimand was used for all primary and key secondary endpoints. Two supportive estimands were also used, 1 for all categorical endpoints and 1 for all continuous endpoints (Table 15).

As per the SAPs, the primary estimand is a hybrid estimand representing the primary clinical question of interest: "What is the difference between treatment conditions, i.e., Lebrikizumab vs Placebo, in the target patient population, in successful responses or means after 16 weeks achieved without use of rescue medication and if all patients continued with treatment except those who discontinued due to lack of efficacy?"

For the primary and key secondary analyses conducted relative to the primary estimand, patients who received topical rescue medications (any TCS, TCI, or crisaborole for Study KGAB and Study KGAC patients or only high-potency TCS for Study KGAD patients) or systemic rescue therapies or discontinued treatment due to lack of efficacy had values set to their baseline value subsequent to this time through Week 16 which, when dichotomised, implies non-response; data after treatment discontinuation due to any other reasons were treated as missing, and all the missing data were imputed with the MCMC-MI method. The MCMC-MI method takes into account each patient's own data trajectory and leverages information from other patients within the same treatment (including the afore-mentioned imputed data according patients' baseline values) to impute plausible values for the missing data: Twenty-five imputations were conducted within each treatment group independently so the pattern of missing observations in one treatment group cannot influence missing value imputation in another. IGA scores were rounded to (0, 1, 2, 3, or 4) from the continuous values generated by the MCMC algorithm after which IGA (0,1) response derived based on the rounded values. For derivation of an EASI-75 and EASI-90 response, no rounding will be performed.

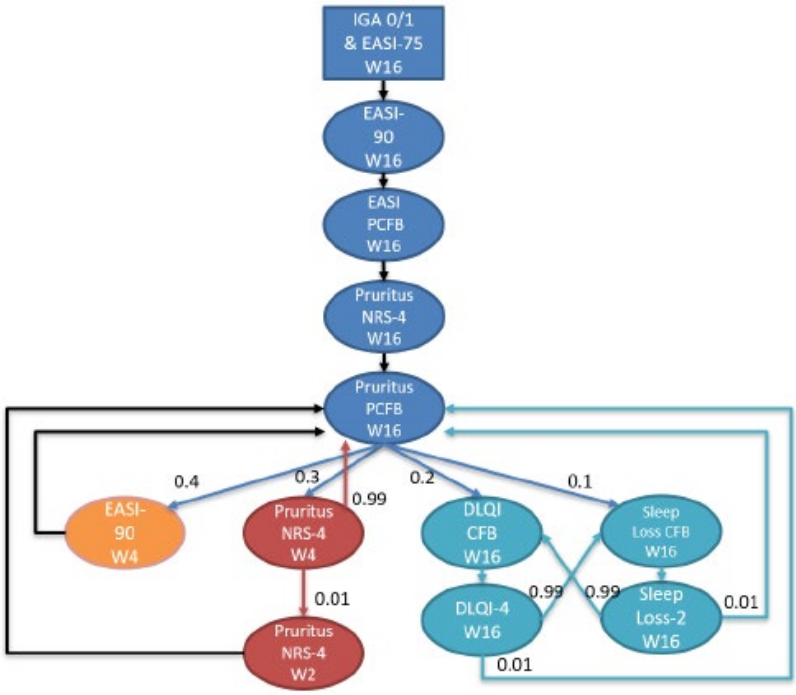
Table 15: Description of Primary and Supportive Estimands

Estimand	Analysis Strategy for Intercurrent Events				Missing Data Imputation Method
	ICE: Used Rescue Medication	ICE: Treatment Discontinuation			
		Due to Lack of Efficacy	Due to Adverse Event	Due to Any Other Reasons	
Primary estimand (hybrid)	Composite: Set to baseline	Composite: Set to baseline	Hypothetical: Set to missing	Hypothetical: Set to missing	Primary analysis: MCMC-MI Sensitivity analysis: Tipping point analysis
Supportive estimand for categorical endpoints (composite)	Composite: Set to nonresponder	Composite: Set to nonresponder	Composite: Set to nonresponder	Composite: Set to nonresponder	NRI
Supportive estimand for continuous endpoints (hypothetical)	Hypothetical: Set to missing	Hypothetical: Set to missing	Hypothetical: Set to missing	Hypothetical: Set to missing	MMRM, LOCF
Additional FDA-requested estimand (hybrid)	Composite: Set to baseline	Composite: Set to baseline	Composite: Set to baseline	Treatment policy: Observed	MCMC-MI

Abbreviations: ICE = intercurrent event; LOCF = last observation carried forward; MCMC-MI = Markov Chain Monte Carlo multiple imputation; MMRM = mixed model repeated measures; NRI = nonresponder imputation.

In D120 LoQ, a set of supplementary analyses was requested in accordance with ITT principle, i.e., treatment policy estimand for which observed data are used regardless of any intercurrent events. Any data that remained missing was imputed using MCMC-MI even if the Applicant was requested to use imputation strategy that considers what is known about the subjects' status with respect to these intercurrent events. The results of these supplementary analyses are presented for the co-primary endpoints and also for DLQI because of the considerable impact of the analysis strategy on the results. For the pivotal Phase 3 studies, a prespecified graphical multiple testing approach was implemented to control the overall Type I error rate at 2-sided alpha of 0.05 for all primary and key secondary endpoints in the 16-week treatment periods. The primary and key secondary endpoints for the pivotal Phase 3 studies differed between US and EU based on regulator requests. The graphical testing scheme used for Study KGAB and Study KGAC for EMA is provided in Figure 9. The graphical testing scheme for Study KGAD FOR EMA is provided in Figure 10.

Figure 9: Graphical approach to control type 1 error for induction period in studies KGAB and KGAC



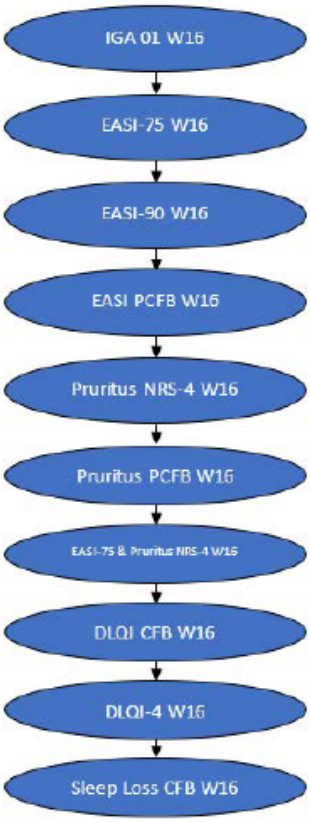
The CSR's report observed results excluding data collected after rescue medication or treatment discontinuation. In addition, in line with the estimand definitions (Table 15), for dichotomised endpoints, response rates and, for quantitative endpoints, LS means were presented following data handling/imputation rules as specified below. Treatment effect estimates were, for dichotomised endpoints, based on stratified difference in the proportion of responders and, for quantitative endpoints, based on an ANCOVA model as further specified below.

Analysis models

For the dichotomised endpoints, Cochran-Mantel-Haenszel (CMH) test was used for testing the null hypothesis of no treatment effect, stratified by randomisation strata: geographic region (US versus EU versus rest of world), age (adolescent patients 12 to <18 versus adults >=18 years) and disease severity (IGA 3 versus 4). The difference in the proportion of responders was also estimated with stratification by the randomisation strata. The confidence intervals were calculated using Mantel-Haenszel-Sato method. [NB: In the study reports, the above-mentioned stratified analyses are referred to as CMH test and common risk difference "adjusted" by geographic region (US versus EU versus rest of world), age (adolescent versus adult), and disease severity (IGA 3 versus 4).]

For the quantitative endpoints, an ANCOVA model was applied including treatment, geographic region (US vs EU vs rest of the world), age group (adolescent patients 12 to <18 versus adults >=18 years) and baseline IGA score (3,4) as fixed factors and baseline value as covariate. The analysis results were combined across all multiply imputed datasets using SAS procedure MIANALYZE. In response to D120 LoQ, the Applicant clarified that for estimation of treatment-arm specific LS means, the default covariate weights of the respective SAS procedure were used. These imply a target population where a third of patients are from each region, half are adolescents and half have IGA of 3.

Figure 10: Study KGAD graphical testing scheme



Abbreviations: CFB = change from Baseline; DLQI = Dermatology Life Quality Index; DLQI-4 = 4-point or greater improvement from Baseline in DLQI among participants with baseline score of 4 or more; EASI = Eczema Area and Severity Index; EASI 90 = 90% improvement from Baseline in EASI; IGA = Investigator's Global Assessment; IGA 0,1 = IGA score of 0 or 1, with a 2-point or greater reduction from Baseline; NRS = numeric rating scale; PCFB = percentage change from Baseline; Pruritus NRS-4 = 4-point or greater improvement from Baseline in Pruritus NRS among participants with baseline score of 4 or more; W = week.

Maintenance Periods in Study KGAB and Study KGAC

Primary and supportive estimands for Maintenance Periods

Four types of estimands were used to address different clinical questions of interest and ICEs for the Maintenance Period. These four estimands were defined for the Maintenance Populations in the Maintenance Blinded Period (Table 16).

The maintenance primary estimand was used for all key secondary endpoints for the Maintenance Period. Three secondary maintenance estimands were also used:

- a hybrid estimand for all key and other secondary endpoints
- a composite estimand for all key and other secondary categorical endpoints, and
- a hypothetical estimand for all key and other secondary continuous endpoints

Three types of ICEs were used to estimate the treatment effects for Maintenance Period, including

- initiation of rescue medication
- permanent treatment discontinuation, and
- transfer to escape arm.

For the Maintenance Week 16 Escape Population, results were reported for efficacy analyses performed using observed values at each time point, with no imputation for missing values. In addition, a hybrid estimand considering permanent treatment discontinuation as the only ICE is also reported as a supportive analysis.

Table 16: Analysis of Primary and Supportive Estimands for Maintenance Period of Study KGAB and Study KGAC

Maintenance Estimand	Analysis Strategy for Intercurrent Events					Missing Data Imputation Method
	ICE: Rescue Medication		ICE: Treatment Discontinuation		ICE: Transfer to Escape Arm	
	Topical Rescue Medication	Systemic Rescue Medication	Due to Lack of Efficacy	Due to Any Other Reasons		
Maintenance primary estimand (hybrid)	Hypothetical: Set to missing	Composite: Set to baseline	Composite: Set to baseline	Hypothetical: Set to missing	Composite: Set to baseline	MCMC-MI
Maintenance supportive estimand (hybrid)	Treatment policy: As observed	Composite: Set to baseline	Composite: Set to baseline	Hypothetical: Set to missing	Composite: Set to baseline	MCMC-MI
Maintenance supportive estimand for categorical endpoints (composite)	Composite: Set to nonresponder	Composite: Set to nonresponder	Composite: Set to nonresponder	Composite: Set to nonresponder	Composite: Set to nonresponder	NRI
Maintenance supportive estimand for continuous endpoints (hypothetical)	Hypothetical: Set to missing	Hypothetical: Set to missing	Hypothetical: Set to missing	Hypothetical: Set to missing	Hypothetical: Set to missing	LOCF

Abbreviations: ICE = intercurrent event; LOCF = last observation carried forward; MCMC-MI = Markov Chain Monte Carlo multiple imputation; MMRM = mixed model repeated measures; NRI = nonresponder imputation.

Multiplicity control for Maintenance Period

For the Maintenance Period of Study KGAB and Study KGAC, a multiplicity testing scheme was implemented which used alpha control with a family-wise error rate at 0.05. The hierarchical testing scheme is provided in Table 16.

Table 17: Hierarchy for Key Secondary Endpoints at Week 52

Lebrikizumab 250mg Q2W Maintenance Therapy
Percentage of patients from those rerandomized to Q2W maintenance therapy having achieved EASI 75 at Week 16 who continue to exhibit EASI 75 at Week 52 (EASI 75 calculated relative to Baseline EASI).
Percentage of patients from those rerandomized to Q2W maintenance therapy having achieved IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 16 who continue to exhibit an IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 52.
Percentage of patients from those with a Pruritus NRS of ≥4 points at Baseline and rerandomized to Q2W maintenance therapy having achieved ≥4-point reduction from Baseline at Week 16 who continue to report ≥4-point reduction from Baseline at Week 52.
Lebrikizumab 250mg Q4W Maintenance Therapy
Percentage of patients from those rerandomized to Q4W maintenance therapy having achieved EASI 75 at Week 16 who continue to exhibit EASI 75 at Week 52 (EASI 75 calculated relative to Baseline EASI).
Percentage of patients from those rerandomized to Q4W maintenance therapy having achieved IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 16 who continue to exhibit an IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 52.
Percentage of patients from those with a Pruritus NRS of ≥4 points at Baseline and rerandomized to Q4W maintenance therapy having achieved ≥4-point reduction from Baseline at Week 16 who continue to report ≥4-point reduction from Baseline at Week 52.
Lebrikizumab 250mg Q2W Maintenance Therapy
Percentage change in EASI from Baseline at Week 52 for those patients rerandomized to Q2W maintenance therapy at Week 16.
Lebrikizumab 250mg Q4W Maintenance Therapy
Percentage change in EASI from Baseline at Week 52 for those patients rerandomized to Q4W maintenance therapy at Week 16.

Abbreviations: EASI = Eczema Area and Severity Index; EASI 75 = 75% improvement from Baseline in EASI; IGA = Investigator's Global Assessment; IGA 0,1 = IGA score of 0 or 1, with a 2-point or greater reduction from Baseline; NRS = numeric rating scale; Q2W = every 2 weeks; Q4W = every 4 weeks.

Use of Study KGAB and Study KGAC Pooled Data

Data from Study KGAB and Study KGAC were pooled where applicable. This pooled analysis set was prespecified in the integrated efficacy analysis plan. Study KGAB and Study KGAC had identical study designs, which enabled the creation of these pooled populations.

Subgroup analyses

Subpopulation analyses were performed to examine how patient baseline demographic, disease characteristics, or treatment history affects response to treatment with lebrikizumab. All subgroup analyses were performed on data pooled from Study KGAB and Study KGAC.

Induction Period

Subgroup analyses for the Induction Period were conducted using the Pooled Induction set, which is the combination of patients from Study KGAB and Study KGAC. Subgroup analyses were conducted relative to primary estimand (hybrid), comparing the lebrikizumab 250 mg Q2W treatment group to placebo.

Effect modification by subgroups on odds ratio scale was evaluated using logistic regression including a treatment by subgroup interaction term. Treatment group differences in responder rates were evaluated within each subgroup using the Cochran-Mantel-Haenszel (CMH) test stratified by study (KGAB, KGAC; but not by randomisation strata within study) regardless of whether the interaction was statistically significant.

Maintenance Period

Subgroup analyses for the Maintenance Period were conducted in the Pooled Maintenance Primary Set, which is the combination of patients from Study KGAB and Study KGAC. Subgroup analyses were

conducted relative to maintenance primary estimand (hybrid), comparing the treatment group re-randomised to lebrikizumab 250 mg Q4W to those re-randomised to placebo (lebrikizumab withdrawal) and the treatment group re-randomised to lebrikizumab 250 mg Q2W to those re-randomised to placebo (lebrikizumab withdrawal).

Analyses for Efficacy Outcomes for Study KGAD Patients in Study KGAA

Descriptive statistics were used to summarise the efficacy results from Study KGAA. The efficacy analyses were conducted relative to the primary estimand as defined in the study. No statistical tests were performed.

Primary and supportive estimands of efficacy objectives

Three types of estimands were used to handle missing data in analyses of Study KGAA. The primary estimand was used for all efficacy endpoints. Two supportive estimands were also used for all efficacy endpoints. Table 18 summarises the primary and supportive estimands used in the Study KGAA analyses.

Treatment discontinuation, whether due to lack of efficacy or any other reason, was the only intercurrent event considered in the estimation of the treatment effect in Study KGAA.

Table 18: Estimands Used in Analyses of Efficacy Endpoints for Study KGAD Patients in Study KGAA

Estimand	ICE: Treatment Discontinuation		Missing Data Imputation Method
	Due to Lack of Efficacy	Due to Any Other Reasons	
Primary	Composite: Set to baseline	Hypothetical: Set to missing	MCMC-MI
Supportive	As observed	As observed	As observed analysis
Supportive	Hypothetical: Set to missing	Hypothetical: Set to missing	LOCF

Abbreviations: ICE = intercurrent event; LOCF = last observation carry forward; MCMC-MI = Markov Chain Monte Carlo multiple imputation.

Results

Participant flow

Induction period (0 to 16 weeks)

KGAB: A total of 536 patients entered the study, and 424 patients were randomly assigned to a treatment group. A total of 383 patients completed the Week 16 Induction Period, including 85.1% of patients receiving placebo and 92.9% of patients in the lebrikizumab treatment group.

KGAC: A total of 606 patients entered the study, and 445 patients were randomly assigned to a treatment group. Following findings of a site audit, data from all 18 patients at a specific site were excluded, creating an mITT Population of 427 patients. A total of 389 patients completed the Week 16 Induction Period, including 89% of patients receiving placebo and 92.2% of patients in the lebrikizumab treatment group.

KGAD: A total of 312 patients entered the study. A total of 228 patients were randomly assigned to a treatment group. Following findings of a site audit, data from all 17 patients at a specific site were excluded, creating a mITT population of 211. A total of 192 patients completed the 16 Week study, including 87.9% in placebo + TCS group and 92.4% in the lebrikizumab treatment group (Table 19).

Table 19: Treatment Disposition for Induction Period

	Study KGAB N = 424		Study KGAC N = 427		Study KGAD N = 211	
Treatment Disposition, n (%)	**PBO**	**LEB 250mg Q2W**	**PBO**	**LEB 250mg Q2W**	**PBO + TCS**	**LEB 250mg Q2W + TCS**
	N = 141	**N = 283**	**N = 146**	**N = 281**	**N = 66**	**N = 145**
Completed W16	120 (85.1)	263 (92.9)	130 (89.0)	259 (92.2)	58 (87.9)	134 (92.4)
Rerandomized to Maintenance Population[a]	24 (17.0)	157 (55.5)	22 (15.1)	134 (47.7)	NA	NA
Enrolled in Escape Arm at Week 16[b]	96 (68.1)	106 (37.5)	108 (74.0)	125 (44.5)	NA	NA
Discontinued prior to W16	21 (14.9)	20 (7.1)	16 (11.0)	22 (7.8)	8 (12.1)	11 (7.6)
Reason for discontinuation prior to W16						
Adverse event	1 (0.7)	2 (0.7)	4 (2.7)	6 (2.1)	0 (0.0)	3 (2.1)
Due to epidemic/pandemic	1 (0.7)	2 (0.7)	1 (0.7)	4 (1.4)	1 (1.5)	1 (0.7)
Lack of efficacy	7 (5.0)	2 (0.7)	4 (2.7)	1 (0.4)	1 (1.5)	3 (2.1)
Lost to follow-up	1 (0.7)	4 (1.4)	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)
Protocol deviation	5 (3.5)	6 (2.1)	0 (0.0)	6 (2.1)	2 (3.0)	2 (1.4)
Withdrawal by participant	6 (4.3)	3 (1.1)	5 (3.4)	4 (1.4)	3 (4.5)	2 (1.4)

Abbreviations: CSR = clinical study report; LEB = lebrikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroids; W16 = Week 16.

[a] Seven participants in Study KGAB and 3 participants in Study KGAC were erroneously rerandomized at Week 16.

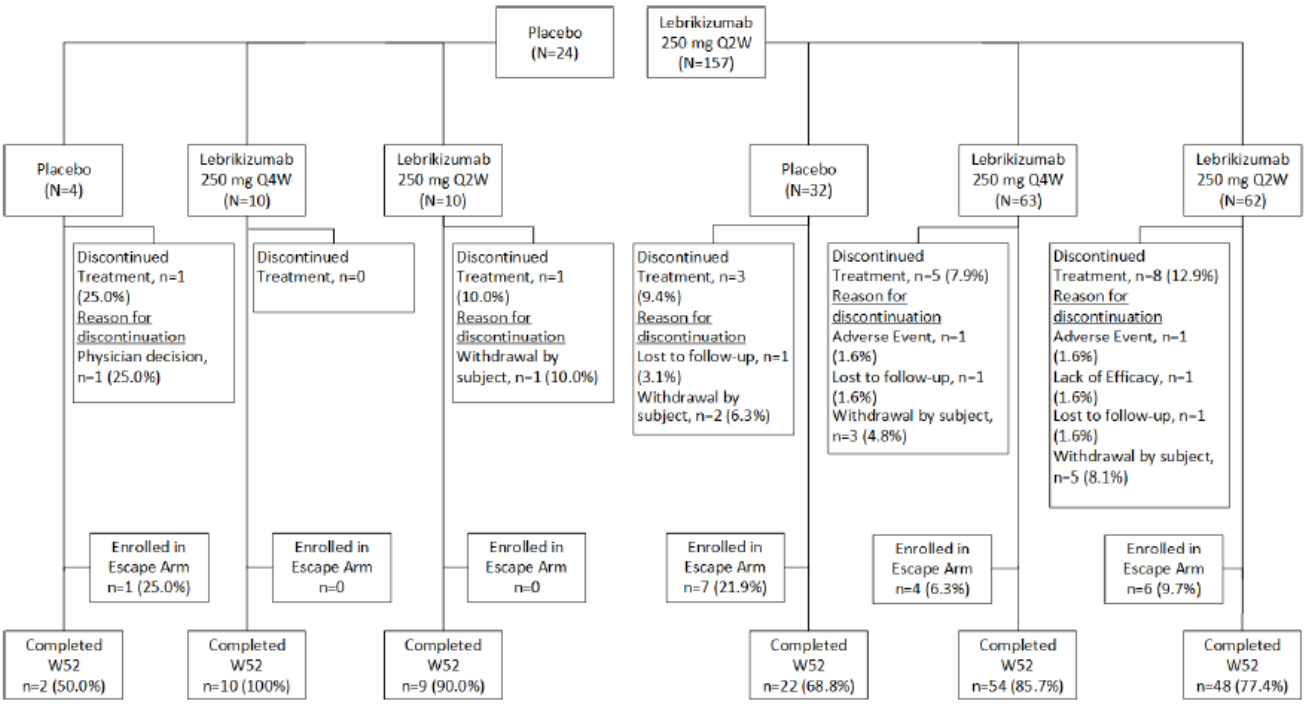
[b] Six participants in Study KGAB and 14 participants in Study KGAC were erroneously assigned to the Escape Arm at Week 16.

Maintenance blinded Period (16 to 52 weeks)

KGAB: Of the lebrikizumab-treated and placebo-treated patients from the Induction Period, 181 (42.7%) entered the Maintenance Blinded Period as induction responders. Of these patients randomly reassigned at Week 16, 87.5% from the Induction placebo group (21 of 24 patients), and 79.0% from the Induction lebrikizumab group (124 of 157 patients) completed treatment at Week 52 (Figure 11).

KGAC: Of the lebrikizumab-treated and placebo-treated patients from the Induction Period, 156 patients (36.5%) entered the Maintenance Blinded Period as induction responders. Of these patients randomly reassigned at Week 16, 86.4% from the induction placebo group (19 of 22 patients), and 85.1% from the induction lebrikizumab group (114 of 134 patients) completed treatment at Week 52 (Figure 12).

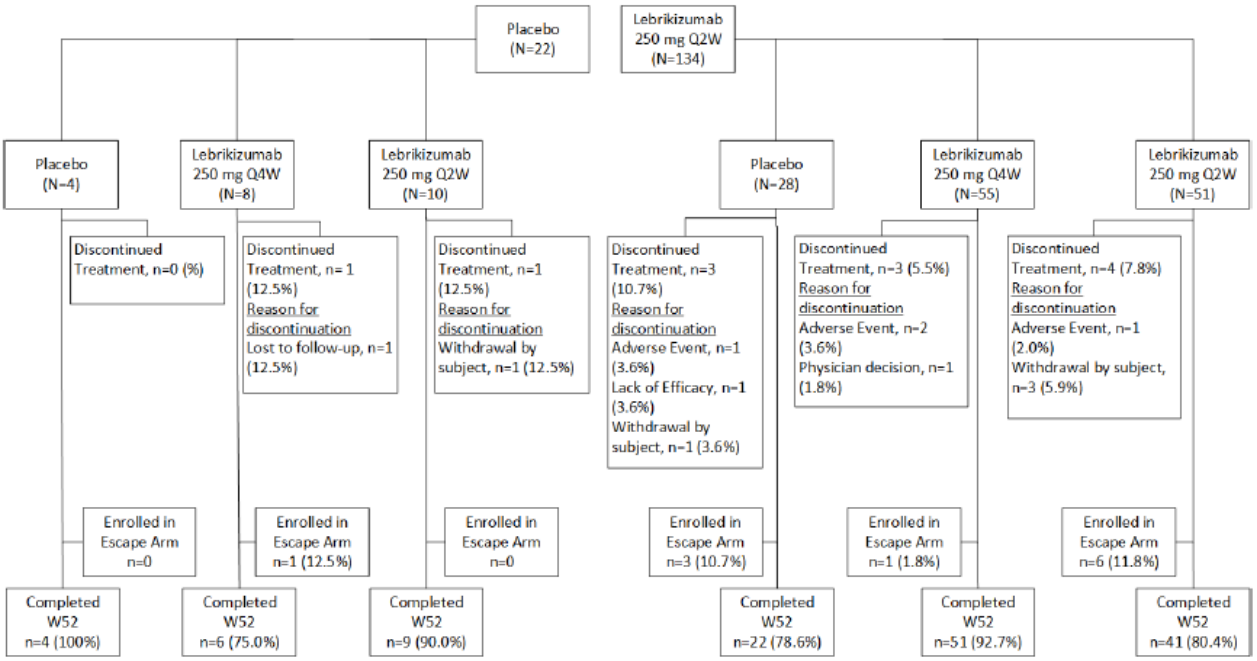
Figure 11: Disposition during the maintenance blinded period (KGAB)



Abbreviations: N = number of participants in the group; n = number of participants in the subgroup; Q2W = every 2 weeks; Q4W = every 4 weeks; W52 = Week 52.

Note: Four participants who were nonresponders at Week 16 were incorrectly randomly assigned to the Maintenance Primary Population, and 3 placebo-treated participants who were nonresponders at Week 16 of the Induction Period were incorrectly randomly reassigned to the Maintenance Secondary Population.

Figure 12: Disposition during the maintenance blinded period (KGAC)



Abbreviations: EASI 75 = at least 75% in the Eczema Area and Severity Index; N = number of participants in the analysis population; n = number of participants in the specified category; Q2W = every 2 weeks; Q4W = every 4 weeks; W16 = Week 16; W52 = Week 52.

Note: 3 participants who did not meet the definition of responder at Week 16 were randomly assigned to the Maintenance Primary Population. 10 lebrikizumab-treated participants and 4 placebo-treated participants who achieved EASI 75 during the Induction Period without rescue medication use were incorrectly assigned to the Escape Arm at W16.

Maintenance Escape Period

KGAB: Of the 202 patients who entered the Escape Arm at Week 16, 154 patients (76.2%) completed treatment at Week 52.

KGAC: Of the 233 patients who entered the Escape Arm at Week 16, 168 patients (72.1%) completed treatment at Week 52 (Table 20).

Table 20: Patient Dispositions After Entering Maintenance Escape Arms of Study KGAB and Study KGAC at Week 16 (Maintenance Week 16 Escape Population)

Study Disposition, n (%)	Study KGAB (N = 202)		Study KGAC (N =233)		Pooled Studies KGAB and KGAC (N = 435)	
Induction Period/Maintenance Period Treatment	PBO/LEB 250mg Q2W N = 96	LEB/LEB 250mg Q2W N = 106	PBO/LEB 250mg Q2W N = 108	LEB/LEB 250mg Q2W N = 125	PBO/LEB 250mg Q2W N = 204	LEB/LEB 250mg Q2W N = 231
Completed treatment through W52	77 (80.2)	77 (72.6)	85 (78.7)	83 (66.4)	162 (79.4)	160 (69.3)
Discontinued treatment	19 (19.8)	29 (27.4)	23 (21.3)	42 (33.6)	42 (20.6)	71 (30.7)
Reason for treatment discontinuation						
Adverse event	1 (1.0)	4 (3.8)	3 (2.8)	3 (2.4)	4 (2.0)	7 (3.0)
Lack of efficacy	11 (11.5)	17 (16.0)	16 (14.8)	27 (21.6)	27 (13.2)	44 (19.0)
Lost to follow-up	1 (1.0)	2 (1.9)	0 (0.0)	1 (0.8)	1 (0.5)	3 (1.3)
Physician decision	1 (1.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.4)
Pregnancy	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Withdrawal by patient	5 (5.2)	2 (1.9)	4 (3.7)	9 (7.2)	9 (4.4)	11 (4.8)
Other	0 (0.0)	2 (1.9)	0 (0.0)	2 (1.6)	0 (0.0)	4 (1.7)

Abbreviations: CSR = clinical study report; LEB = lebrikizumab; LEB/LEB 250mg Q2W = lebrikizumab 250 mg Q2W treatment during Induction Period and lebrikizumab 250 mg Q2W treatment during Maintenance Period; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; PBO/LEB 250 mg Q2W = placebo treatment during Induction Period and lebrikizumab 250 mg Q2W treatment during Maintenance Period; Q2W = every 2 weeks; W52 = Week 52.

Recruitment

KGAB study

Date of first subject first visit: 24 September 2019

Date of last subject last visit: 3 May 2022

Data lock point 1 (week 16 DBL): 19 July 2021

Data lock point 2 (week 52 DBL): 29 April 2022

KGAC study

Date of first subject first visit: 29 October 2019

Date of last subject last visit: 28 April 2022

Data lock point 1 (week 16 DBL): 6 August 2021

Data lock point 2 (week 52 DBL): 3 May 2022

KGAD study

Date of first subject first visit: 3 February 2020

Date of last subject last visit: 16 September 2021

Data lock point 1 (week 16 DBL): 13 September 2021

Data lock point 2 (final DBL): 16 December 2021

Conduct of the study

Site exclusion

Following primary outcome database lock, a site audit triggered by statistically implausible data at one study site resulted in a critical finding. The site audit revealed GCP noncompliance with protocol entry criteria and the associated efficacy data was considered unreliable. The site was closed for all active lebrikizumab studies. As a result, the patients from the affected study site with the critical finding were excluded from the modified intent-to-treat (mITT) population and the Modified Safety population for the KGAC and KGAD studies. In total, 35 patients were excluded, 18 from Study KGAC and 17 from Study KGAD. According to the Applicant, due to the unreliable baseline AD values, any efficacy analyses performed on the data of these patients would lead to inconclusive and unreliable results. For this reason, efficacy analyses in this population were not performed.

Protocol amendments

KGAB and KGAC studies

The following substantial changes were made to studies KGAB and KGAC.

Amendment 1 (dated 16 October 2019):

- Clarification of primary, co-primary, and secondary endpoints to be analysed for the FDA and EMA.
- Updated inclusion criterion 10 for contraceptive use after the last dose of study drug (increased from 17 to 18 weeks).
- Added inclusion criterion 11 to require male participants to use an effective method of contraception if sexually active with a female of child-bearing potential.
- Other minor clarifications and editorial changes.

Amendment 2 (dated 20 May 2020):

- Added hormone testing for adolescent participants.
- Removed requirement for TB screening serology at screening visit.
- Added PK sample at Week 4 and at the safety follow-up visit.
- Clarifications on analysis timing, study procedures, and protocol wording.

KGAD study

Amendment 1

- Added hormone testing for adolescent participants
- Removed requirement for TB screening serology at screening visit
- Added PK sample at Week 4
- Added PK and ADA sample at follow-up visit
- Clarifications on analysis timing, study procedures, and protocol wording, including
    - Clarified inclusion criterion [6] to reflect that use of topical corticosteroids is necessary
    - Inclusion criterion [10] was modified to require 'highly-effective' contraceptive measures

Protocol deviations

Important protocol deviations included those that might have meaningful effects on the accuracy, completeness, or reliability of study data or those that could affect the rights, safety, or well-being of a study participant.

KGAB and KGAC studies

In KGAB study, altogether 69 patients (16.3% of the total ITT population) and 33 patients (8.6% of the total Maintenance Population) were identified to have at least 1 important protocol deviation during the induction and maintenance periods, respectively.

In KGAC study, 69 patients (15.5% of the total ITT Population) and 32 patients (7.9% of the total Maintenance Population), were identified to have at least 1 important protocol deviation during the induction and maintenance periods, respectively.

KGAD study

Altogether, 120 patients (52.6% of the ITT population), were identified to have at least 1 important protocol deviation (Table 21).

Table 21: Summary of Important Protocol Deviations by Category (ITT Population) (KGAD)

Protocol Deviation Category	PBO + TCS (N = 75) n (%)	LEB 250 mg Q2W + TCS (N = 153) n (%)	Total (N = 228) n (%)
Participants with ≥1 important protocol deviation	41 (54.7)	79 (51.6)	120 (52.6)
Study procedure/Missing safety assessments	23 (30.7)	50 (32.7)	73 (32.0)
Inclusion/Exclusion	12 (16.0)	16 (10.5)	28 (12.3)
Study procedure/site staff authorization, delegation, training	3 (4.0)	15 (9.8)	18 (7.9)
Informed consent form/other	3 (4.0)	7 (4.6)	10 (4.4)
Study procedure/missed procedures	2 (2.7)	7 (4.6)	9 (3.9)
IP/IP dosing	2 (2.7)	1 (0.7)	3 (1.3)
Study procedure/missing efficacy assessments	0	1 (0.7)	1 (0.4)

Abbreviations: ITT = intent-to-treat; IP = investigational product; LEB = lebrikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroids.

Baseline data

Demographic and other baseline characteristics

KGAB study

The mean age of patients was 35.5 years, with 13% of the population made up of adolescents aged 12 years to less than 18 years. The mean duration of time since AD onset was 22.6 years, and similar percentages of females and males were included. The majority of patients were White (68.2%), followed by Asian (16.5%) and Black or African American (11.6%) (Table 22).

Table 22: Summary Baseline Characteristics (Induction Period, ITT Population)

Attribute	PBO (N = 141)	LEB 250mg Q2W (N = 283)	Total (N = 424)
Age (years), mean (SD)	34.2 (16.4)	36.1 (17.8)	35.5 (17.3)
Adolescents (12 to <18 years; ≥40 kg), n (%)	18 (12.8)	37 (13.1)	55 (13.0)
Adults (≥18 years), n (%)	123 (87.2)	246 (86.9)	369 (87.0)
Female, n (%)	73 (51.8)	141 (49.8)	214 (50.5)
Male, n (%)	68 (48.2)	142 (50.2)	210 (49.5)
Race, n (%)			
American Indian or Alaska Native	0	7 (2.5)	7 (1.7)
Asian	31 (22.0)	39 (13.8)	70 (16.5)
Black or African American	16 (11.3)	33 (11.7)	49 (11.6)
Native Hawaiian or Other Pacific Islander	0	2 (0.7)	2 (0.5)
White	93 (66.0)	196 (69.3)	289 (68.2)
Multiple	1 (0.7)	4 (1.4)	5 (1.2)
Other	0	1 (0.4)	1 (0.2)
Not reported	0	1 (0.4)	1 (0.2)
Duration since AD onset (years), mean (SD)	23.8 (15.4)	22.0 (14.9)	22.6 (15.0)
Weight (kg), mean (SD)	79.0 (22.7)	77.0 (19.7)	77.7 (20.8)
<60 kg, n (%)	31 (22.0)	60 (21.3)	91 (21.5)
≥60 to <100 kg, n (%)	93 (66.0)	188 (66.7)	281 (66.4)
≥100 kg, n (%)	17 (12.1)	34 (12.1)	51 (12.1)
Body mass index (kg/m^2), mean (SD)	27.8 (7.2)	26.6 (5.8)	27.0 (6.4)
Country, n (%)			
Australia	13 (9.2)	26 (9.2)	39 (9.2)
Canada	7 (5.0)	16 (5.7)	23 (5.4)
Estonia	4 (2.8)	4 (1.4)	8 (1.9)
France	0	7 (2.5)	7 (1.7)
Latvia	6 (4.3)	5 (1.8)	11 (2.6)
Lithuania	7 (5.0)	11 (3.9)	18 (4.2)
Poland	25 (17.7)	56 (19.8)	81 (19.1)
Spain	4 (2.8)	9 (3.2)	13 (3.1)
South Korea	13 (9.2)	21 (7.4)	34 (8.0)
US	62 (44.0)	128 (45.2)	190 (44.8)

Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; ITT = intent to treat; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; SD = standard deviation.

KGAC study

The mean age of patients was 36.2 years, with 11% of the population made up of adolescents, aged 12 years to less than 18 years. The mean duration of time since AD onset was 20.5 years, and similar percentages of females and males were included. The majority of patients were white (59.3%), followed by Asian (28.6%), and Black or African American (8.2%) (Table 23).

Table 23: Summary of Baseline Characteristics (Induction Period, mITT Population)

Attribute	PBO (N = 146)	LEB 250 mg Q2W (N = 281)	Total (N = 427)
Age (years), mean (SD)	35.3 (17.2)	36.6 (16.8)	36.2 (16.9)
Adolescents (12 to <18 years; ≥40 kg), n (%)	17 (11.6)	30 (10.7)	47 (11.0)
Adults (≥18 years), n (%)	129 (88.4)	251 (89.3)	380 (89.0)
Female, n (%)	75 (51.4)	136 (48.4)	211 (49.4)
Male, n (%)	71 (48.6)	145 (51.6)	216 (50.6)
Race, n (%)			
American Indian or Alaska Native	2 (1.4)	3 (1.1)	5 (1.2)
Asian	44 (30.1)	78 (27.8)	122 (28.6)
Black or African American	10 (6.8)	25 (8.9)	35 (8.2)
Native Hawaiian or Other Pacific Islander	1 (0.7)	2 (0.7)	3 (0.7)
White	85 (58.2)	168 (59.8)	253 (59.3)
Multiple	3 (2.1)	4 (1.4)	7 (1.6)
Other	1 (0.7)	1 (0.4)	2 (0.5)
Duration since AD onset (years), mean (SD)	20.1 (14.1)	20.8 (15.2)	20.5 (14.8)
Weight (kg), mean (SD)	76 (21.1)	76.7 (20.5)	76.5 (20.7)
<60 kg, n (%)	32 (22.1)	57 (20.3)	89 (20.9)
≥60 to <100 kg, n (%)	100 (69.0)	188 (66.9)	288 (67.6)
≥100 kg, n (%)	13 (9.0)	36 (12.8)	49 (11.5)
Body mass index (kg/m^2), mean (SD)	26.3 (6.3)	26.7 (6.6)	26.5 (6.5)
Country, n (%)			
Bulgaria	7 (4.8)	15 (5.3)	22 (5.2)
Canada	16 (11.0)	42 (14.9)	58 (13.6)
Germany	28 (19.2)	53 (18.9)	81 (19.0)
Mexico	3 (2.1)	6 (2.1)	9 (2.1)
Singapore	8 (5.5)	11 (3.9)	19 (4.4)
Taiwan (Province of China)	21 (14.4)	39 (13.9)	60 (14.1)
Ukraine	3 (2.1)	8 (2.8)	11 (2.6)
US	60 (41.1)	107 (38.1)	167 (39.1)

Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; mITT = modified intent-to-treat; N = number of participant in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; SD = standard deviation.

KGAD study

The mean age of patients was 37.2 years, with 21.8% of the population made up of adolescents, aged 12 years to less than18 years. The mean duration of time since AD onset was 21.1 years, and the population was divided nearly evenly between females and males. The majority of patients were white (61.6%), followed by Asian (14.7%), and Black or African American (13.3%) (Table 24).

Table 24: Summary of Baseline Characteristics (mITT Population)

Attribute	PBO + TCS (N = 66)	LEB 250 mg Q2W + TCS (N = 145)	Total (N = 211)
Age (years), mean (SD)	36.7 (17.9)	37.5 (19.9)	37.2 (19.3)
Adolescents (12 to <18 years; ≥40kg), n (%)	14 (21.2)	32 (22.1)	46 (21.8)
Adults (≥18 years), n (%)	52 (78.8)	113 (77.9)	165 (78.2)
Female, n (%)	33 (50.0)	70 (48.3)	103 (48.8)
Race, n (%)			
American Indian or Alaska Native	2 (3.0)	5 (3.4)	7 (3.3)
Asian	13 (19.7)	18 (12.4)	31 (14.7)
Black or African American	9 (13.6)	19 (13.1)	28 (13.3)
Native Hawaiian or Other Pacific Islander	0	3 (2.1)	3 (1.4)
White	40 (60.6)	90 (62.1)	130 (61.6)
Multiple	1 (1.5)	8 (5.5)	9 (4.3)
Other	1 (1.5)	2 (1.4)	3 (1.4)
Duration since AD onset (years), mean (SD)	21.2 (13.9)	21.0 (17.4)	21.1 (16.3)
Weight (kg), mean (SD)	79.8 (24.4)	74.6 (23.3)	76.2 (23.7)
<60 kg, n (%)	15 (22.7)	44 (30.3)	59 (28.0)
60 to <100 kg, n (%)	37 (56.1)	81 (55.9)	118 (55.9)
≥100 kg, n (%)	14 (21.2)	20 (13.8)	34 (16.1)
Body mass index (kg/m^2), mean (SD)	27.9 (7.5)	26.5 (7.2)	26.9 (7.3)
Country, n (%)			
Canada	8 (12.1)	14 (9.7)	22 (10.4)
Germany	2 (3.0)	9 (6.2)	11 (5.2)
Poland	8 (12.1)	19 (13.1)	27 (12.8)
US	48 (72.7)	103 (71.0)	151 (71.6)

Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; SD = standard deviation; TCS = topical corticosteroids.

Baseline disease characteristics

KGAB study

At Baseline, 40.3% of patients had severe AD, based on their IGA score, and the rest of the patients had moderate AD. The mean EASI was 29.6 and mean Pruritus NRS score was 7.3 (Table 25).

Table 25: Summary of Baseline Disease Characteristics (Induction Period, ITT Population)

Baseline Attribute	PBO (N = 141)	LEB 250mg Q2W (N = 283)	Total (N = 424)
IGA score, n (%)			
3, moderate	83 (58.9)	170 (60.1)	253 (59.7)
4, severe	58 (41.1)	113 (39.9)	171 (40.3)
EASI, mean (SD)	31.0 (12.9)	28.8 (11.3)	29.6 (11.9)
Pruritus NRS, mean (SD)	7.3 (1.7)	7.2 (1.9)	7.3 (1.8)
≥4, n/Nx (%)	130 (95.6)	263 (94.9)	393 (95.2)
Sleep-Loss Scale score, mean (SD)	2.3 (1.0)	2.3 (1.0)	2.3 (1.0)
≥2, n/Nx (%)	91 (66.9)	195 (70.7)	286 (69.4)
DLQI, mean (SD)	15.7 (7.2)	15.3 (7.4)	15.4 (7.3)
POEM, mean (SD)	20.5 (6.3)	20.9 (5.9)	20.8 (6.0)
PROMIS Anxiety score, mean (SD)			
Adolescents (12 to <18 years; ≥40 kg),	53.6 (12.7)	52.0 (9.4)	52.5 (10.5)
Adults (≥18 years)	54.3 (9.3)	52.9 (10.1)	53.4 (9.9)
PROMIS Depression score, mean (SD)			
Adolescents (12 to <18 years; ≥40 kg),	55.8 (13.8)	52.5 (9.8)	53.6 (11.2)
Adults (≥18 years)	50.0 (9.2)	49.8 (10.0)	49.9 (9.7)
EQ-5 D VAS Score, mean (SD)	67.0 (22.2)	68.2 (22.0)	67.8 (22.1)

Abbreviations: DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EQ-5 D = European Quality of Life-5 Dimensions; IGA = Investigator Global Assessment; ITT = intent to treat; LEB = lebrikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; Nx = number of participants in the analysis population with nonmissing data for the specified endpoint; NRS = numeric rating scale; PBO = placebo; POEM = Patient Oriented Eczema Measure; PROMIS = Patient-Reported Outcomes Measurement Information System; Q2W = every 2 weeks; SD = standard deviation; VAS = visual analog scale.

KGAC study

At baseline, 36.8% of patients had severe AD, based on their IGA score, and the rest of the patients had moderate AD. The mean EASI was 29.7 and mean Pruritus NRS score was 7.1 (Table 26).

Table 26: Summary of Baseline Disease Characteristics (Induction Period, mITT Population)

Baseline Attribute	PBO (N = 146)	LEB 250 mg Q2W (N = 281)	Total (N = 427)
IGA score, n (%)			
3, moderate	95 (65.1)	175 (62.3)	270 (63.2)
4, severe	51 (34.9)	106 (37.7)	157 (36.8)
EASI, mean (SD)	29.6 (10.8)	29.7 (12.0)	29.7 (11.6)
Pruritus NRS, mean (SD)	7.2 (1.9)	7.1 (1.9)	7.1 (1.9)
≥4, n/Nx (%)	134 (93.7)	253 (94.1)	387 (93.9)
Sleep-Loss Scale score, mean (SD)	2.2 (0.9)	2.2 (0.9)	2.2 (0.9)
≥2, n/Nx (%)	97 (67.8)	161 (60.1)	258 (62.8)
POEM, mean (SD)	21.4 (5.6)	20.4 (5.6)	20.8 (5.6)
DLQI, mean (SD)	15.9 (7.6)	15.4 (7.0)	15.5 (7.2)
PROMIS Anxiety score, mean (SD)			
Adolescents (12 to <18 years; ≥40 kg)	52.2 (13.3)	49.9 (11.5)	50.8 (12.1)
Adults (≥18 years)	55 (10.4)	54.4 (8.9)	54.6 (9.5)
PROMIS Depression score, mean (SD)			
Adolescents (12 to <18 years; ≥ 40kg)	52.9 (11.7)	49.6 (11.2)	50.8 (11.4)
Adults (≥18 years)	51.2 (10.4)	51.3 (9.2)	51.2 (9.6)
EQ-5D VAS score, mean (SD)	68.6 (21.6)	66.7 (20.7)	67.4 (21.0)

Abbreviations: DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment; LEB = lebrikizumab; mITT = modified intent-to-treat; N = number of participants in the analysis population; n = number of participants in the specified category; NRS = numeric rating scale; Nx = number of participants in the analysis population with nonmissing data for the specified endpoint; PBO = placebo; POEM = Patient Oriented Eczema Measure; PROMIS = Patient-Reported Outcomes Measurement Information System; Q2W = every 2 weeks; SD = standard deviation; VAS = visual analog scale.

KGAD study

At baseline, 30.8% of patients had severe AD, based on their IGA score, and the rest of the patients had moderate AD. The mean EASI was 27.3 and mean pruritus NRS score was 7.1 (Table 27).

Table 27: Summary of Baseline Disease Characteristics

Baseline Attribute	PBO + TCS N = 66	LEB 250 mg Q2W + TCS N =145	Total N=211
IGA Score, n/N (%)			
3, moderate	48/66 (72.7)	98/145 (67.6)	146/211 (69.2)
4, severe	18/66 (27.3)	47/145 (32.4)	65/211 (30.8)
EASI, mean (SD)	26.4 (10.6)	27.7 (11.1)	27.3 (10.9)
SCORAD[a], mean (SD)	63.4 (11.1)	64.8 (11.8)	64.3 (11.6)
% BSA affected, mean (SD)	38.2 (20.8)	40.4 (21.9)	39.7 (21.5)
Pruritus NRS[b], mean (SD)	6.8 (2.0)	7.3 (1.8)	7.1 (1.9)
≥4, n/Nx (%)	57/63 (90.5)	130/139 (93.5)	187/202 (92.6)
Sleep-loss score[b], mean (SD)	1.9 (0.9)	2.1 (0.9)	2.0 (0.9)
≥2, n/Nx (%)	34/63 (54.0)	88/139 (63.3)	122/202 (60.4)
POEM[a], mean (SD)	19.5 (6.2)	19.5 (6.4)	19.5 (6.3)
DLQI[c], mean (SD)	13.5 (7.5)	14.9 (7.2)	14.4 (7.3)
CDLQI[c], mean (SD)	10.7 (6.4)	11.8 (7.2)	11.5 (6.9)
PROMIS[d] Anxiety Score, mean (SD)			
Adolescents (12 to <18 years; ≥40kg),	49.6 (12.5)	48.1 (11.9)	48.5 (12.0)
Adults (≥18 years)	50.8 (8.1)	52.4 (9.4)	51.9 (9.0)
PROMIS[d] Depression Score, mean (SD)			
Adolescents (12 to <18 years; ≥40kg),	50.5 (15.1)	48.2 (9.8)	48.9 (11.5)
Adults (≥18 years)	47.0 (8.6)	48.9 (8.9)	48.3 (8.8)

Abbreviations: AD = atopic dermatitis; BSA = body surface area; CDLQI = Children Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; IGA = Investigator's Global Assessment for AD; LEB = lebrikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; Nx = number of participants in the analysis population with non-missing data for specified endpoint; NRS = numeric rating scale; PBO = placebo; POEM = Patient-Oriented Eczema Measure; PROMIS = Patient-Reported Outcomes Measurement Information System; Q2W = every 2 weeks; SCORAD = SCORing Atopic Dermatitis; SD = standard deviation; TCS = topical corticosteroids.

[a] Mean value at baseline was calculated from number of participants with non-missing data (SCORAD: PBO N = 65, LEB N = 140; POEM: PBO N = 64, LEB N = 135.

[b] The number of participants with non-missing data for mean and score calculations of Pruritus NRS and Sleep-loss was PBO N = 63, LEB N = 139.

[c] Adult participants with non-missing data at Baseline for the DLQI were PBO N = 51, LEB N = 109. Adolescent participants with non-missing data a baseline for the CDLQI were PBO N = 12, LEB N = 25.

[d] Adult participants with non-missing data at baseline for PROMIS were PBO N = 44, LEB N = 101. Adolescent participants with non-missing data a baseline for the PROMIS was PBO N = 13, LEB N = 31.

Previous AD treatments

KGAB study

The most common prior therapies used, reported by 10% of patients or more, were topical corticosteroids (96.9%) and topical calcineurin inhibitors (43.4%). Prior systemic treatment use was reported by 49.3%, mainly systemic corticosteroids (41.5%) and cyclosporine (15.1%). Prior phototherapy was reported by 15.1% of the patients. (Table 28).

Table 28: Summary of AD Treatment History at Baseline (ITT Population)

Prior Therapy	PBO (N = 141) n (%)	LEB 250mg Q2W (N = 283) n (%)	Total (N = 424) n (%)
None	3 (2.1)	4 (1.4)	7 (1.7)
Topical corticosteroids	136 (96.5)	275 (97.2)	411 (96.9)
Topical calcineurin inhibitors	65 (46.1)	119 (42.0)	184 (43.4)
Systemic treatment	79 (56.0)	130 (45.9)	209 (49.3)
Systemic corticosteroids	70 (49.6)	106 (37.5)	176 (41.5)
Cyclosporine	25 (17.7)	39 (13.8)	64 (15.1)
Mycophenolate-mofetil	3 (2.1)	4 (1.4)	7 (1.7)
IFN-gamma	0	1 (0.4)	1 (0.2)
Janus kinase inhibitors	9 (6.4)	16 (5.7)	25 (5.9)
Azathioprine	6 (4.3)	6 (2.1)	12 (2.8)
Methotrexate	9 (6.4)	12 (4.2)	21 (5.0)
Phototherapy	32 (22.7)	35 (12.4)	67 (15.8)
Photochemotherapy	3 (2.1)	9 (3.2)	12 (2.8)
Other biologics (e.g., cell-depleting biologics)	6 (4.3)	10 (3.5)	16 (3.8)
Other nonbiologic medication/treatment	22 (15.6)	35 (12.4)	57 (13.4)

Abbreviations: AD = atopic dermatitis; IFN = interferon; ITT = intent to treat; LEB = lebrikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks.

KGAC study

The most common prior therapies, reported by 10% or more of patients were topical corticosteroids (98.8%) and topical calcineurin inhibitors (36.1%). Prior systemic treatment use was reported by 46.4%, mainly systemic corticosteroids (37.7%) and cyclosporine (10.5%). Prior phototherapy was reported by 23.7% of the patients (Table 29).

Table 29: Summary of AD Treatment History at Baseline (mITT Population)

Prior therapy	PBO (N = 146) n (%)	LEB 250 mg Q2W (N = 281) n (%)	Total (N = 427) n (%)
None	2 (1.4)	2 (0.7)	4 (0.9)
Topical corticosteroids	144 (98.6)	278 (98.9)	422 (98.8)
Topical calcineurin inhibitors	55 (37.7)	99 (35.2)	154 (36.1)
Systemic treatment	62 (42.5)	136 (48.4)	198 (46.4)
Systemic corticosteroids	49 (33.6)	112 (39.9)	161 (37.7)
Cyclosporine	19 (13.0)	26 (9.3)	45 (10.5)
Mycophenolate-mofetil	0	0	0
IFN-gamma	0	0	0
Janus kinase inhibitors	8 (5.5)	19 (6.8)	27 (6.3)
Azathioprine	12 (8.2)	13 (4.6)	25 (5.9)
Methotrexate	18 (12.3)	31 (11.0)	49 (11.5)
Phototherapy	35 (24.0)	66 (23.5)	101 (23.7)
Photochemotherapy (PUVA)	1 (0.7)	6 (2.1)	7 (1.6)
Other biologics (eg, cell depleting biologics)	6 (4.1)	10 (3.6)	16 (3.7)
Other non-biologic medication/treatment	9 (6.2)	17 (6.0)	26 (6.1)

Abbreviations: AD = atopic dermatitis; IFN = interferon; LEB = lebrikizumab; mITT = modified intent to treat; N = number of participants in the analysis population; n = number of participant in the specified category; PBO = placebo; PUVA = psoralen + UVA; Q2W = every 2 weeks.

KGAD study

All patients had previously used TCS, and 33.6% had used topical calcineurin inhibitors. Altogether 47.4% of patients had previously used some systemic treatment, most commonly systemic corticosteroids (29.9%), phototherapy (18.0%) dupilumab (13.7%) and cyclosporine (10.4%) (Table 30).

Table 30: Summary of AD Treatment History at Baseline

Prior therapy	PBO + TCS (N = 66) n (%)	LEB 250 mg Q2W + TCS (N = 145) n (%)	Total (N = 211) n (%)
None	**0**	**0**	**0**
Topical corticosteroids	**66 (100)**	**145 (100)**	**211 (100)**
Topical calcineurin inhibitors	**23 (34.8)**	**48 (33.1)**	**71 (33.6)**
Systemic treatment	**34 (51.5)**	**66 (45.5)**	**100 (47.4)**
Systemic corticosteroids	22 (33.3)	41 (28.3)	63 (29.9)
Phototherapy	14 (21.2)	24 (16.6)	38 (18.0)
Dupilumab	9 (13.6)	20 (13.8)	29 (13.7)
Cyclosporine	4 (6.1)	18 (12.4)	22 (10.4)
Methotrexate	6 (9.1)	13 (9.0)	19 (9.0)
Janus kinase inhibitors	4 (6.1)	5 (3.4)	9 (4.3)
Photochemotherapy (PUVA)	2 (3.0)	3 (2.1)	5 (2.4)
Mycophenolate-mofetil	0	4 (2.8)	4 (1.9)
Tralokinumab	1 (1.5)	1 (0.7)	2 (0.9)
Other biologics	5 (7.6)	16 (11.0)	21 (10.0)
Other non-biologic medication/treatment	**5 (7.6)**	**16 (11.0)**	**21 (10.0)**

Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; PUVA = psoralen + UV-A; Q2W = every 2 weeks; TCS = topical corticosteroids.

Numbers analysed

KGAB and KGAC studies

In the KGAB study, the **ITT population** included 424 patients in lebrikizumab 250 mg Q2W (n=283) and placebo (n=141) groups. The **Maintenance Primary Population** included 157 patients in lebrikizumab 250 mg Q2W (n=62), lebrikizumab 250 Q4W (n=63) and placebo (n=32) groups.

In the KGAC study, the **mITT population** included 427 patients in lebrikizumab 250 mg Q2W (n=281) and placebo (n=146) groups. The **Modified Maintenance Primary Population (mMPP)** included 134 patients in lebrikizumab 250 mg Q2W (n=51), lebrikizumab 250 Q4W (n=55) and placebo (n=28) groups.

KGAD study

The **mITT population** included 211 patients in lebrikizumab 250 mg Q2W (n=145) and placebo (n=66) groups.

Outcomes and estimation

Study KGAB, KGAC and KGAD Induction Period Results

Co-primary endpoint: IGA 0 or 1 with ≥2-Point reduction at week 16

A significantly greater percentage of patients achieved an IGA 0,1 with ≥2 points reduction (IGA 0,1) at week 16 in the lebrikizumab group compared to placebo in all pivotal Phase 3 studies based on the primary analysis of the "hybrid" estimand. In KGAB and KGAC, 43.1% and 33.2% of patients treated

with lebrikizumab and 12.7% and 10.8% of patients treated with placebo achieved IGA 0,1. In KGAD, 41.2% of patients treated with lebrikizumab + TCS and 22.1% of patients treated with placebo + TCS achieved IGA 0,1. The treatment difference between lebrikizumab and placebo was 29.7% and 21.9% in KGAB and KGAC, respectively, and 18.3% in KGAD where TCS was used (Table 31).

The supportive "composite" estimand yielded similar results to the primary analysis. In KGAB and KGAC, 41.0% and 31.3% of patients treated with lebrikizumab and 11.3% and 9.6% of patients treated with placebo achieved IGA 0,1 (p<0.001 in both studies). In KGAD, 39.3% and 19.7% of patients treated with lebrikizumab + TCS and placebo + TCS, respectively, achieved IGA 0,1 (p=0.006).

Table 31: IGA 0 or 1 with ≥2-Point Reduction at Week 16 Primary Estimand (Hybrid) with MCMC-MI

	Study KGAB		Study KGAC		Study KGAD	
	PBO N = 141	LEB 250mg Q2W N = 283	PBO N = 146	LEB 250mg Q2W N = 281	PBO + TCS N = 66	LEB 250mg Q2W + TCS N = 145
IGA 0,1 response, n (%)	18 (12.7)	122 (43.1)	16 (10.8)	93 (33.2)	15 (22.1)	60 (41.2)
Diff from PBO (95% CI)	29.7 (21.6, 37.8)		21.9 (14.2, 29.6)		18.3 (5.1, 31.5)	
p-value vs. PBO[a]	<.001		<.001		.011	

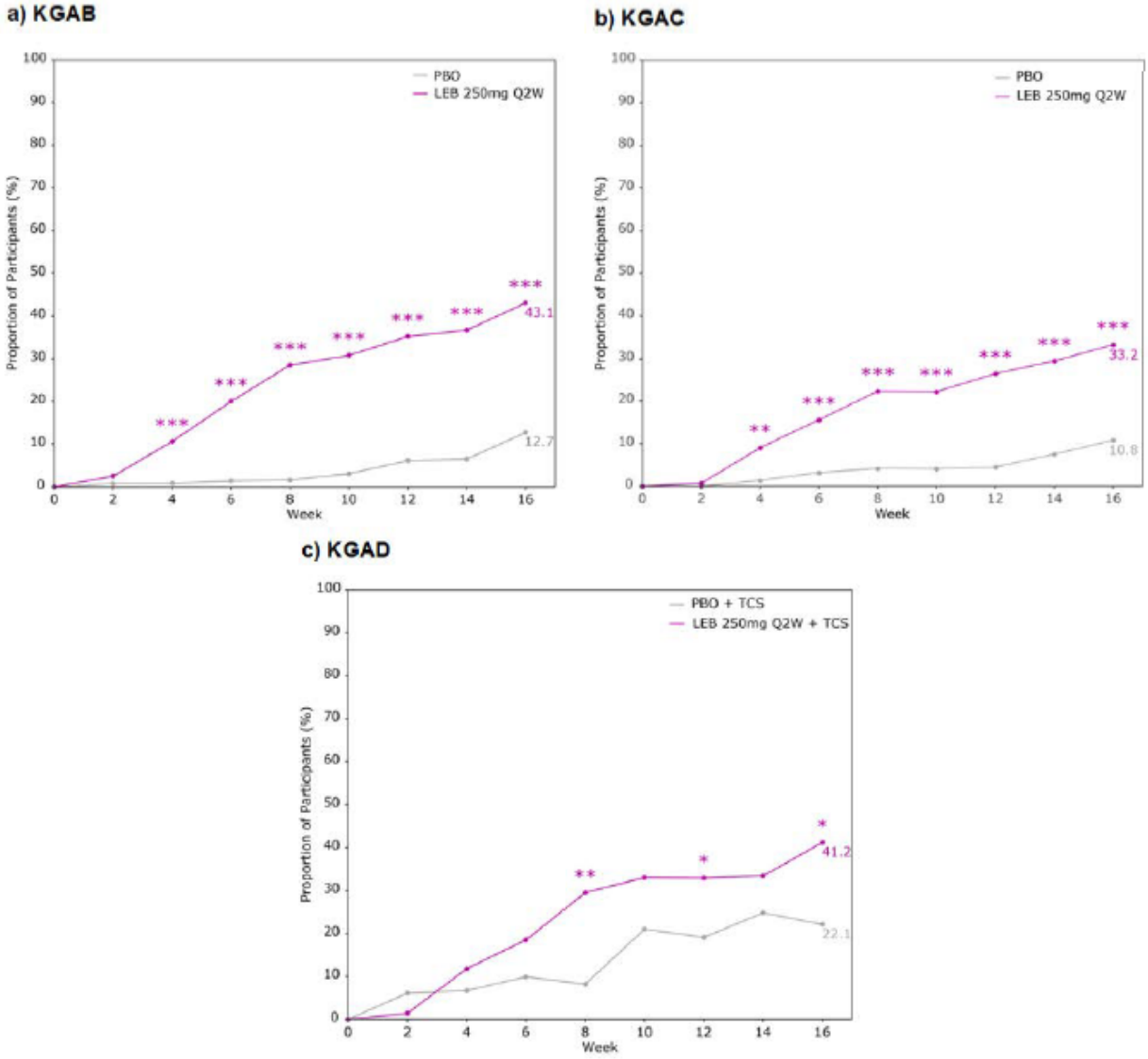
Abbreviations: CSR = clinical study report; CI = confidence interval; Diff = difference; IGA = Investigator's Global Assessment; IGA 0,1 = IGA score of 0 or 1, with a 2-point or greater reduction from Baseline; LEB = lebrikizumab; MCMC-MI = Markov Chain Monte Carlo multiple imputation; N = number of participants in the analysis population; n = number of participants in the specified category; NA = not applicable; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroids.

[a] Cochran-Mantel-Haenszel test adjusted by geographic region (US versus EU versus rest of world), age (adolescent versus adult), and disease severity (IGA 3 versus 4).

Figure 13 shows the IGA 0,1 responses by visit throughout the 16-week induction period.

A supplementary post hoc analysis that used all observed data regardless of any intercurrent events yielded similar results to the primary analysis. In KGAB and KGAC, 45.6% and 36.6% of patients treated with lebrikizumab and 14.2% and 12.6% of patients treated with placebo achieved IGA 0,1 (p<0.001 in both studies). In KGAD, 43.5% and 22.2% of patients treated with lebrikizumab + TCS and placebo + TCS, respectively, achieved IGA 0,1 (p=0.004).

Figure 13: Proportion of patients achieving IGA 0 or 1, with a ≥2-point improvement from Baseline through Week 16. Primary estimand (hybrid) with MCMC-MI.



Abbreviations: IGA = Investigator's Global Assessment; IGA 0,1 = IGA score of 0 or 1, with a 2-point or greater reduction from Baseline; LEB = lebrikizumab; MCMC-MI = Markov Chain Monte Carlo multiple imputation; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroid.
vs. PBO: *p <.05, **p <.01, ***p <.001.

Co-primary endpoint: EASI 75 (≥75% reduction from Baseline in EASI score) at Week 16

A significantly greater percentage of patients achieved EASI 75 at week 16 in the lebrikizumab-treated group compared to the placebo-treated group in all pivotal Phase 3 studies based on the primary analysis of the "hybrid" estimand.

In KGAB and KGAC, 58.8% and 52.1% of patients treated with lebrikizumab and 16.2% and 18.1% of patients treated with placebo achieved EASI 75. In KGAD, 69.5% of patients treated with lebrikizumab + TCS and 42.2% of patients treated with placebo + TCS achieved EASI 75. The treatment difference between lebrikizumab and placebo was 42.0% and 33.3% in KGAB and KGAC, respectively, and 26.4% in KGAD where TCS was used (Table 32).

The supportive "composite" estimand yielded similar results to the primary analysis. In KGAB and KGAC, 56.5% and 50.2% of patients treated with lebrikizumab and 14.2% and 17.1% of patients treated with placebo achieved EASI 75 (p<0.001 in both studies). In KGAD, 66.9% and 39.4% of patients treated with lebrikizumab + TCS and placebo + TCS, respectively, achieved EASI 75 (p<0.001).

A supplementary post hoc analysis that used all observed data regardless of any intercurrent events yielded similar results to the primary analysis. In KGAB and KGAC, 63.1% and 59.9% of patients treated with lebrikizumab and 20.6% and 26.7% of patients treated with placebo achieved EASI 75 (p<0.001 in both studies). In KGAD, 72.6% and 42.5% of patients treated with lebrikizumab + TCS and placebo + TCS, respectively, achieved EASI 75 (p<0.001).

Table 32: Percentage of Patients Achieving EASI 75 and EASI 90 at Week 16 Primary Estimand (Hybrid) with MCMC-MI

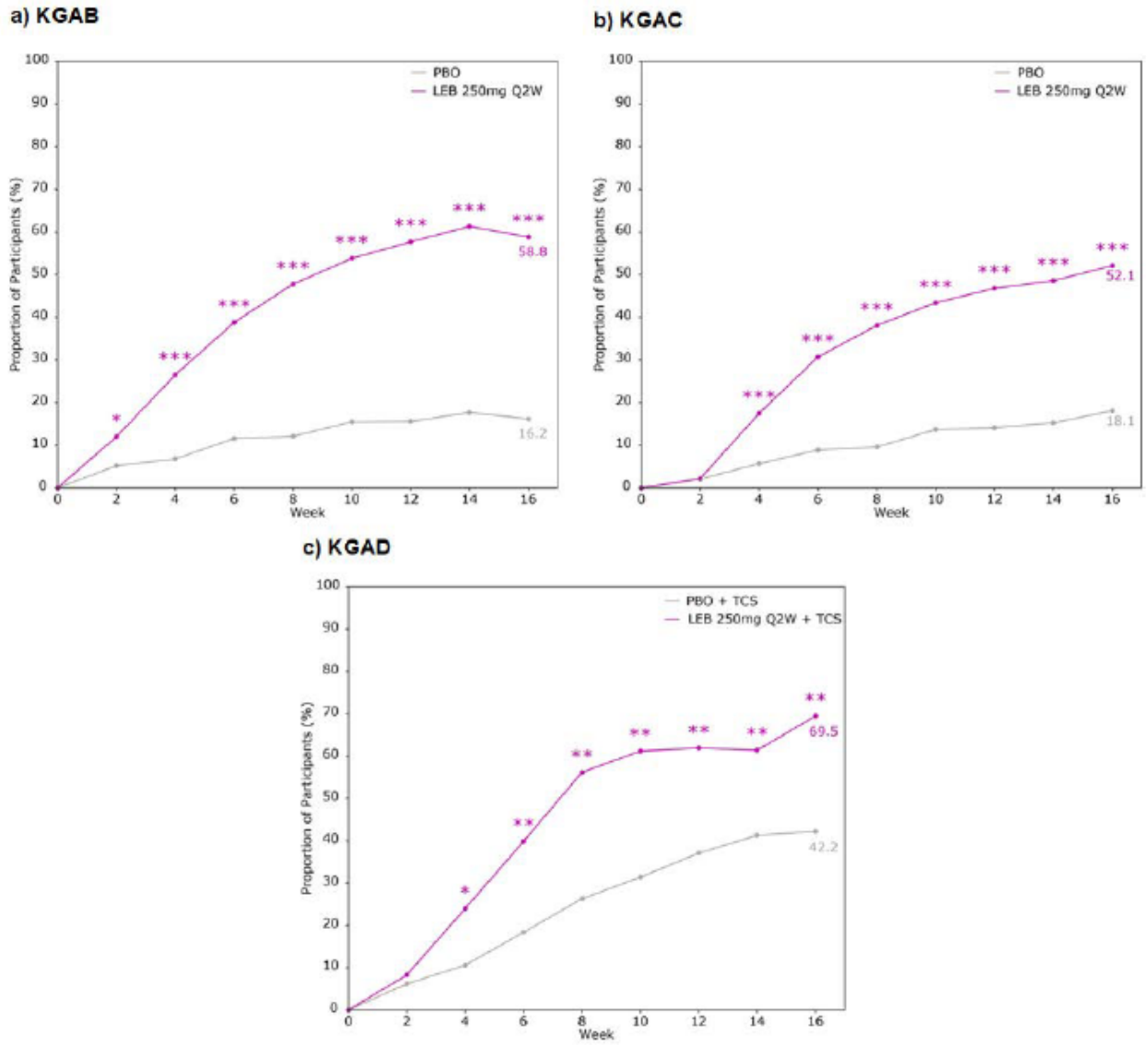
	Study KGAB		Study KGAC		Study KGAD	
	PBO	LEB 250mg Q2W	PBO	LEB 250mg Q2W	PBO + TCS	LEB 250mg Q2W + TCS
	N = 141	N = 283	N = 146	N = 281	N = 66	N = 145
EASI 75						
Response, n (%)	23 (16.2)	166 (58.8)	26 (18.1)	146 (52.1)	28 (42.2)	101 (69.5)
Difference vs. PBO, % (95% CI)	42.0 (33.3, 50.6)		33.3 (24.4, 42.2)		26.4 (12.1, 40.8)	
p-value vs. PBO[a]	<.001		<.001		<.001	
EASI 90						
Response, n (%)	13 (9.0)	108 (38.3)	14 (9.5)	86 (30.7)	14 (21.7)	60 (41.2)
Difference vs. PBO, % (95% CI)	28.8 (21.3, 36.3)		20.7 (13.3, 28.1)		18.9 (6.1, 31.7)	
p-value vs. PBO[a]	<.001		<.001		.008	

Abbreviations: CSR = clinical study report; CI = confidence interval; EASI = Eczema Area and Severity Index; EASI 75 = 75% improvement from Baseline in EASI; EASI 90 = 90% improvement from Baseline in EASI; IGA = Investigator's Global Assessment; LEB = lebrikizumab; MCMC-MI = Markov Chain Monte Carlo multiple imputation; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroids.

[a] Cochran-Mantel-Haenszel test adjusted by geographic region (US versus EU versus rest of world), age (adolescent versus adult), and disease severity (IGA 3 versus 4).

Figure 14 shows the EASI 75 responses by visit throughout the 16-week induction period.

Figure 14: Proportion of patients achieving EASI 75 through Week 16. Primary estimand (hybrid) with MCMC-MI.



Abbreviations: EASI = Eczema Area and Severity Index; EASI 75 = 75% reduction from Baseline in EASI; LEB = lebrikizumab; MCMC-MI = Markov Chain Monte Carlo multiple imputation; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroids.
vs. PBO: *p <.05, **p <.01, ***p <.001

Key secondary endpoints:

Percentage of patients achieving EASI90 at Week 16

As shown in Table 32, a significantly greater percentage of patients achieved EASI 90 at Week 16 in the lebrikizumab-treated group compared to the placebo-treated group in all Phase 3 studies.

In KGAB and KGAC, 38.3% and 30.7% of patients treated with lebrikizumab and 9.0% and 9.5% of patients treated with placebo achieved EASI 90. In KGAD, 41.2% of patients treated with lebrikizumab + TCS and 21.7% of patients treated with placebo + TCS achieved EASI 90. The treatment difference between lebrikizumab and placebo was 28.8% and 20.7% in KGAB and KGAC, respectively, and 18.9% in KGAD where TCS was used.

In KGAB and KGAC, **Percentage of patients achieving EASI90 at Week 4**, was also listed as a Major secondary endpoint. In KGAB study, 12.4% vs. 1.6% of the patients in lebrikizumab and placebo groups, respectively, achieved EASI 90 at Week 4 resulting in a treatment difference of 10.7% (p<0.001). In KGAC study, 6.3% vs. 1.5% of the patients in lebrikizumab and placebo groups, respectively, achieved EASI 90 at Week 4 with a treatment difference of 4.9% (p=0.023).

Percentage change in EASI score from Baseline to Week 16

In KGAB and KGAC, the percentage change (LSM) in EASI score was -64.31% and -61.5% in lebrikizumab groups and -26.01% and -28.0% in placebo groups at Week 16 (p<0.001 in both studies). In KGAD, the corresponding change was -76.8% in lebrikizumab + TCS group and -53.1% in placebo + TCS group (p<0.001). The decrease in EASI score with lebrikizumab reached statistical significance vs. placebo from week 2 onwards in KGAB and KGAC studies, and from week 4 onwards in KGAD study.

Percentage of patients with a Pruritus NRS of ≥4-points at Baseline who achieve a ≥4-point reduction from Baseline to Week 16

In KGAB and KGAC, 45.9% and 39.8% of patients treated with lebrikizumab and 13.0% and 11.5% of patients treated with placebo achieved a ≥4 reduction in NRS at Week 16 (p<0.001). In KGAD, 50.6% of patients treated with lebrikizumab + TCS and 31.9% of patients treated with placebo + TCS achieved a ≥4 reduction in NRS at Week 16 (p<0.017). The treatment difference between lebrikizumab and placebo was 32.9% and 28.3% in KGAB and KGAC, respectively, and 19.2% in KGAD where TCS was used. A statistically significant difference between lebrikizumab vs. placebo was reached from 2 weeks onwards in KGAB study and from 4 week onwards in KGAC and KGAD studies.

Percentage change in Pruritus NRS score from Baseline to Week 16

In KGAB and KGAC, the percentage change (LSM) in Pruritus NRS Score was -45.5% and -36.6% in lebrikizumab groups and -15.1% and -9.0% in placebo groups at Week 16 (p<0.001 in both studies). In KGAD, the corresponding change was -50.7% in lebrikizumab + TCS group and -35.5% in placebo + TCS group (p<0.017). A statistically significant reduction between lebrikizumab vs. placebo was observed in Pruritus NRS score from 1 week onwards in KGAB and KGAC studies and from 6 weeks onwards in KGAD study.

Percentage of patients with a DLQI total score of ≥4-points at Baseline who achieve a ≥4-point improvement from baseline to Week 16 and Change from baseline in DLQI total score at Week 16

As shown in Table 33, a significantly greater percentage of patients with a baseline DLQI of ≥4 reported a ≥4-point reduction at Week 16 in lebrikizumab group compared to placebo group. The mean change from baseline in DLQI was also significantly greater in lebrikizumab-treated vs. placebo-treated patients.

Table 33: **Proportion of Patients with a 4-Point or Greater Improvement in DLQI and DLQI Mean Change from Baseline at Week 16 Primary Estimand (Hybrid) with MCMC-MI**

	Study KGAB		Study KGAC		Study KGAD	
	PBO	LEB 250mg Q2W	PBO	LEB 250mg Q2W	PBO + TCS	LEB 250mg Q2W + TCS
Percentage of participants with 4-point or greater improvement						
Participants with DLQI ≥4 at BL[a], N	116	226	115	215	48	105
Response, n (%)	39 (33.8)	171 (75.6)	39 (33.6)	143 (66.3)	28 (58.7)	81 (77.4)
Diff vs. PBO, % (95% CI)[b]	41.8 (31.2, 52.3)		33.0 (22.2, 43.8)		17.2 (0.1, 34.3)	
p-value vs. PBO[b]	<.001		<.001		.036	
Mean change from Baseline in DLQI						
N[c]	121	239	118	218	51	109
Baseline DLQI (SD)	15.7 (7.2)	15.3 (7.4)	15.9 (7.6)	15.4 (7.0)	13.5 (7.5)	14.9 (7.2)
LSM change (SE)	-2.9 (1.1)	-8.7 (1.1)	-2.4 (1.2)	-7.3 (1.2)	-6.5 (1.9)	-9.8 (1.8)
LSM Diff vs. PBO (SE)[d]	-5.8 (0.68)		-4.9 (0.71)		-3.3 (1.0)	
p-value vs. PBO[d]	<.001		<.001		.001	

Abbreviations: ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; CSR = clinical study report; Diff = difference; DLQI = Dermatology Life Quality Index; IGA = Investigator's Global Assessment; LEB = lebrikizumab; LSM = least standard mean; MCMC-MI = Markov Chain Monte Carlo multiple imputation; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; SD = standard deviation; SE = standard error; TCS = topical corticosteroids.

a DLQI 4-point improvement response was analyzed in participants with a Baseline DLQI score of 4 or more.

b Cochran-Mantel-Haenszel test adjusted by geographic region (US versus EU versus rest of world), age (adolescent versus adult), and disease severity (IGA 3 versus 4).

c Change from Baseline in DLQI analyzed in participants with nonmissing DLQI baseline values.

d The ANCOVA model includes treatment, geographic region (US versus EU versus rest of the world), age group (adolescent participants 12 to <18 versus adults ≥18 years) and baseline IGA score (3,4) as fixed factors and baseline value as covariate.

In a supplementary post hoc analysis that used all observed data regardless of any intercurrent events, smaller treatment effect on DLQI ≥4-point improvement rates was observed as compared with the primary analysis. In KGAB and KGAC, 84.7% and 80.9% of patients treated with lebrikizumab and 56.5% and 61.9% of patients treated with placebo achieved DLQI ≥4-point improvement (p<0.001 in both studies). The corresponding results in KGAD were 83.6% and 63.9% for lebrikizumab + TCS and placebo + TCS, respectively (p=0.025).

Change from Baseline in Sleep-loss Scale score at Week 16 and Percentage of patients with a Sleep-loss score ≥2 points at Baseline who achieve a ≥2 points reduction from Baseline at Week 16 (Major secondary endpoint only in KGAB and KGAC Studies)

Patients in lebrikizumab-treated group reported significantly greater reductions in Sleep-Loss Scale Score compared to placebo. Further, the proportion of patients with Sleep-Loss Scale Score ≥2 at baseline who had ≥2-point reduction at Week 16 was greater in lebrikizumab group vs. placebo group in all Phase 3 studies (Table 34).

Table 34: **Proportion of Patients with a 2-Point or Greater Reduction in Sleep-Loss Scale Score and Mean Change from Baseline in Sleep-Loss Scale Score at Week 16 Primary Estimand (Hybrid) with MCMC-MI**

	Study KGAB		Study KGAC		Study KGAD	
	PBO	LEB 250mg Q2W	PBO	LEB 250mg Q2W	PBO + TCS	LEB 250mg Q2W + TCS
Percentage of participants with 2-point or greater reduction						
Participants with score ≥2 at BL[a], N	91	195	97	161	34	88
Response, n (%)	4 (4.7)	76 (39.0)	8 (8.2)	45 (28.0)	6 (18.4)	30 (34.5)
Diff vs. PBO, % (95% CI)[b]	34.6 (26.2, 43.0)		18.9 (9.6, 28.1)		20.8 (2.1, 39.5)	
p-value vs. PBO[b]	<.001		<.001		.048	
Mean change from Baseline in Sleep-Loss Scale score						
N[c]	136	276	143	268	63	139
Baseline score (SD)	2.3 (1.0)	2.3 (1.0)	2.2 (0.9)	2.2 (0.9)	1.9 (0.9)	2.1 (0.9)
LSM change (SE)	-0.38 (0.1)	-1.13 (0.1)	-0.35 (0.1)	-1.05 (0.1)	-0.80 (0.1)	-1.10 (0.1)
LSM Diff vs. PBO (SE)[d]	-0.75 (0.1)		-0.70 (0.1)		-0.30 (0.1)	
p-value vs. PBO[d]	<.001		<.001		.025	

Abbreviations: ANCOVA = analysis of covariance; BL = baseline; CI = confidence interval; CSR = clinical study report; IGA = Investigator's Global Assessment; LEB = lebrikizumab; LSM = least-standard mean; MCMC-MI = Markov Chain Monte Carlo multiple imputation; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; SD = standard deviation; SE = standard error; TCS = topical corticosteroids.

a Sleep-Loss Scale score 2-point improvement response was analyzed in participants with a Baseline score of 2 or more.

b Cochran-Mantel-Haenszel test adjusted by geographic region (US versus EU versus rest of world), age (adolescent versus adult), and disease severity (IGA 3 versus 4).

c Change from Baseline in Sleep-Loss Scale score was analyzed in participants with nonmissing baseline values.

d The ANCOVA model includes treatment, geographic region (US versus EU versus rest of the world), age group (adolescent participants 12 to <18 versus adults ≥18 years) and baseline IGA score (3,4) as fixed factors and baseline value as covariate.

Percentage of patients with a Pruritus NRS score of ≥4 points at Baseline who achieve both EASI-75 and a ≥4-point reduction in NRS score from Baseline at Week 16 (Major secondary endpoint only in KGAD Study)

Lebrikizumab + TCS resulted in statistically significant improvement compared with placebo + TCS in percentage of patients experiencing both EASI 75 and a 4-point reduction in NRS score from baseline to Week 16 among patients with a score of ≥4 at baseline.

Other secondary endpoints:

KGAB, KGAC and KGAD studies had several secondary endpoints. Selected secondary endpoints have been presented in the Summary of Clinical Efficacy SCE by the Applicant and shown below.

Lebrikizumab-treated patients had a statistically significantly greater reduction in Patient-Oriented Eczema Measure (POEM), than placebo-treated patients in Phase 3 studies (Table 35).

Table 35: **Total Change from Baseline in POEM at Week 16 Supportive Estimand (Hypothetical) with MMRM**

	Study KGAB		Study KGAC		Study KGAD	
	PBO	LEB 250mg Q2W	PBO	LEB 250mg Q2W	PBO + TCS	LEB 250mg Q2W + TCS
N[a]	133	275	141	266	64	135
Baseline score (SD)	20.5 (6.3)	20.9 (5.9)	21.4 (5.6)	20.4 (5.6)	19.5 (6.2)	19.5 (6.4)
LSM, (SE)	-3.9 (0.7)	-11.3 (0.5)	-3.5 (0.8)	-9.5 (0.5)	-6.2 (1.0)	-10.2 (0.7)
LSM diff vs. PBO, (SE)[b]	-7.3 (0.8)		-6.0 (0.9)		-4.0 (1.1)	
p-value vs. PBO[b]	<.001		<.001		<.001	

Abbreviations: CSR = clinical study report; diff = difference; LEB = lebrikizumab; LSM = least square mean; MMRM = mixed model repeated measures; N = number of participants in the analysis population; PBO = placebo; POEM = Patient-Oriented Eczema Measure; Q2W = every 2 weeks; SD = standard deviation; SE = standard error; TCS = topical corticosteroids.

a Change from Baseline in POEM score was analyzed in participants with nonmissing baseline values.

b The MMRM model includes treatment, baseline value, visit, the interaction of the baseline value-by-visit, the interaction of treatment by-visit, geographic region, age group, baseline IGA score.

In patient-reported outcome measures (PROMIS) in anxiety and depression in adults, KGAB and KGAC showed statistically significant improvements in lebrikizumab groups vs. placebo. In KGAD, the difference was smaller and did not reach statistical significance (Table 36).

Table 36: **Change from Baseline in PROMIS Scores at Week 16 Supportive Estimand (Hypothetical) with LOCF (Adult Patients)**

	Study KGAB		Study KGAC		Study KGAD	
	PBO N = 122	LEB 250 mg Q2W N = 244	PBO N = 128	LEB 250 mg Q2W N = 246	PBO + TCS N = 52	LEB 250 mg Q2W + TCS N = 113
Anxiety						
Baseline score (SD)	54.3 (9.3)	52.9 (10.1)	55.0 (10.4)	54.4 (8.9)	50.8 (8.2)	52.4 (9.4)
LSM, (SE)	-0.6 (0.7)	-3.9 (0.5)	-0.5 (0.6)	-3.2 (0.4)	-1.1 (1.4)	-1.9 (1.0)
LSM diff vs. PBO[a], (SE)	-3.3 (0.8)		-2.7 (0.7)		-0.8 (1.4)	
p-value vs. PBO[a]	<.001		<.001		.571	
Depression						
Baseline score (SD)	50.0 (9.2)	49.8 (10.0)	51.2 (10.4)	51.3 (9.2)	47.2 (8.6)	48.9 (8.9)
LSM, (SE)	-0.4 (0.6)	-3.1 (0.4)	0.2 (0.5)	-2.6 (0.4)	-1.2 (1.1)	-1.4 (0.8)
LSM diff vs. PBO[a], (SE)	-2.7 (0.7)		-2.8 (0.7)		-0.2 (1.1)	
p-value vs. PBO[a]	<.001		<.001		.882	

Abbreviations: ANCOVA = analysis of covariance; CSR = clinical study report; diff = difference; LEB = lebrikizumab; LOCF = last observation carried forward; LSM = least standard mean; N = number of participants in the analysis population; PBO = placebo; PROMIS = Patient-Reported Outcomes Measurement Information System; Q2W = every 2 weeks; SD = standard definition; SE = standard error; TCS = topical corticosteroids.

[a] The ANCOVA model includes treatment, geographic region (US versus EU versus rest of the world) and baseline IGA score (3,4) as fixed factors and baseline value as covariate.

Study KGAB and KGAC Maintenance Period Results

Key secondary endpoints specific for maintenance period:

Percentage of patients from those re-randomised having achieved EASI-75 at Week 16 who continue to exhibit EASI-75 at Week 52 (EASI-75 calculated relative to baseline EASI score)

Lebrikizumab-responders who were re-randomised to treatment with lebrikizumab maintained EASI 75 response at Week 52 at numerically higher rates compared with those who were re-randomised to placebo (lebrikizumab withdrawal) (Table 37). Among patients in the pooled population, maintenance of EASI 75 was higher at Week 52 for patients re-randomised to lebrikizumab 250 mg Q4W (81.7%) or lebrikizumab 250 mg Q2W (78.4%) compared to those re-randomised to placebo (lebrikizumab withdrawal) (66.4%).

Overall, the rates of maintenance of EASI 75 at Week 52 and throughout the Maintenance Period were similar for patients re-randomised to either lebrikizumab 250 mg Q4W or Q2W, although in Study KGAC the percentage of patients maintaining EASI 75 was numerically higher in the group treated with lebrikizumab Q4W compared with Q2W.

Table 37: **Percentage of Patients Maintaining EASI 75 at Week 52 Maintenance Primary Estimand (Hybrid) with MCMC-MI LEB-Responders**

	Study KGAB			Study KGAC			Pooled Studies KGAB and KGAC		
Maintenance Period Rerandomization	**PBO (LEB Withdrawal) N = 32**	**LEB 250mg Q4W N = 63**	**LEB 250mg Q2W N = 62**	**PBO (LEB Withdrawal) N = 28**	**LEB 250mg Q4W N = 55**	**LEB 250mg Q2W N = 51**	**PBO (LEB Withdrawal) N = 60**	**LEB 250mg Q4W N = 118**	**LEB 250mg Q2W N = 113**
EASI 75 Responders at W16 (Nx)	**30**	**62**	**61**	**27**	**53**	**51**	**57**	**115**	**112**
Maintained Response at W52, n (%)	18 (61.3)	49 (79.2)	48 (79.2)	19 (72.0)	45 (84.7)	39 (77.4)	38 (66.4)	94 (81.7)	88 (78.4)
Diff vs. PBO, % (95% CI)		17.9 (-2.3, 38.1)	17.5 (-4.5, 39.5)		12.8 (-9.5, 35.1)	4.8 (-17.8, 27.3)		15.5 (0.3, 30.8)	11.6 (-4.5, 27.6)
p-value vs. PBO[a]		.072	.107		.238	.612		.038	.147

Abbreviations: CI = confidence interval; CSE = clinical summary of efficacy; CSR = clinical study report; diff = difference; EASI = Eczema Area and Severity Index; EASI 75 = 75% improvement from Baseline in EASI; LEB = lebrikizumab; MCMC-MI = Markov Chain Monte Carlo multiple imputation; N = total number of participants; n = number of participants in the specified category; Nx = number of participants in analysis population; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; W16 = Week 16; W52 = Week 52.

[a] Cochran-Mantel-Haenszel test adjusted for geographic region (US versus EU versus rest of world). Pooled analysis additionally adjusted for study factor (KGAB versus KGAC). All p-values are nominal.

Percentage of patients from those re-randomised having achieved IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 16 who continue to exhibit an IGA 0 or 1 and a ≥2-point improvement from Baseline at Week 52

Lebrikizumab-responders who were re-randomised to treatment with lebrikizumab maintained IGA 0,1 response at Week 52 at higher rates compared to those who were re-randomised to placebo (lebrikizumab withdrawal) (Table 38). Among patients in the pooled population, maintenance of IGA 0,1 was higher at Week 52 for patients re-randomised to lebrikizumab 250 mg Q4W (76.9%) or lebrikizumab 250 mg Q2W (71.2%) compared to those re-randomised to placebo (lebrikizumab withdrawal) (47.9%).

Overall, the rates of maintenance of IGA 0,1 response were similar for patients treated with lebrikizumab 250 mg Q4W or Q2W, although in Study KGAC the percentage of patients maintaining IGA 0,1 response was numerically higher in the group treated with lebrikizumab Q4W compared with Q2W.

Table 38: **Percentage of Patients Maintaining IGA 0, 1 at Week 52 Maintenance Primary Estimand (Hybrid) with MCMC-MI LEB-Responders with IGA 0,1 at Week 16**

	Study KGAB			Study KGAC			Pooled Studies KGAB and KGAC		
Maintenance Period Rerandomization	**PBO (LEB Withdrawal) N = 32**	**LEB 250mg Q4W N = 63**	**LEB 250mg Q2W N = 62**	**PBO (LEB Withdrawal) N = 28**	**LEB 250mg Q4W N = 55**	**LEB 250mg Q2W N = 51**	**PBO (LEB Withdrawal) N = 60**	**LEB 250mg Q4W N = 118**	**LEB 250mg Q2W N = 113**
W16 LEB-responders with IGA 0,1 (Nx)	**22**	**45**	**45**	**16**	**32**	**32**	**38**	77	77
Maintained Response at W52, n (%)	10 (46.5)	33 (74.2)	34 (75.8)	8 (49.8)	26 (80.6)	21 (64.6)	18 (47.9)	59 (76.9)	55 (71.2)
Diff vs. PBO, % (95% CI)		28.0 (2.8, 53.2)	29.0 (4.6, 53.3)		32.6 (2.6, 62.5)	13.4 (-17.5, 44.3)		29.9 (10.5, 49.3)	22.6 (3.2, 42.0)
p-value vs. PBO[a]		.030	.020		.034	.407		.003	.022

Abbreviations: CI = confidence interval; CSE = clinical summary of efficacy; CSR = clinical study report; Diff = difference; IGA = Investigator's Global Assessment; IGA 0,1 = IGA score of 0 or 1, with a 2-point or greater reduction from Baseline; LEB = lebrikizumab; MCMC-MI = Markov Chain Monte Carlo multiple imputation; N = total number of participants; n = number of participants in the specified category; Nx = number of participants in analysis population PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; W16 = Week 16; W52 = Week 52.

[a] Cochran-Mantel-Haenszel test adjusted for geographic region (US versus EU versus rest of world). Pooled analysis additionally adjusted for study factor (KGAB versus KGAC). All p-values were nominal.

Percentage of patients from those with a Pruritus NRS of ≥4-points at baseline re-randomised having achieved ≥4-point reduction from baseline at Week 16 who continue to exhibit ≥4-point reduction from baseline at Week 52

Lebrikizumab-responders who were re-randomised to treatment with lebrikizumab maintained Pruritus NRS 4-point improvement at Week 52 at numerically higher rates compared with those who were re-randomised to placebo (lebrikizumab withdrawal) (Table 39). Among patients in the pooled population, approximately 85% of patients treated with lebrikizumab 250 mg, either Q4W or Q2W, maintained Pruritus NRS 4-point improvement at Week 52, whereas 66.3% of patients in the placebo (lebrikizumab withdrawal) group maintained this response at Week 52.

Overall, the rates of maintenance of Pruritus NRS 4-point improvement were similar for patients treated with either lebrikizumab 250 mg Q4W or Q2W.

Table 39: Percentage of Patients Maintaining Pruritus NRS 4-Point Improvement at Week 52 Maintenance Primary Estimand (Hybrid) with MCMC-MI Week 16 LEB-Responders

	Study KGAB			Study KGAC			Pooled Studies KGAB and KGAC		
Maintenance Period	**PBO (LEB Withdrawal) N = 32**	**LEB 250mg Q4W N = 63**	**LEB 250mg Q2W N = 62**	**PBO (LEB Withdrawal) N = 28**	**LEB 250mg Q4W N = 55**	**LEB 250mg Q2W N = 51**	**PBO (LEB Withdrawal) N = 60**	**LEB 250mg Q4W N = 118**	**LEB 250mg Q2W N = 113**
Participants with Pruritus NRS 4-pt Improvement at W16 (Nx)	**17**	**29**	**38**	**11**	**36**	**23**	**28**	**65**	**61**
Maintained Response at W52, n (%)	11 (65.4)	23 (80.4)	31 (81.2)	7 (67.6)	32 (88.1)	21 (90.3)	19 (66.3)	55 (84.7)	52 (84.6)
Diff vs. PBO, % (95% CI)		15.8 (-12.2, 43.8)	16.6 (-9.4, 42.7)		20.3 (-11.4, 52.0)	20.4 (-10.6, 51.4)		17.7 (-3.1, 38.6)	18.1 (-1.7, 37.9)
p-value vs. PBO[a]		.268	.193		.159	.165		.077	.058

Abbreviations: CI = confidence interval; CSE = clinical summary of efficacy; CSR = clinical study report; Diff = difference; LEB = lebrikizumab; MCMC-MI = Markov Chain Monte Carlo multiple imputation; N = total number of participants; n = number of participants in the specified category; NRS = numeric rating scale; Nx = number of participants in analysis population; PBO = placebo; Pruritus NRS 4-pt Improvement = 4-point or greater improvement in Pruritus NRS, among participants with a baseline score of at least 4; Q2W = every 2 weeks; Q4W = every 4 weeks; W16 = Week 16; W52 = Week 52.

a Cochran-Mantel-Haenszel test adjusted for geographic region (US versus EU versus rest of world). Pooled analysis additionally adjusted for study factor (KGAB versus KGAC). All p-values are nominal.

Percentage change in EASI score from Baseline at Week 52 in the subset of patients who were re-randomised at Week 16

Lebrikizumab responders who were randomly reassigned to lebrikizumab Q4W or Q2W maintained numerically higher mean percentage improvement from Baseline in EASI response up to Week 52 compared with responders who were randomly reassigned to placebo (lebrikizumab withdrawal) (Table 40 and Table 41).

Table 40: Percentage change in EASI from Baseline at Week 52 in the subset of patients who were randomly reassigned at Week 16 (Study KGAB)

Percentage Change in EASI from Baseline	**PBO (LEB Withdrawal) N = 32**	**LEB Res/LEB 250mg Q4W N = 62**	**LEB Res/LEB 250mg Q2W N = 61**
Maintenance primary estimand (Hybrid): ANCOVA with MCMC-MI			
LSM (SE)	-60.67 (6.3)	-79.44 (4.5)	-77.93 (4.5)
p-value vs. PBO	NA	.012	.025

Table 41: Percentage change in EASI from Baseline at Week 52 in the subset of patients who were randomly reassigned at Week 16 (Study KGAC)

Percentage Change in EASI from Baseline	PBO (LEB Withdrawal) N = 28	LEB Res/LEB 250mg Q4W N = 55	LEB Res/LEB 250mg Q2W N = 51
Primary estimand (Hybrid): ANCOVA with MCMC-MI			
LSM (SE)	-72.9 (6.3)	-87.6 (4.4)	-77.2 (4.4)
p-Value vs. PBO	NA	0.057	0.575

For the above-mentioned endpoints for Maintenance Period (EASI 75; IGA 0, 1; Pruritus NRS ≥4-Point Improvement and EASI percent change from baseline) the results remained consistent when analysed according to the Maintenance Supportive Estimand (hybrid), i.e., including data regardless of topical rescue medication use.

Other Secondary Endpoints Specific for Maintenance Period

Among lebrikizumab-responders with EASI 75 at Week 16, proportions of patients achieving EASI 90 increased from Week 16 to Week 52 for groups re-randomised to treatment with lebrikizumab 250 mg Q4W or Q2W, while proportions of patients achieving EASI 90 decreased in groups re-randomised to placebo (lebrikizumab withdrawal). In the pooled population, 66.4% of patients treated Q4W and 64.0% of patients treated Q2W achieved EASI 90 at Week 52, compared with 41.9% of patients in the placebo (lebrikizumab withdrawal) group.

Table 42: Percentage of Patients with EASI 90 at Week 16 and Week 52 Maintenance Primary Estimand (Hybrid) with MCMC-MI Week 16 LEB-Responders

	Study KGAB			Study KGAC			Pooled Studies KGAB and KGAC		
Maintenance Period Rerandomization	PBO (LEB Withdrawal) N = 32	LEB 250mg Q4W N = 63	LEB 250mg Q2W N = 62	PBO (LEB Withdrawal) N = 28	LEB 250mg Q4W N = 55	LEB 250mg Q2W N = 51	PBO (LEB Withdrawal) N = 60	LEB 250mg Q4W N = 118	LEB 250mg Q2W N = 113
EASI 75 Responders at W16, Nx[a]	**30**	**62**	**61**	**27**	**53**	**51**	**57**	**115**	**112**
EASI 75 Responders with EASI 90 at W16, n (%)	21 (70.0)	39 (62.9)	40 (65.6)	15 (55.6)	30 (56.6)	29 (56.9)	36 (63.2)	69 (60.0)	69 (61.6)
EASI 75 Responders with EASI 90 at W52, n (%)	14 (45.2)	41 (66.6)	40 (66.1)	10 (38.2)	35 (66.2)	31 (61.5)	24 (41.9)	76 (66.4)	72 (64.0)
Diff vs. PBO, % (95% CI)		21.4 (-1.2, 44.1)	20.2 (-2.9, 43.2)		28.5 (4.4, 52.7)	23.3 (-1.0, 47.6)		24.8 (8.4, 41.1)	21.6 (4.9, 38.4)
p-value vs. PBO[b]		.064	.088		.024	.064		.004	.012

Abbreviations: CI = confidence interval; CSE = clinical summary of efficacy; CSR = clinical study report; Diff = difference; EASI = Eczema Area and Severity Index; EASI 75 = 75% improvement from Baseline in EASI; EASI 90 = 90% improvement from Baseline in EASI; LEB = lebrikizumab; MCMC-MI = Markov Chain Monte Carlo multiple imputation; N = total number of participants; n = number of participants in the specified category; Nx = number of participants in analysis population PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; W16 = Week 16; W52 = Week 52.

a Results for EASI 90 response were analyzed in lebrikizumab-responders with EASI 75 at Week 16.

b Cochran-Mantel-Haenszel test adjusted for geographic region (US versus EU versus rest of world). Pooled analysis additionally adjusted for study factor (KGAB versus KGAC). All p-values are nominal.

Study KGAB and KGAC Maintenance Week 16 Escape Population Results

Among patients who were treated with lebrikizumab 250 mg Q2W during the Induction Period and remained on lebrikizumab 250 mg Q2W through Week 52, 64 (40.0%) patients achieved IGA 0,1, 123 (76.9%) patients achieved EASI 75 and 76 (47.5%) patients achieved EASI 90.

Among patients who received placebo during the Induction Period, transitioned to lebrikizumab 250 mg Q2W treatment at Week 16, and remained on lebrikizumab 250 mg Q2W treatment through Week 52, 84 (52.5%) patients achieved IGA 0,1, 135 (83.9%) patients achieved EASI 75 and 98 (60.9%) patients achieved EASI 90.

Rescue medications

KGAB study

The most commonly used rescue treatment during both the Induction and Maintenance Blinded Periods was TCS (Table 43 and Table 44). During the Induction Period, 29.8% of the patients in the placebo group vs. 8.5% in the lebrikizumab group used TCS.

Table 43: Summary of AD Rescue therapy Induction Period (ITT Population)

AD Treatment	PBO (N = 141) n (%)	LEB 250mg Q2W (N = 283) n (%)	Total (N = 424) n (%)
Subjects with ≥1 rescue medication	47 (33.3)	31 (11.0)	78 (18.4)
Topical treatment	44 (31.2)	27 (9.5)	71 (16.7)
Topical corticosteroids	42 (29.8)	24 (8.5)	66 (15.6)
Low-moderate potency	38 (27.0)	20 (7.1)	58 (13.7)
High potency	15 (10.6)	6 (2.1)	21 (5.0)
Topical calcineurin inhibitor	9 (6.4)	4 (1.4)	13 (3.1)
Systemic treatment	11 (7.8)	7 (2.5)	18 (4.2)
Systemic corticosteroids	9 (6.4)	6 (2.1)	15 (3.5)
Immunosuppressant	1 (0.7)	2 (0.7)	3 (0.7)
Biologics	1 (0.7)	0	1 (0.2)
Phototherapy	0	0	0

Abbreviations: AD = atopic dermatitis; ITT = intent to treat; LEB = lebrikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks

Time to use of rescue therapy

Patients randomised to lebrikizumab 250 mg Q2W demonstrated a 73% reduction in the risk of initiating rescue therapy during the Induction Period compared to patients given placebo in Study KGAB (hazard ratio: 0.27, 95% CI: 0.17 to 0.42)

Table 44: Summary of AD Rescue therapy Maintenance Blinded Period (Maintenance Primary Population)

AD Treatment	PBO (LEB Withdrawal) (N = 32) n (%)	LEB 250mg Q4W (N = 63) n (%)	LEB 250mg Q2W (N = 62) n (%)	Total (N = 157) n (%)
Subjects with ≥1 rescue medication	5 (15.6)	11 (17.5)	6 (9.7)	22 (14.0)
Topical treatment	5 (15.6)	9 (14.3)	6 (9.7)	20 (12.7)
Topical corticosteroids	3 (9.4)	8 (12.7)	5 (8.1)	16 (10.2)
Low-Moderate Potency	2 (6.3)	6 (9.5)	2 (3.2)	10 (6.4)
High potency	2 (6.3)	3 (4.8)	3 (4.8)	8 (5.1)
Topical calcineurin inhibitor	2 (6.3)	1 (1.6)	2 (3.2)	5 (3.2)
Systemic treatment	0	2 (3.2)	0	2 (1.3)
Systemic corticosteroids	0	2 (3.2)	0	2 (1.3)
Immunosuppressant	0	0	0	0
Biologics	0	0	0	0
Phototherapy	0	0	0	0

Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.

In the Week 16 escape arm of the KGAB study (Week 16 to 52), any rescue therapy was used by:

- 40.6% of patients entering the escape arm from the Induction Period placebo arm (PBO/LEB), and
- 24.5% of those entering from the Induction Period lebrikizumab 250 mg Q2W arm (LEB/LEB)

Topical rescue therapy was used by 35.4% (PBO/LEB) and 23.6% (LEB/LEB), and systemic rescue therapy by 5.2% (PBO/LEB) and 2.8% (LEB/LEB), respectively.

KGAC study

The most commonly used rescue treatment during both the Induction and Maintenance Blinded Periods was TCS (Table 45 and Table 46). During the Induction Period, 37% of the patients in the placebo group vs. 16.7% in the lebrikizumab group used TCS.

Table 45: Summary of AD Rescue therapy Induction Period (mITT Population)

AD treatment	PBO (N = 146) n (%)	LEB 250 mg Q2W (N = 281) n (%)	Total (N = 427) n (%)
Participants with ≥1 rescue medication	**58 (39.7)**	**52 (18.5)**	**110 (25.8)**
Topical treatment	54 (37.0)	48 (17.1)	102 (23.9)
Topical corticosteroids	54 (37.0)	47 (16.7)	101 (23.7)
Low-moderate potency	24 (16.4)	27 (9.6)	51 (11.9)
High potency	36 (24.7)	25 (8.9)	61 (14.3)
Topical calcineurin inhibitor	6 (4.1)	8 (2.8)	14 (3.3)
Systemic treatment	9 (6.2)	8 (2.8)	17 (4.0)
Systemic corticosteroids	8 (5.5)	7 (2.5)	15 (3.5)
Immunosuppressant	2 (1.4)	2 (0.7)	4 (0.9)
Biologics	0	1 (0.4)	1 (0.2)
Phototherapy or photochemotherapy	0	0	0

Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; mITT = modified intent to treat; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks.

Time to first use of rescue therapy

Patients randomised to lebrikizumab 250 mg Q2W demonstrated a 65% reduction in the risk of initiating rescue therapy during the Induction Period compared to patients given placebo in Study KGAC (hazard ratio: 0.35, 95% CI: 0.24 to 0.52).

Table 46: Summary of AD Rescue therapy Maintenance Blinded Period (Modified Maintenance Primary Population)

AD treatment	PBO (LEB Withdrawal) (N = 28) n (%)	LEB 250 mg Q4W (N = 55) n (%)	LEB 250 mg Q2W (N = 51) n (%)	Total (N = 134) n (%)
Participants with ≥1 rescue medication	6 (21.4)	8 (14.5)	8 (15.7)	22 (16.4)
Topical treatment	6 (21.4)	7 (12.7)	7 (13.7)	20 (14.9)
Topical corticosteroids	5 (17.9)	6 (10.9)	6 (11.8)	17 (12.7)
Low-moderate potency	1 (3.6)	3 (5.5)	4 (7.8)	8 (6.0)
High potency	4 (14.3)	3 (5.5)	2 (3.9)	9 (6.7)
Topical calcineurin inhibitor	1 (3.6)	1 (1.8)	2 (3.9)	4 (3.0)
Systemic treatment	0	1 (1.8)	2 (3.9)	3 (2.2)
Systemic corticosteroids	0	1 (1.8)	1 (2.0)	2 (1.5)
Immunosuppressant	0	0	1 (2.0)	1 (0.7)
Biologics	0	0	0	0
Phototherapy or photochemotherapy	0	0	0	0

Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.

In the Week 16 Escape Arm of the KGAC study (Week 16 to 52), any rescue therapy was used by

- 43.5% of patients entering the escape arm from the Induction Period placebo arm (PBO/LEB), and
- 32% of those entering from the Induction Period lebrikizumab 250 mg Q2W arm (LEB/LEB)

Topical rescue therapy was used by 40.7% (PBO/LEB) and 32% (LEB/LEB), and systemic rescue therapy by 3.7% (PBO/LEB) and 2.4% (LEB/LEB), respectively.

KGAD study

In Study KGAD, which allowed use of low-to-mid-potency TCS and TCI by all patients, smaller proportions of patients in either treatment group used rescue therapy compared to the monotherapy studies. A total of 7 (10.6%) placebo-treated patients required 1 or more rescue therapies during the study, and rescue therapy was used by 6 (4.1%) lebrikizumab-treated patients (Table 47).

Table 47: Summary of Type of Rescue Medication Used

	PBO + TCS (N = 66) n (%)	LEB 250 mg Q2W + TCS (N = 145) n (%)
Participants with ≥1 AD rescue therapy	**7 (10.6)**	**6 (4.1)**
High potency TCS	**3 (4.5)**	**2 (1.4)**
Betamethasone	1 (1.5)	1 (0.7)
Clobetasol	1 (1.5)	1 (0.7)
Mometasone	1 (1.5)	0
Prednicarbate	1 (1.5)	0
Systemic therapy	**5 (7.6)**	**5 (3.4)**
Oral corticosteroids	4 (6.1)	5 (3.4)
Prednisone	2 (3.0)	3 (2.1)
Dexamethasone	0	1 (0.7)
Methylprednisolone; lidocaine	0	1 (0.7)
Prednisolone	1 (1.5)	0
Triamcinolone	1 (1.5)	0
Immunosuppressant	1 (1.5)	1 (0.7)
Ciclosporine	1 (1.5)	0
Methotrexate	0	1 (0.7)

Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; TCS = topical corticosteroids.

Concomitant topical treatment for AD in KGAD study

Topical corticosteroids

All patients in Study KGAD were required to use TCS at the start of the trial. Patients were allowed to taper, stop, and restart use as needed throughout the 16 weeks of the trial. Data from both the CRFs and patient diaries showed percentages of TCS use close to 100%. The 2 most commonly used TCS were triamcinolone and hydrocortisone, which were the products supplied by the study sites (Table 48).

Topical calcineurin inhibitors

TCI were permitted for use on sensitive areas only, but they were not supplied by the study sites. While case report form data showed similar rates of use between treatment groups, patient diary data indicated that a greater percentage of lebrikizumab-treated patients used TCI (Table 48).

Table 48: Summary of Concomitant Topical Treatment for AD

AD Treatment	PBO + TCS (N = 66) n (%)	LEB 250 mg Q2W + TCS (N = 145) n (%)	Total (N = 211) n (%)
Participants using topical therapy (case report form data)	**64 (97.0)**	**140 (96.6)**	**204 (96.7)**
Mild or moderate topical corticosteroids	**64 (97.0)**	**140 (96.6)**	**204 (96.7)**
Triamcinolone	61 (92.4)	130 (89.7)	191 (90.5)
Hydrocortisone	46 (69.7)	99 (68.3)	145 (68.7)
Desonide	0	1 (0.7)	1 (0.5)
Topical calcineurin inhibitors	**3 (4.5)**	**5 (3.4)**	**8 (3.8)**
Tacrolimus	3 (4.5)	3 (2.1)	6 (2.8)
Pimecrolimus	0	3 (2.1)	3 (1.4)
Crisaborole	0	0	0
Participants with ≥1 AD treatment (Participant Diary Data)	**66 (100)**	**144 (99.3)**	**210 (99.5)**
Topical corticosteroids	**62 (93.9)**	**140 (96.6)**	**202 (95.7)**
Triamcinolone acetonide cream 0.1%	53 (80.3)	124 (85.5)	177 (83.9)
Hydrocortisone 1% cream	47 (71.2)	103 (71.0)	150 (71.1)
Other TCS	13 (19.7)	31 (21.4)	44 (20.9)
Topical calcineurin inhibitors	**23 (34.8)**	**67 (46.2)**	**90 (42.7)**
Pimecrolimus 1%	13 (19.7)	27 (18.6)	40 (19.0)
Tacrolimus 0.03%	7 (10.6)	14 (9.7)	21 (10.0)
Tacrolimus 0.1%	21 (31.8)	33 (22.8)	54 (25.6)
Other TCI	12 (18.2)	42 (29.0)	54 (25.6)

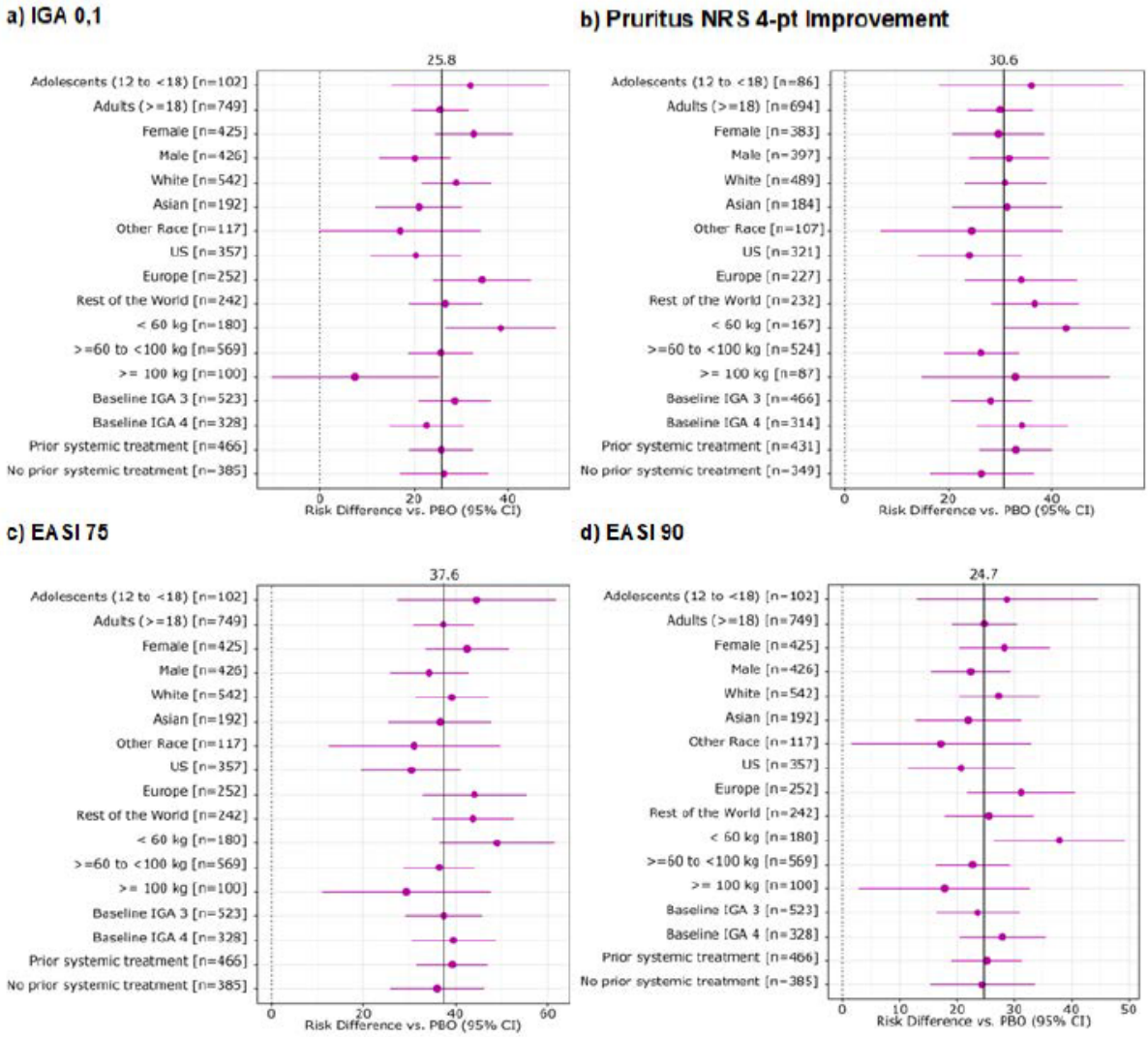
Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W = every 2 weeks; TCI = topical calcineurin inhibitor; TCS = topical corticosteroids.

Ancillary analyses

Subgroup Analysis - Induction period

Subgroup analyses of pooled data from the Induction Periods of Study KGAB and Study KGAC are shown in Figure 15. Subgroup analyses were conducted relative to primary estimand (hybrid), comparing the lebrikizumab 250 mg Q2W treatment group to placebo.

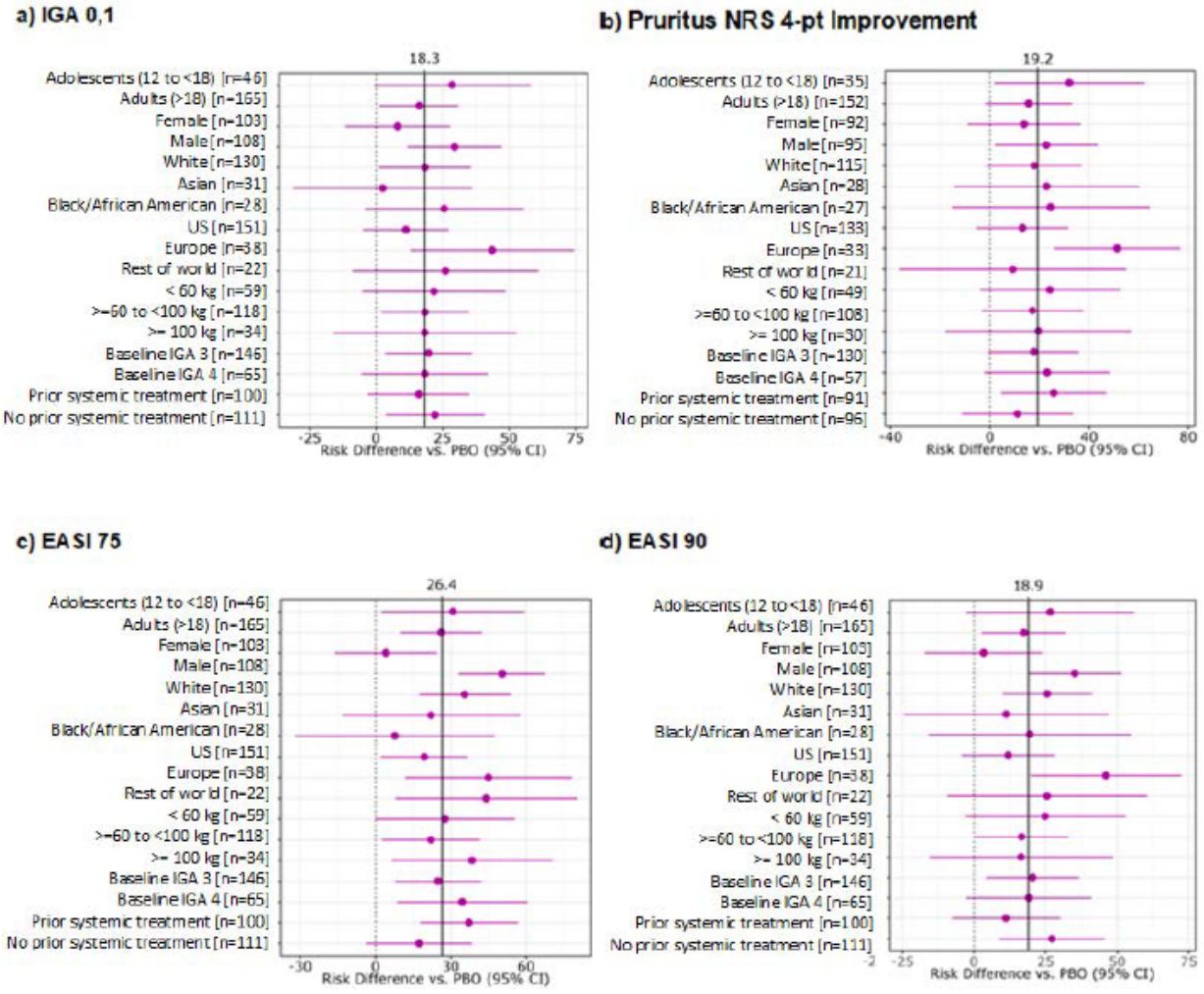
Figure 15: Subgroup analysis of pooled data from the Induction Periods of Study KGAB and Study KGAC at Week 16.



Abbreviations: CI = confidence interval; CSE = clinical summary of efficacy; EASI = Eczema Area and Severity Index; EASI 75 = 75% reduction from Baseline in EASI; EASI 90 = 90% reduction from Baseline in EASI; IGA = Investigator's Global Assessment; IGA 0,1 = IGA score of 0 or 1, with a 2-point or greater reduction from Baseline; n = number of participants in the specified category; NRS = numeric rating scale; PBO = placebo; Pruritus NRS 4-point Improvement = improvement of 4 or more points in Pruritus NRS among participants with a baseline score of at least 4.
Note: Risk differences adjusted for study factor (KGAB versus KGAC).

Figure 16 shows the subgroup analysis in KGAD study. According to the Applicant, if any group within the subgroup made up less than 10% of the total population, the subgroup was not included in the figure due to large variability.

Figure 16: Subgroup analysis of data from Study KGAD at Week 16.

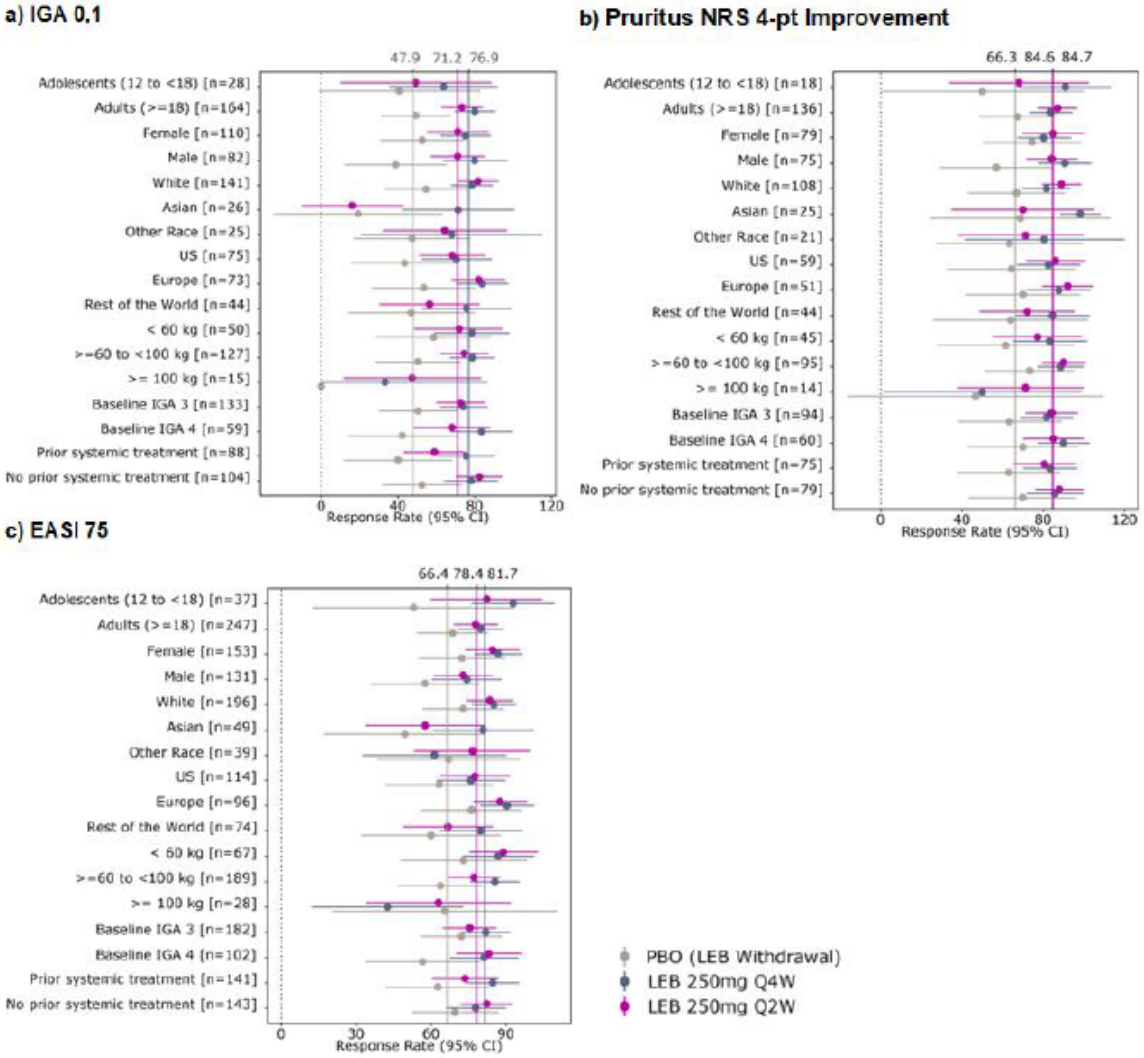


Abbreviations: CI = confidence interval; EASI = Eczema Area and Severity Index; EASI 75 = 75% reduction in EASI; EASI 90 = 90% reduction in EASI; IGA = Investigator's Global Assessment; IGA 0,1 = IGA score of 0 or 1, with a 2-point or greater reduction from Baseline; n = number of participants in the specified category; NRS = numeric rating scale; PBO = placebo; Pruritus NRS 4-point Improvement = improvement of 4 or more points in Pruritus NRS among participants with a baseline score of at least 4.

Subgroup Analysis – Maintenance period

Subgroup analyses of pooled data from the Maintenance Period of Study KGAB and Study KGAC are shown in Figure 17. Subgroup analyses were conducted relative to maintenance primary estimand (hybrid), comparing the treatment group re-randomised to lebrikizumab 250 mg Q4W to those re-randomised to placebo (lebrikizumab withdrawal) and the treatment group re-randomised to lebrikizumab 250 mg Q2W to those re-randomised to placebo (lebrikizumab withdrawal).

Figure 17: Subgroup analyses of pooled data from the Maintenance Periods of Study KGAB and Study KGAC at Week 52 for proportion of patients maintaining response. Populations with respective responses at Week 16.



Abbreviations: CI = confidence interval; CSE = clinical summary of efficacy; EASI = Eczema Area and Severity Index; EASI 75 = 75% improvement from Baseline in EASI; IGA = Investigator's Global Assessment; IGA 0,1 = IGA score of 0 or 1, with a 2-point or greater reduction from Baseline; LEB = lebrikizumab; MCMC-MI = Markov Chain Monte Carlo multiple imputation; NRS = numeric rating scale; PBO = placebo; Pruritus NRS 4-point Improvement = improvement of 4 or more points in Pruritus NRS among participants with a baseline score of at least 4; Q2W = every 2 weeks; Q4W = every 4 weeks.

Efficacy in adolescent population

The results for the adolescent population from the pivotal Phase 3 studies KGAB, KGAC and KGAD and shown in Table 49. The efficacy results for adolescents at Week 52 in studies KGAB and KGAC are shown in Table 50.

Table 49: Adolescent Results at Week 16 across Studies (MCMC-MI)

	Study KGAB		Study KGAC		Study KGAD	
	Week 16		Week 16		Week 16	
	PBO N = 18 n (%)	LEB 250 mg Q2W N = 37 n (%)	PBO N = 17 n (%)	LEB 250 mg Q2W N = 30 n (%)	PBO + TCS N = 14 n (%)	LEB 250 mg Q2W + TCS N = 32 n (%)
IGA 0 or 1[a]	4 (22.2)	18 (48.6)	1 (5.9)	13 (44.1)**	4 (28.6)	18 (57.3)
EASI 75[b]	4 (22.2)	23 (62.2)**	2 (12.0)	19 (61.7)**	8 (57.1)	28 (88.0)*
EASI 90[b]	3 (16.7)	17 (45.9)*	1 (6.1)	10 (34.3)*	4 (28.6)	18 (55.1)
Pruritus NRS (≥ 4-point improvement)[c]	4 (22.8)	17 (54.3)*	0 (0.3)	11 (42.1)[d]	2 (13.8)	11 (45.8)

Abbreviations: EASI = Eczema Area and Severity Index; EASI 75 = at least 75% improvement from baseline in EASI; EASI 90 = at least 90% improvement from baseline in EASI; IGA = Investigator's Global Assessment; KGAB = J2T-DM-KGAB; KGAC = J2T-DM-KGAC; KGAD = J2T-DM-KGAD; LEB = lebrikizumab; N = number of participants in adolescent subgroup; n = number of participants in specified category; Q2W = every 2 weeks; TCS = topical corticosteroid.

[a] At Week 16, participants with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥2 points from Baseline on a 0 to 4 IGA scale.

[b] At Week 16, participants with a 75% or 90% reduction in EASI from Baseline to Week 16.

[c] The percentage is calculated relative to the number of participants with a baseline Pruritus NRS ≥4. (KGAB Ns: PBO=17, LEB=31; KGAC Ns: PBO=13, LEB=25; KGAD Ns: PBO=11; LEB=24)

[d] Adolescent participants with baseline Pruritus NRS ≥4 made up less than 10% of the total population for Study KGAC; therefore, only summary statistics were prepared for this outcome.

*p<.05; **p<.01 versus placebo.

Table 50: Adolescent Results for Study KGAB and Study KGAC at Week 52 (MCMC-MI)

	Placebo (LEB Withdrawal)	Lebrikizumab 250 mg Q4W	Lebrikizumab 250 mg Q2W
IGA 0 or 1[a]			
Adolescent participants with response at W16, N	6	15	7
Participants maintaining response at W52, n (%)	2 (40.7)	10 (63.7)	3 (49.1)
EASI 75[b]			
Adolescent participants with response at W16, N	8	16	13
Participants maintaining response at W52, n (%)	4 (53.0)	15 (92.8)*	11 (82.2)
Pruritus NRS (≥ 4-point improvement), [c]			
Adolescent participants with response at W16, N	2	8	8
Participants maintaining response at W52, n (%)	1 (50.0)	7 (91.0)	5 (68.0)

Abbreviations: EASI = Eczema Area and Severity Index; EASI 75 = at least 75% improvement from baseline in EASI; IGA = Investigator's Global Assessment; KGAB = J2T-DM-KGAB; KGAC = J2T-DM-KGAC; LEB = lebrikizumab; N = number of participants in adolescent subgroup; n = number of participants in specified category; NRS = Numeric Rating Scale; Q2W = every 2 weeks; Q4W = every 4 weeks; W = Week.

[a] At Week 52, participants with IGA 0 or 1 with a ≥2-point improvement from Baseline at Week 16 who continued to exhibit IGA 0 or 1 with a ≥2-point improvement at Week 52.

[b] At Week 52, participants who achieved EASI 75 response at Week 16 and continued to exhibit EASI 75 at Week 52.

[c] The percentage is calculated relative to the number of participants with a baseline Pruritus NRS ≥4.

* p<.05

In study KGAE, the adolescent patients achieved IGA 0,1 response at rates of 46.3% at Week 16 and 62.6% at Week 52, and EASI 75 response at rates of 73.2% at Week 16 and 81.9% at Week 52 (see section 3.3.4.4).

2.6.5.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 51: Summary of Efficacy for Study KGAB

Title: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF LEBRIKIZUMAB IN PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS		
Study Identifier	J2T-DM-KGAB; DRM06-AD04	
Design	Phase 3, randomised, double-blind, placebo-controlled, parallel-group study	
	Duration of Induction Period Duration of Maintenance Period	16 weeks 36 weeks
Treatment Groups	The study comprises 2 treatment periods: • Induction: Participants were randomly assigned 2:1 to LEB 500-mg loading dose at baseline and Week 2 then 250 mg or PBO Q2W. • Maintenance: Participants who were LEB responders were randomly assigned 2:2:1 to LEB 250 mg Q2W, LEB 250 mg Q4W, or PBO (LEB withdrawal). • Participants who achieved neither IGA 0,1 nor EASI 75 at Week 16 or who received rescue therapy from baseline to Week 16 were assigned to an escape arm and received LEB 250 mg Q2W (following blinded 500-mg loading dose at Weeks 16 and 18 for participants who received PBO during Induction) as an open-label treatment through Week 52.	
Hypothesis	Superiority	
Induction Period	LEB Q2W subcutaneous injection	Randomised N = 283 LEB 500-mg at baseline and at Week 2 (loading dose), and LEB 250 mg Q2W from Week 4 through Week 14.
	PBO Q2W subcutaneous injection	Randomised N = 141 4-mL PBO at baseline and at Week 2, and 2-mL PBO Q2W from Week 4 through Week 14.
Maintenance Period	Maintenance Primary population (LEB responders)	Randomised N = 157 • LEB 250 mg Q2W (N = 62) • LEB 250 mg Q4W (N = 63) • PBO (LEB withdrawal) (N = 32)
	Maintenance Week 16 escape population	Assigned N = 202 Open-label LEB 250 mg Q2W through Week 52

	Participants who achieved neither IGA 0,1 nor EASI 75 at Week 16 or used any rescue medication during the Induction Period		• LEB 250 mg Q2W to LEB 250 mg Q2W (N = 106) • PBO to LEB 250 mg Q2W (N = 96)
Endpoints **Induction Period**	Coprimary endpoint	IGA 0,1	Percentage of participants with an IGA 0,1 and a reduction of ≥2 points from baseline to Week 16
	Coprimary endpoint	EASI 75	Percentage of participants achieving EASI 75 (≥75% reduction from baseline in EASI) at Week 16
	Major secondary endpoint	EASI 90, W16	Percentage of participants achieving EASI 90 (≥90% reduction from baseline in EASI) at Week 16
	Major secondary endpoint	EASI 90, W4	Percentage of participants achieving EASI 90 at Week 4
	Major secondary endpoint	EASI PCFB	Percentage change in EASI from baseline to Week 16
	Major secondary endpoint	Pruritus NRS PCFB	Percentage change in pruritus NRS score from baseline to Week 16
	Major secondary endpoint	Pruritus NRS 4-point improvement, W16	Percentage of participants with a pruritus NRS of ≥4 points at baseline who achieved a ≥4-point reduction from baseline to Week 16
	Major secondary endpoint	Pruritus NRS 4-point improvement, W4	Percentage of participants with a pruritus NRS of ≥4 points at baseline who achieved a ≥4-point reduction from baseline to Week 4
	Major secondary endpoint	Pruritus NRS 4-point improvement, W2	Percentage of participants with a pruritus NRS of ≥4 points at baseline who achieved a ≥4-point reduction from baseline to Week 2
	Major secondary endpoint	DLQI CFB	CFB in DLQI total score at Week 16
	Major secondary endpoint	DLQI 4-point improvement	Percentage of participants with a DLQI total score of ≥4 points at baseline who achieved a ≥4-point improvement from baseline to Week 16
	Major secondary endpoint	Sleep-Loss CFB	CFB in Sleep-Loss score at Week 16
	Major secondary endpoint	Sleep-Loss, 2-point improvement	Percentage of participants with a Sleep-Loss score ≥2 points at baseline who achieve a ≥2-points reduction from baseline at Week 16
	Other endpoint	POEM	CFB in POEM at Week 16

Endpoints **Maintenance Period**	Major secondary endpoint	EASI 75	Percentage of participants from those randomly reassigned having achieved EASI 75 at Week 16 who continue to exhibit EASI 75 at Week 52 (EASI 75 calculated relative to baseline EASI)	
	Major secondary endpoint	IGA 0,1	Percentage of participants from those randomly reassigned having achieved IGA 0,1 and a ≥2-point improvement from baseline at Week 16 who continue to exhibit IGA 0,1 and a ≥2-point improvement from baseline at Week 52	
	Major secondary endpoint	Pruritus 4-point improvement	Percentage of participants from those with a pruritus NRS of ≥4-points at baseline randomly reassigned having achieved ≥4-point reduction from baseline at Week 16 who continue to exhibit ≥4-point reduction from baseline at Week 52	
	Major secondary endpoint	EASI PCFB	Percentage change in EASI from baseline at Week 52 in the subset of participants who were randomly reassigned at Week 16	
	Other endpoint	EASI 90	Percentage of participants with EASI 90 at Week 52 in the subset of participants who achieved EASI 75 and randomly reassigned at Week 16 (EASI 90 calculated relative to baseline EASI)	
Endpoints **Maintenance Week 16** **Escape Population**	Other endpoint	IGA 0,1	Percentage of participants with IGA 0,1 and a ≥2-point improvement at Week 52	
	Other endpoint	EASI 75	Percentage of participants with EASI 75 at Week 52 (EASI 75 calculated relative to baseline EASI)	
	Other endpoint	EASI 90	Percentage of participants with EASI 90 at Week 52 (EASI 90 calculated relative to baseline EASI)	
	Other endpoint	Pruritus NRS	Percentage of participants with a pruritus NRS of ≥4 points at baseline with ≥4-point reduction at Week 52	
Multiplicity Adjustment	Two families for alpha control were defined: 1 for induction and 1 for maintenance with each family-wise error rate at 0.05. For all primary and key secondary endpoints for Induction Period, a prespecified graphical multiple testing approach was implemented to control the overall Type I error rate at 2-sided alpha of 0.05. For all maintenance key secondary endpoints, a hierarchal testing scheme with a prespecified order was implemented with a family-wise error rate at 0.05.			
Database Lock	29 April 2022			
Induction Period – Results and Analysis – IGA 0,1 at Week 16				
Analysis Description	**Coprimary endpoint:** Percentage of participants with an IGA 0,1 and a reduction of ≥2 points from baseline to Week 16			
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]			
	Treatment group		PBO	LEB 250 mg Q2W
	Number of participants (Nx)		141	283

Descriptive Statistics and Estimate Variability	Response, n (%)	18 (12.7)	122 (43.1)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	Common risk difference (95% CI)		29.7 (21.6, 37.8)
	p-value		<.001
Induction Period – Results and Analysis – EASI 75 at Week 16			
Analysis Description	**Coprimary endpoint:** Percentage of participants achieving EASI 75 (≥75% reduction from baseline in EASI) at Week 16		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants (Nx)	141	283
	Response, n (%)	23 (16.2)	166 (58.8)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	Common risk difference (95% CI)		42.0 (33.3, 50.6)
	p-value		<.001
Induction Period – Results and Analysis – EASI 90 at Week 16			
Analysis Description	**Major secondary endpoint:** Percentage of participants achieving EASI 90 (≥90% reduction from baseline in EASI) at Week 16		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants (Nx)	141	283
	Response, n (%)	13 (9.0)	108 (38.3)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	Common risk difference (95% CI)		28.8 (21.3, 36.3)
	p-value		<.001
Induction Period – Results and Analysis – EASI 90 at Week 4			
Analysis Description	**Major secondary endpoint:** Percentage of participants achieving EASI 90 at Week 4		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
	Treatment group	PBO	LEB 250 mg Q2W

Descriptive Statistics and Estimate Variability	Number of participants (Nx)	141	283
	Response, n (%)	2 (1.6)	35 (12.4)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	Common risk difference (95% CI)		10.7 (6.2, 15.2)
	p-value		<.001
Induction Period – Results and Analysis – EASI PCFB			
Analysis Description	**Major secondary endpoint:** Percentage change in EASI from baseline to Week 16		
Statistical Model	Primary estimand (hybrid): ANCOVA with MCMC-MI[b]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants (Nx)	141	283
	LSM (SE)	− 26.0 (4.0)	− 64.3 (3.2)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	LSM difference (95% CI)		−38.3 (−46.4, −30.2)
	p-value		<.001
Induction Period – Results and Analysis – Pruritus NRS PCFB			
Analysis Description	**Major secondary endpoint:** Percentage change in pruritus NRS score from baseline to Week 16		
Statistical Model	Primary estimand (hybrid): ANCOVA with MCMC-MI[b]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants with baseline Pruritis NRS score greater than 0 (Nx)	136	276
	LSM (SE)	−15.1 (3.8)	−45.5 (3.1)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	LSM difference (95% CI)		−30.4 (−38.1, −22.7)
	p-value		<.001
Induction Period – Results and Analysis – Pruritus NRS 4-Point Iimprovement at Week 16			
Analysis Description	**Major secondary endpoint:** Percentage of participants with a pruritus NRS of ≥4 points at baseline who achieve a ≥4-point reduction from baseline to Week 16		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		

Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants with baseline pruritus NRS score ≥4 (Nx)	130	263
	Response, n (%)	17 (13.0)	121 (45.9)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	Common risk difference (95% CI)		32.9 (24.6, 41.3)
	p-value		<.001
Induction Period – Results and Analysis – Pruritus NRS 4-Point Improvement at Week 4			
Analysis Description	**Major secondary endpoint:** Percentage of participants with a pruritus NRS of ≥4 points at baseline who achieve a ≥4-point reduction from baseline to Week 4		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants with baseline pruritus NRS score ≥4 (Nx)	130	263
	Response, n (%)	3 (2.3)	56 (21.5)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	Common risk difference (95% CI)		19.3 (13.7, 25.0)
	p-value		<.001
Induction Period – Results and Analysis – Pruritus NRS 4-Point Improvement at Week 2			
Analysis Description	**Major secondary endpoint:** Percentage of participants with a pruritus NRS of ≥4 points at baseline who achieve a ≥4-point reduction from baseline to Week 2		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants with baseline pruritus NRS score ≥4 (Nx)	130	263
	Response, n (%)	1 (0.9)	16 (6.1)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	Common risk difference (95% CI)		5.3 (1.9, 8.6)
	p-value		.017
Induction Period – Results and Analysis – DLQI CFB			
Analysis Description	**Major secondary endpoint:** CFB in DLQI total score at Week 16		

Statistical Model	Primary estimand (hybrid): ANCOVA with MCMC-MI[b]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants with non-missing baseline DLQI score (Nx)	121	239
	LSM (SE)	−2.9 (1.1)	−8.7 (1.1)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	LSM difference (95% CI)		−5.8 (−7.1, −4.5)
	p-value		<.001
Induction Period – Results and Analysis – DLQI 4-Point Improvement at Week 16			
Analysis Description	**Major secondary endpoint:** Percentage of participants with a DLQI total score of ≥4 points at baseline who achieve a ≥4-point improvement from baseline to Week 16		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants with baseline DLQI score of at least 4 (Nx)	116	226
	Response, n (%)	39 (33.8)	171 (75.6)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	Common risk difference (95% CI)		41.8 (31.2, 52.3)
	p-value		<.001
Induction Period – Results and Analysis – Sleep-Loss Scale Score CFB			
Analysis Description	**Major secondary endpoint:** CFB in Sleep-Loss score at Week 16		
Statistical Model	Primary estimand (hybrid): ANCOVA with MCMC-MI[b]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants with non-missing baseline Sleep-Loss scale score (Nx)	136	276
	LSM (SE)	−0.4 (0.1)	−1.1 (0.1)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	LSM difference (95% CI)		−0.8 (−0.9, −0.6)
	p-value		<.001
Induction Period – Results and Analysis – Sleep-Loss Scale Score 2-Point Improvement at Week 16			

Analysis Description	**Major secondary endpoint:** Percentage of participants with a Sleep-Loss scale score of ≥2 points at baseline who achieve a ≥2-point reduction from baseline at Week 16		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants with baseline Sleep-Loss score of at least 2 (Nx)	91	195
	Response, n (%)	4 (4.7)	76 (39.0)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q2W versus PBO	
	Common risk difference (95% CI)	34.6 (26.2, 43.0)	
	p-value	<.001	
Induction Period – Results and Analysis – POEM CFB			
Analysis Description	**Other endpoint:** CFB in POEM at Week 16		
Statistical Model	Supportive estimand for continuous endpoints (hypothetical): MMRM[c]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants (Nx)	133	275
	LSM (SE)	−3.9 (0.7)	−11.3 (0.5)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q2W versus PBO	
	LSM difference (SE)	−7.3 (0.8)	
	p-value	<.001	
Maintenance Period – Results and Analysis – EASI 75 at Week 52			
Analysis Description	**Maintenance major secondary endpoint:** Percentage of participants from those randomly reassigned, having achieved EASI 75 at Week 16 who continue to exhibit EASI 75 at Week 52 (EASI calculated relative to baseline EASI score)		
Statistical Model	Maintenance primary estimand (hybrid): CMH with MCMC-MI[d]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO (LEB withdrawal)	LEB 250 mg Q4W	LEB 250 mg Q2W
	Participants with EASI 75 at Week 16 (Nx)	30	62	61
	Maintained response at Week 52, n (%)	18 (61.3)	49 (79.2)	48 (79.2)
	Comparison groups	LEB 250 mg Q4W vs PBO		LEB 250 mg Q2W vs PBO

Effect Estimate per Comparison	Common risk difference n, (95% CI)	17.9 (−2.3, 38.1)		17.5 (−4.5, 39.5)
	p-value	.072		.107
Maintenance Period – Results and Analysis – IGA 0,1 at Week 52				
Analysis Description	**Maintenance major secondary endpoint:** Percentage of participants from those randomly reassigned, having achieved IGA 0,1 and a >2-point improvement from baseline at Week 16 who continue to exhibit an IGA 0,1 and a >2-point improvement from baseline at Week 52			
Statistical Model	Maintenance primary estimand (hybrid): CMH with MCMC-MI[d]			
Descriptive Statistics and Estimate Variability	Treatment group	PBO (LEB withdrawal)	LEB 250 mg Q4W	LEB 250 mg Q2W
	Participants with IGA 0,1 at W16 (Nx)	22	45	45
	Maintained response at Week 52, n (%)	10 (46.5)	33 (74.2)	34 (75.8)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q4W vs PBO		LEB 250 mg Q2W vs PBO
	Common risk difference n, (95% CI)	28.0 (2.8, 53.2)		29.0 (4.6, 53.3)
	p-value	.030		.020
Maintenance Period – Results and Analysis – Pruritus NRS 4-Point Improvement at Week 52				
Analysis Description	**Maintenance major secondary endpoint:** Percentage of participants from those with a pruritus NRS of ≥4 points at baseline who were randomly reassigned having achieved ≥4-point reduction from baseline at Week 16 who continue to exhibit ≥4-point reduction from baseline at Week 52			
Statistical Model	Maintenance primary estimand (hybrid): CMH with MCMC-MI[d]			
Descriptive Statistics and Estimate Variability	Treatment group	PBO (LEB withdrawal)	LEB 250 mg Q4W	LEB 250 mg Q2W
	Participants with pruritus NRS 4-point improvement at W16 (Nx)	17	29	38
	Maintained response at Week 52, n (%)	11 (65.4)	23 (80.4)	31 (81.2)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q4W vs PBO		LEB 250 mg Q2W vs PBO
	Common risk difference n, (95% CI)	15.8 (−12.2, 43.8)		16.6 (−9.4, 42.7)
	p-value	.268		.193
Maintenance Period – Results and Analysis – EASI PCFB				
Analysis Description	**Maintenance major secondary endpoint:** Percentage change in EASI from baseline at Week 52 in the subset of participants who were randomly reassigned at Week 16			
Statistical Model	Maintenance primary estimand (hybrid): ANCOVA with MCMC-MI[e]			

Descriptive Statistics and Estimate Variability	Treatment group	PBO (LEB withdrawal)	LEB 250 mg Q4W	LEB 250 mg Q2W
	Number of participants (Nx)	32	62	61
	LSM (SE)	−60.67 (6.3)	−79.44 (4.5)	−77.93 (4.5)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q4W vs PBO		LEB 250 mg Q2W vs PBO
	LSM difference (95% CI)	−18.77 (7.5)		−17.26 (7.7)
	p-value	.012		.025
Maintenance Period – Results and Analysis – EASI 90 at Week 52				
Analysis Description	**Other endpoint:** Percentage of participants with EASI 90 at Week 52 in the subset of participants who achieved EASI 75 and were randomly reassigned at Week 16 (EASI 90 calculated relative to baseline EASI)			
Statistical model	Maintenance primary estimand (hybrid): CMH with MCMC-MI[d]			
Descriptive statistics and estimate variability	Treatment group	PBO (LEB withdrawal)	LEB 250 mg Q4W	LEB 250 mg Q2W
	Participants with EASI 75 at Week 16 (Nx)	30	62	61
	Response, n (%)	14 (45.2)	41 (66.6)	40 (66.1)
Effect estimate per comparison	Comparison groups	LEB 250 mg Q4W vs PBO		LEB 250 mg Q2W vs PBO
	Common risk difference n, (95% CI)	21.4 (−1.2, 44.1)		20.2 (−2.9, 43.2)
	p-value	.064		.088
Maintenance Week 16 Escape Population – Results and Analysis – IGA 0,1 and 2-Point Improvement at Week 52				
Analysis Description	**Other endpoint:** Percentage of participants with IGA 0,1 and a ≥2-point improvement at Week 52			
Statistical Model	Descriptive statistics with observed data			
Descriptive Statistics and Estimate Variability	Treatment group	PBO nonresponders to LEB 250 mg Q2W		LEB nonresponders to LEB 250 mg Q2W
	Number of participants (Nx)	76		77
	Response, n (%)	42 (55.3)		30 (39.0)
Maintenance Week 16 Escape Population – Results and Analysis – EASI 75 at Week 52				
Analysis Description	Percentage of participants with EASI 75 at Week 52 (EASI 75 calculated relative to baseline EASI)			
Statistical Model	Descriptive statistics with observed data			

Descriptive Statistics and Estimate Variability	Treatment group	PBO nonresponders to LEB 250 mg Q2W	LEB nonresponders to LEB 250 mg Q2W
	Number of participants (Nx)	76	77
	Response, n (%)	66 (86.8)	62 (80.5)
Maintenance Week 16 Escape Population – Results and Analysis – EASI 90 at Week 52			
Analysis Description	**Other endpoint:** Percentage of participants with EASI 90 at Week 52 (EASI 90 calculated relative to baseline EASI)		
Statistical Model	Descriptive statistics with observed data		
Descriptive Statistics and Estimate Variability	Treatment group	PBO nonresponders to LEB 250 mg Q2W	LEB nonresponders to LEB 250 mg Q2W
	Number of participants (Nx)	76	77
	Response, n (%)	52 (68.4)	38 (49.4)
Maintenance Week 16 Escape Population – Results and Analysis – Pruritus NRS 4-Point Improvement at Week 52			
Analysis Description	**Other endpoint:** Percentage of participants with a pruritus NRS of ≥4 points at baseline with ≥4-point reduction at Week 52		
Statistical Model	Descriptive statistics with observed data		
Descriptive Statistics and Estimate Variability	Treatment group	PBO nonresponders to LEB 250 mg Q2W	LEB nonresponders to LEB 250 mg Q2W
	Number of participants (Nx)	73	67
	Response, n (%)	46 (63.0)	52 (77.6)
Analyses			
[a] Primary estimand (hybrid), CMH-MCMC-MI: Participants who received any topical or systemic rescue medication, or discontinued treatment due to lack of efficacy had values set to their baseline value after this time through Week 16; MCMC-MI was used to handle the remaining missing data. CMH test stratified by geographic region, age group, and baseline IGA. [b] Primary estimand (hybrid), ANCOVA with MCMC-MI: Participants who received any topical or systemic rescue medication, or discontinued treatment due to lack of efficacy had values set to their baseline value after this time through Week 16; MCMC-MI was used to handle the remaining missing data. ANCOVA model adjusted for treatment group, baseline value, geographic region, age group, and baseline IGA. [c] Supportive estimand (hypothetical), MMRM: Data after topical or systemic rescue medication or treatment discontinuation were treated as missing and missing data were handled by MMRM. The MMRM model includes treatment, baseline value, visit, the interaction of the baseline value-by-visit, the interaction of treatment-by-visit, and the stratification factors as fixed factors.			

[d] Maintenance primary estimand (hybrid), CMH-MCMC-MI: Participants who received systemic rescue medication, discontinued treatment due to lack of efficacy, or transferred to escape arm had values set to their baseline value after this time through Week 52; participants who received topical rescue medication or discontinued treatment due to other reasons had values set to missing; MCMC-MI was used to handle the remaining missing data. CMH test stratified by geographic region.

[e] Maintenance primary estimand (hybrid), ANCOVA with MCMC-MI: Participants who received systemic rescue medication, discontinued treatment due to lack of efficacy, or transferred to escape arm had values set to their baseline value after this time through Week 52; participants who received topical rescue medication or discontinued treatment due to other reasons had values set to missing; MCMC-MI was used to handle the remaining missing data. ANCOVA model adjusted for geographic region.

Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI 75 = at least 75% reduction in EASI; EASI 90 = at least 90% reduction in EASI; IGA = Investigator's Global Assessment; LEB = lebrikizumab; LSM = least squares mean; MCMC-MI = Markov Chain Monte Carlo Multiple Imputation; MMRM = Mixed Model Repeated Measures; N = total number of participants; n = calculated number of participants experiencing endpoint; NRS = Numerical Rating Scale; Nx = number of participants in the analysis population; PBO = placebo; PCFB = percentage change from baseline; POEM = Patient Oriented Eczema Measure; Q2W = every 2 weeks; Q4W = every 4 weeks; SE = standard error; vs = versus; W= week.

Table 52: Summary of Efficacy for Study KGAC

Title: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF LEBRIKIZUMAB IN PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS		
Study Identifier	J2T-DM-KGAC; DRM06-AD05	
Design	Phase 3, randomised, double-blind, placebo-controlled, parallel-group study	
	Duration of Induction Period Duration of Maintenance Period	16 weeks 36 weeks
Treatment Groups	The study comprises 2 treatment periods: • Induction: Participants were randomly assigned 2:1 to LEB 500 mg loading dose at baseline and Week 2 then 250 mg Q2W or PBO. • Maintenance: Participants who were LEB responders were randomly assigned 2:2:1 to LEB 250 mg Q2W, LEB 250 mg Q4W, or PBO (LEB withdrawal). • Participants who achieved neither IGA 0,1 nor EASI 75 at Week 16 or who received rescue therapy from Baseline to Week 16 were assigned to an escape arm and received LEB 250 mg Q2W (following blinded 500 mg loading dose at Weeks 16 and 18 for participants who received PBO during Induction) as an open-label treatment through Week 52.	
Hypothesis	Superiority	
Induction Period	LEB Q2W subcutaneous injection	Randomised N = 295 LEB 500-mg at baseline and at Week 2 (loading dose), and LEB 250 mg Q2W from Week 4 through Week 14

	PBO Q2W subcutaneous injection		Randomised N = 150 4-mL PBO at baseline and at Week 2, and 2-mL PBO Q2W from Week 4 through Week 14
Maintenance Period	Maintenance primary population (LEB responders)		Re-randomised N = 148 • LEB 250 mg Q2W (N = 30) • LEB 250 mg Q4W (N = 59) • PBO (LEB withdrawal) (N = 59)
	Maintenance Week 16 Escape Population: Participants who achieved neither IGA 0,1 nor EASI 75 at Week 16 or used any rescue medication during the Induction Period		Assigned N = 233 Open-label LEB 250 mg Q2W through Week 52 • LEB 250 mg Q2W to LEB 250 mg Q2W (N = 125) • PBO to LEB 250 mg Q2W (N = 108)
Endpoints **Induction Period**	Coprimary endpoint	IGA 0,1	Percentage of participants with an IGA score of 0 or 1 and a reduction ≥2 points from baseline to Week 16
	Coprimary endpoint	EASI 75	Percentage of participants achieving EASI 75 (at least 75% reduction from baseline in EASI) at Week 16
	Major secondary endpoint	EASI 90, W16	Percentage of participants achieving EASI 90 at least (≥90% reduction from baseline in EASI) at Week 16
	Major secondary endpoint	EASI 90, W4	Percentage of participants achieving EASI 90 at Week 4
	Major secondary endpoint	EASI PCFB	Percentage change in EASI score from baseline to Week 16
	Major secondary endpoint	Pruritus NRS PCFB	Percentage change in pruritus NRS score from baseline to Week 16
	Major secondary endpoint	Pruritus NRS 4-point Improvement, W16	Percentage of participants with a pruritus NRS score of ≥4 points at baseline who achieved a ≥4-point reduction from baseline to Week 16
	Major secondary endpoint	Pruritus NRS 4-point Improvement, W4	Percentage of participants with a pruritus NRS score of ≥4 points at baseline who achieved a ≥4-point reduction from baseline to Week 4
	Major secondary endpoint	Pruritus NRS 4-point Improvement, W2	Percentage of participants with a pruritus NRS of ≥4 points at baseline who achieve a ≥4-point reduction from baseline to Week 2

	Major secondary endpoint	DLQI CFB	CFB in DLQI total score at Week 16
	Major secondary endpoint	DLQI 4-pt Improvement	Percentage of participants with a DLQI total score of ≥4 points at baseline who achieve a ≥4-point improvement from baseline to Week 16
	Major secondary endpoint	Sleep-Loss CFB	CFB in Sleep-Loss scale score at Week 16
	Major secondary endpoint	Sleep-Loss, 2-point Improvement	Percentage of participants with a Sleep-Loss scale score ≥2 points at baseline who achieve a ≥2-point reduction from baseline at Week 16
	Other Endpoint	POEM	CFB in POEM at Week 16
Endpoints **Maintenance Period**	Major secondary endpoint	EASI 75	Percentage of participants having achieved EASI 75 at Week 16 who continued to experience EASI 75 at Week 52 (EASI 75 calculated relative to baseline EASI)
	Major secondary endpoint	IGA 0,1	Percentage of participants from those randomly re-assigned, having achieved IGA 0,1 and a ≥2-point improvement from baseline at Week 16 who continue to exhibit an IGA 0,1 and a ≥2-point improvement from baseline at Week 52
	Major secondary endpoint	Pruritus 4-point Improvement	Percentage of participants from those with a pruritus NRS of ≥4-points at baseline randomly re-assigned, having achieved ≥4-point reduction from baseline at Week 16 who continue to exhibit ≥4-point reduction from baseline at Week 52
	Major secondary endpoint	EASI PCFB	Percentage change in EASI from baseline at Week 52 in the subset of participants who were randomly reassigned at Week 16
	Other endpoint	EASI 90	Percentage of participants with EASI 90 at Week 52 in the subset of participants who achieved EASI 75 and randomly reassigned at Week 16 (EASI 90 calculated relative to baseline EASI)
Endpoints Maintenance **Escape Population**	Other endpoint	IGA 0,1	Percentage of participants achieving an IGA score of 0 or 1 and a ≥2-point improvement from baseline at Week 52
	Other endpoint	EASI 75	Percentage of participants with EASI 75 at Week 52 (EASI 75 calculated relative to baseline EASI)
	Other endpoint	EASI 90	Percentage of participants with EASI 90 at Week 52 (EASI 90 calculated relative to baseline EASI)

	Other endpoint	Pruritus NRS	Percentage of participants reporting a pruritus NRS score of ≥4 points at baseline with ≥4-point reduction from baseline at Week 52	
Multiplicity Adjustment	Two families for alpha control were defined: 1 for induction and 1 for maintenance with each family-wise error rate at 0.05. For all primary and key secondary endpoints for Induction Period, a prespecified graphical multiple testing approach was implemented to control the overall Type I error rate at 2-sided alpha of 0.05. For all maintenance key secondary endpoints, a hierarchal testing scheme with a prespecified order was implemented with a family-wise error rate at 0.05.			
Database Lock	03 May 2022			
Induction Period – Results and Analysis – IGA 0,1 at Week 16				
Analysis Description	**Coprimary endpoint:** Percentage of participants with an IGA score of 0 or 1 and a reduction of ≥2 points from baseline to Week 16			
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]			
Descriptive Statistics and Estimate Variability	Treatment group		PBO	LEB 250 mg Q2W
	Number of participants (Nx)		146	281
	Response, n (%)		16 (10.8)	93 (33.2)
Effect Estimate per Comparison	Comparison groups			LEB 250 mg Q2W versus PBO
	Common risk difference (95% CI)			21.9 (14.2, 29.6)
	p-value			<.001
Induction Period – Results and Analysis – EASI 75 at Week 16				
Analysis Description	**Coprimary endpoint:** Percentage of participants achieving EASI 75 at least (≥75% reduction from baseline in EASI) at Week 16			
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]			
Descriptive Statistics and Estimate Variability	Treatment group		PBO	LEB 250 mg Q2W
	Number of participants (Nx)		146	281
	Response, n (%)		26 (18.1)	146 (52.1)
Effect Estimates per Comparison	Comparison groups			LEB 250 mg Q2W versus PBO
	Common risk difference (95% CI)			33.3 (24.4, 42.2)
	p-value			<.001
Induction Period – Results and Analysis – EASI 90 at Week 16				
Analysis Description	**Major secondary endpoint:** Percentage of participants achieving EASI 90 at least (≥90% reduction from baseline in EASI) at Week 16			
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]			
	Treatment group		PBO	LEB 250 mg Q2W

Descriptive Statistics and Estimate Variability	Number of participants (Nx)	146	281
	Response, n (%)	14 (9.5)	86 (30.7)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	Common risk difference (95% CI)		20.7 (13.3, 28.1)
	p-value		<.001
Induction Period – Results and Analysis – EASI 90 at Week 4			
Analysis Description	**Major secondary endpoint:** Percentage of participants achieving EASI 90 at Week 4		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants (Nx)	146	281
	Response, n (%)	2 (1.5)	18 (6.3)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	Common risk difference (95% CI)		4.9 (1.4, 8.4)
	p-value		.023
Induction Period – Results and Analysis – EASI PCFB			
Analysis Description	**Major secondary endpoint:** Percentage change in EASI score from baseline to Week 16		
Statistical Model	Primary estimand (hybrid): ANCOVA with MCMC-MI[b]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants (Nx)	146	281
	LSM (SE)	−28.0 (3.9)	−61.5 (3.3)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	LSM difference (95% CI)		−33.6 (−41.2, -26.0)
	p-value		<.001
Induction Period – Results and Analysis – Pruritus NRS PCFB			
Analysis Description	**Major secondary endpoint:** Percentage change in pruritus NRS score from baseline to Week 16		
Statistical Model	Primary estimand (hybrid): ANCOVA with MCMC-MI[b]		
	Treatment group	PBO	LEB 250 mg Q2W

Descriptive Statistics and Estimate Variability	Number of participants in the mITT population with baseline Pruritis NRS score >0 (Nx)	143	268
	LSM (SE)	−9.0 (3.9)	−36.6 (3.3)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	LSM difference (95% CI)		−27.5 (−34.9, −20.2)
	p-value		<.001
Induction Period – Results and Analysis – Pruritus NRS 4-Point Improvement at Week 16			
Analysis Description	**Major secondary endpoint:** Percentage of participants with a pruritus NRS score of ≥4 points at baseline who achieved a ≥4-point reduction from baseline to Week 16		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants in the mITT population with a baseline pruritus NRS score ≥4 (Nx)	134	253
	Response, n (%)	15 (11.5)	101 (39.8)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q2W versus PBO	
	Common risk difference (95% CI)	28.3 (20.0, 36.5)	
	p-value	<.001	
Induction Period – Results and Analysis – Pruritus NRS 4-Point Improvement at Week 4			
Analysis Description	**Major secondary endpoint:** Percentage of participants with a pruritus NRS score of ≥4 points at baseline who achieved a ≥4-point reduction from baseline to Week 4		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants in the mITT population with a baseline pruritus NRS score ≥4 (Nx)	134	253
	Response, n (%)	4 (3.0)	42 (16.8)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q2W versus PBO	
	Common risk difference (95% CI)	13.2 (7.7, 18.7)	

	p-value	<.001	
Induction Period – Results and Analysis – Pruritus NRS 4-Point Improvement at Week 2			
Analysis Description	**Major secondary endpoint:** Percentage of participants with a Pruritus NRS of ≥4 points at baseline who achieve a ≥4-point reduction from baseline to Week 2		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants in the mITT population with a baseline pruritus NRS score ≥4 (Nx)	134	253
	Response, n (%)	1 (0.7)	9 (3.6)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q2W versus PBO	
	Common risk difference (95% CI)	2.7 (−0.1, 5.4)	
	p-value	.113	
Induction Period – Results and Analysis – DLQI CFB			
Analysis Description	**Major secondary endpoint:** CFB in DLQI total score at Week 16		
Statistical Model	Primary estimand (hybrid): ANCOVA with MCMC-MI[b]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants in the mITT population with non-missing baseline DLQI score (Nx)	118	218
	LSM (SE)	−2.4 (1.2)	−7.3 (1.2)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q2W versus PBO	
	LSM difference (95% CI)	−4.9 (−6.3, −3.5)	
	p-value	<.001	
Induction Period – Results and Analysis – DLQI 4-Point Improvement at Week 16			
Analysis Description	**Major secondary endpoint:** Percentage of participants with a DLQI Total Score of ≥4 points at baseline who achieve a ≥4-point improvement from baseline to Week 16		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants in the mITT population with a baseline DLQI score of ≥4 points (Nx)	115	215

	Response, n (%)	39 (33.6)	143 (66.3)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	Common risk difference (95% CI)		33.0 (22.2, 43.8)
	p-value		<.001
Induction Period – Results and Analysis – Sleep-Loss Scale Score 2-Point Improvement at Week 16			
Analysis Description	**Major secondary endpoint:** Percentage of participants with a Sleep-Loss scale score ≥2 points at baseline who achieved a ≥2-point reduction from baseline at Week 16		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants in the mITT population with baseline Sleep-Loss scale score of ≥2 points (Nx)	97	161
	Response, n (%)	8 (8.2)	45 (28.0)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	Common risk difference (95% CI)		18.9 (9.6, 28.1)
	p-value		<.001
Induction Period – Results and Analysis – Sleep-Loss Scale Score CFB			
Analysis Description	**Major secondary endpoint:** CFB in Sleep-Loss Scale score at Week 16		
Statistical Model	Primary estimand (hybrid): ANCOVA with MCMC-MI[b]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants in the mITT population with non-missing baseline Sleep-Loss scale score (Nx)	143	268
	LSM (SE)	−0.4 (0.1)	−1.1 (0.1)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO
	LSM difference (95% CI)		−0.7 (−0.9, −0.5)
	p-value		<.001
Induction Period – Results and Analysis – POEM CFB			
Analysis Description	**Other endpoint:** CFB in POEM at Week 16		
Statistical Model	Supportive estimand for continuous endpoints (hypothetical): MMRM[c]		
	Treatment group	PBO	LEB 250 mg Q2W
	Number of participants (Nx)	141	266

Descriptive Statistics and Estimate Variability	LSM (SE)	−3.5 (0.8)	−9.5 (0.5)	
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W versus PBO	
	LSM difference (SE)		−6.0 (0.9)	
	p-value		<.001	
Maintenance Period – Results and Analysis – EASI 75 at Week 52				
Analysis Description	**Maintenance major secondary endpoint:** Percentage of participants from those randomly reassigned, having achieved EASI 75 at Week 16 who continued to exhibit EASI 75 at Week 52 (EASI 75 calculated relative to baseline EASI)			
Statistical Model	Maintenance primary estimand (hybrid): CMH with MCMC-MI[d]			
Descriptive Statistics and Estimate Variability	Treatment group	PBO	LEB 250 mg Q4W	LEB 250 mg Q2W
	Participants with EASI 75 at Week 16 (Nx)	27	53	51
	Response, n (%)	19 (72.0)	45 (84.7)	39 (77.4)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q4W vs PBO	LEB 250 mg Q2W vs PBO	
	Common risk difference n, (95% CI)	12.8 (−9.5, 35.1)	4.8 (−17.8, 27.3)	
	p-value	.238	.612	
Maintenance Period – Results and Analysis – IGA 0,1 at Week 52				
Analysis Description	**Maintenance major secondary endpoint:** Percentage of participants from those randomly reassigned having achieved an IGA score of 0 or 1 and a ≥2-point improvement from baseline at Week 16 who continued to exhibit an IGA score of 0 or 1 and a ≥2-point improvement from baseline at Week 52			
Statistical Model	Maintenance primary estimand (hybrid): CMH with MCMC-MI[d]			
Descriptive Statistics and Estimate Variability	Treatment group	PBO (LEB withdrawal)	LEB 250 mg Q4W	LEB 250 mg Q2W
	Participants with IGA 0,1 at W16 (Nx)	16	32	32
	Response, n (%)	8 (49.8)	26 (80.6)	21 (64.6)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q4W vs PBO	LEB 250 mg Q2W vs PBO	
	Common risk difference n, (95% CI)	32.6 (2.6, 62.5)	13.4 (−17.5, 44.3)	
	p-value	.034	.407	

Maintenance Period – Results and Analysis – Pruritus NRS 4-Point Improvement at Week 52				
Analysis Description	**Maintenance major secondary endpoint:** Percentage of participants with a pruritus NRS score of ≥4-points at baseline randomly reassigned, having achieved ≥4-point reduction from baseline at Week 16, who continued to exhibit ≥4-point reduction from baseline at Week 52			
Statistical Model	Maintenance primary estimand (hybrid): CMH with MCMC-MI[d]			
Descriptive Statistics and Estimate Variability	Treatment group	PBO (LEB withdrawal)	LEB 250 mg Q4W	LEB 250 mg Q2W
	Participants with pruritus NRS 4-point improvement at W16 (Nx)	11	36	23
	Response, n (%)	7 (67.6)	32 (88.1)	21 (90.3)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q4W vs PBO	LEB 250 mg Q2W vs PBO	
	Common risk difference n, (95% CI)	20.3 (−11.4, 52.0)	20.4 (−10.6, 51.4)	
	p-value	.159	.165	
Maintenance Period – Results and Analysis – EASI PCFB				
Analysis Description	**Maintenance major secondary endpoint:** Percentage change in EASI from baseline at Week 52 in the subset of participants who were those randomly reassigned at Week 16			
Statistical Model	Maintenance primary estimand (hybrid): ANCOVA with MCMC-MI[e]			
Descriptive Statistics and Estimate Variability	Treatment group	PBO (LEB withdrawal)	LEB 250 mg Q4W	LEB 250 mg Q2W
	Number of participants (Nx)	28	55	51
	LSM (SE)	−72.9 (6.3)	−87.6 (4.4)	−77.2 (4.4)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q4W vs PBO	LEB 250 mg Q2W vs PBO	
	LSM difference (95% CI)	−14.7 (−29.8, 0.4)	−4.3 (−19.4, 10.8)	
	p-value	.057	.575	
Maintenance Period – Results and Analysis – EASI 90 at Week 52				
Analysis Description	**Other endpoint:** Percentage of participants with EASI 90 at Week 52 in the subset of participants who achieved EASI 75 and were randomly reassigned at Week 16 (EASI 90 calculated relative to baseline EASI			
Statistical Model	Maintenance primary estimand (hybrid): CMH with MCMC-MI[d]			
	Treatment group	PBO (LEB withdrawal)	LEB 250 mg Q4W	LEB 250 mg Q2W

Descriptive Statistics and Estimate Variability	Participants with EASI 75 at Week 16 (Nx)	27	53	51
	Response, n (%)	10 (38.2)	35 (66.2)	31 (61.5)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q4W vs PBO	LEB 250 mg Q2W vs PBO	
	Common risk difference n, (95% CI)	28.5 (4.4, 52.7)	23.3 (−1.0, 47.6)	
	p-value	.024	.064	
Maintenance Week 16 Escape Population – Results and Analysis – IGA 0,1 and 2-Point Improvement at Week 52				
Analysis Description	**Other endpoint:** Percentage of participants achieving an IGA score of 0 or 1 and a ≥2-point improvement from baseline at Week 52			
Statistical Model	Descriptive statistic with observed data			
Descriptive Statistics and Estimate Variability	Treatment group	PBO nonresponders to LEB 250 mg Q2W	LEB nonresponders to LEB 250 mg Q2W	
	Number of participants (Nx)	84	83	
	Response, n (%)	42 (50.0)	34 (41.0)	
Maintenance Week 16 Escape Population – Results and Analysis – EASI 75 at Week 52				
Analysis Description	**Other endpoint:** Percentage of participants with EASI 75 at Week 52 (EASI 75 calculated relative to baseline EASI)			
Statistical Model	Descriptive statistics with observed data			
Descriptive Statistics and Estimate Variability	Treatment group	PBO nonresponders to LEB 250 mg Q2W	LEB nonresponders to LEB 250 mg Q2W	
	Number of participants (Nx)	85	83	
	Response, n (%)	69 (81.2)	61 (73.5)	
Maintenance Week 16 Escape Population – Results and Analysis- EASI 90 at Week 52				
Analysis Description	**Other endpoint:** Percentage of participants with EASI 90 at Week 52 (EASI 90 calculated relative to baseline EASI)			
Statistical Model	Descriptive statistics with observed data			
Descriptive Statistics and Estimate Variability	Treatment group	PBO nonresponders to LEB 250 mg Q2W	LEB nonresponders to LEB 250 mg Q2W	
	Number of participants (Nx)	85	83	
	Response, n (%)	46 (54.1)	38 (45.8)	
Maintenance Week 16 Escape Population – Results and Analysis – Pruritus NRS 4-Point Improvement at Week 52				

Analysis Description	**Other endpoint:** Percentage of participants with a pruritus NRS of ≥4 points at baseline with ≥4-point reduction at Week 52		
Statistical Model	Descriptive statistics with observed data		
Descriptive Statistics and Estimate Variability	Treatment group	PBO nonresponders to LEB 250 mg Q2W	LEB nonresponders to LEB 250 mg Q2W
	Number of participants (Nx)	71	67
	Response, n (%)	49 (69.0)	40 (59.7)

Analyses

[a] Primary estimand (hybrid), CMH-MCMC-MI: Participants who received any topical or systemic rescue medication, or discontinued treatment due to lack of efficacy had values set to their baseline value after this time through Week 16; MCMC-MI was used to handle the remaining missing data. CMH test stratified by geographic region, age group, and baseline IGA.

[b] Primary estimand (hybrid), ANCOVA with MCMC-MI: Participants who received any topical or systemic rescue medication, or discontinued treatment due to lack of efficacy had values set to their baseline value after this time through Week 16; MCMC-MI was used to handle the remaining missing data. ANCOVA model adjusted for treatment group, baseline value, geographic region, age group, and baseline IGA.

[c] Supportive estimand (hypothetical), MMRM: Data after topical or systemic rescue medication or treatment discontinuation were treated as missing and missing data were handled by MMRM. The MMRM model includes treatment, baseline value, visit, the interaction of the baseline value-by-visit, the interaction of treatment-by-visit, and the stratification factors as fixed factors.

[d] Maintenance primary estimand (hybrid), CMH-MCMC-MI: Participants who received systemic rescue medication, discontinued treatment due to lack of efficacy, or transferred to escape arm had values set to their baseline value after this time through Week 52; participants who received topical rescue medication or discontinued treatment due to other reasons had values set to missing; MCMC-MI was used to handle the remaining missing data. CMH test stratified by geographic region.

[e] Maintenance primary estimand (hybrid), ANCOVA with MCMC-MI: Participants who received systemic rescue medication, discontinued treatment due to lack of efficacy, or transferred to escape arm had values set to their baseline value after this time through Week 52; participants who received topical rescue medication or discontinued treatment due to other reasons had values set to missing; MCMC-MI was used to handle the remaining missing data. ANCOVA model adjusted for geographic region.

Abbreviations: ANCOVA = analysis of covariance; CFB = change from baseline; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI 75 = at least 75% reduction in EASI; EASI 90 = at least 90% reduction in EASI; IGA = Investigator's Global Assessment; LEB = lebrikizumab; LSM = least squares mean; MCMC-MI = Markov Chain Monte Carlo Multiple Imputation; mITT= modified intent-to-treat population; MMRM = Mixed Model Repeated Measures; N = total number of participants; n = calculated number of participants experiencing endpoint; NRS = Numerical Rating Scale; Nx = number of participants in the analysis population; PBO = placebo; PCFB = percentage change from baseline; POEM = Patient Oriented Eczema Measure; Q2W = every 2 weeks; Q4W = every 4 weeks; SE = standard error; vs = versus; W = week.

Table 53: Summary of Efficacy for Pivotal Study KGAD

Title: RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF LEBRIKIZUMAB WHEN USED IN COMBINATION WITH TOPICAL CORTICOSTEROID TREATMENT IN PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS			
Study Identifier	J2T-DM-KGAD; DRM06-AD06		
Design	Phase 3, randomised, double-blind, placebo-controlled, parallel-group study.		
	This study had a single treatment period of 16 weeks. Participants were randomly assigned at a ratio of 2:1 to LEB 500 mg loading dose at baseline and Week 2 then 250 mg Q2W or PBO. Participants were required to use TCS at baseline and then were allowed to use as needed for the duration of the study.		
Treatment Groups	PBO + TCS		Randomised N = 75 4 mL was administered via 2 preassembled needle safety devices (PFS-NSD) at baseline and Week 2 and 2 mL Q2W was administered through Week 14 via 1 PFS-NSD. TCS treatment was initiated at baseline and applied as needed.
	LEB 250 mg Q2W + TCS		Randomised N = 153 LEB 500 mg at baseline and Week 2 (loading dose) and 250 mg given Q2W through Week 14 with TCS treatment initiated at baseline and applied as needed.
Hypothesis	Superiority		
Endpoints and Definitions	Coprimary endpoint	IGA 0,1, W16	Percentage of participants with an IGA 0,1 and a ≥2-point reduction from baseline to Week 16
	Coprimary endpoint	EASI 75, W16	Percentage of participants achieving EASI 75 (≥75% reduction from baseline in EASI) at Week 16
	Major secondary endpoint	EASI 90, W16	Percentage of participants achieving EASI 90 (≥90% reduction from baseline in EASI) at Week 16
	Major secondary endpoint	EASI PCFB, W16	Percentage change in EASI score from baseline to Week 16
	Major secondary endpoint	Pruritus NRS 4-point improvement, W16	Percentage of participants with a pruritus NRS of ≥4-points at baseline who achieve a ≥4-point reduction from baseline to Week 16
	Major secondary endpoint	Pruritus NRS PCFB, W16	Percentage change in pruritus NRS score from baseline to Week 16

	Major secondary endpoint	Pruritus NRS 4-point improvement and EASI 75, W16	Percentage of participants with a pruritus NRS score of ≥4 points at baseline who achieve both EASI 75 and a ≥4-point reduction in pruritus NRS score from baseline at Week 16
	Major secondary endpoint	DLQI CFB, W16	CFB in DLQI at Week 16
	Major secondary endpoint	DLQI 4-point improvement, W16	Percentage of participants with a DLQI total score of ≥4-points at baseline who achieve ≥4-point improvement in DLQI from baseline to Week 16
	Major secondary endpoint	Sleep-Loss CFB, W16	CFB in Sleep-Loss scale score at Week 16
	Other secondary endpoint	POEM CFB, W16	CFB in POEM at Week 16
Database Lock	16 December 2021		
Multiplicity Adjustment	For all primary and key secondary endpoints, a prespecified gatekeeping approach was implemented to control the overall Type I error rate at a 2-sided alpha of 0.05.		

Results and Analysis			
Analysis Description	**Coprimary endpoint:** Percentage of participants with an IGA 0,1 and a ≥2-point reduction from baseline to Week 16		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO + TCS	LEB 250 mg Q2W + TCS
	Number of participants (Nx)	66	145
	Response, n (%)	15 (22.1)	60 (41.2)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q2W vs PBO	
	Common risk difference (95% CI)	18.3 (5.1, 31.5)	
	p-value	.011	

Results and Analysis			
Analysis Description	**Coprimary endpoint:** Percentage of participants achieving EASI 75 (≥75% reduction from baseline in EASI) at Week 16		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
	Treatment group	PBO + TCS	LEB 250 mg Q2W + TCS

Descriptive Statistics and Estimate Variability	Number of participants (Nx)	66	145
	Response, n (%)	28 (42.2)	101 (69.5)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q2W vs PBO	
	Common risk difference, n (95% CI)	26.4 (12.1, 40.8)	
	p-value	<.001	
Results and Analysis			
Analysis Description	**Major secondary endpoint:** Percentage of participants experiencing EASI 90 (≥90% reduction from baseline in EASI) at Week 16		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO + TCS	LEB 250 mg Q2W + TCS
	Number of participants (Nx)	66	145
	Response, n (%)	14 (21.7)	60 (41.2)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q2W vs	
	Common risk difference (95% CI)	18.9 (6.1, 31.7)	
	p-value	.008	
Results and analysis			
Analysis Description	**Major secondary endpoint:** Percentage change in EASI from baseline to Week 16		
Statistical Model	Primary estimand (hybrid): ANCOVA with MCMC-MI[b]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO + TCS	LEB 250 mg Q2W + TCS
	Number of participants (Nx)	66	145
	LSM (SE)	−53.1 (5.1)	−76.8 (4.1)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q2W vs PBO	
	LSM difference (95% CI)	−23.6 (-33.6, -13.7)	
	p-value	<.001	
Results and analysis			
Analysis Description	**Major secondary endpoint:** Percentage of participants with a pruritus NRS of ≥4 points at baseline who achieve a ≥4-point reduction from baseline to Week 16		
Statistical Model	Primary Estimand (hybrid): CMH with MCMC-MI[a]		

Descriptive Statistics and Estimate Variability	Treatment group	PBO + TCS	LEB 250 mg Q2W + TCS
	Number of participants with baseline pruritus NRS score ≥4 (Nx)	57	130
	Response, n (%)	18 (31.9)	66 (50.6)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W vs PBO
	Common risk difference (95% CI)		19.2 (4.3, 34.1)
	p-value		.017
Results and Analysis			
Analysis Description	**Major secondary endpoint:** Percentage change in pruritus NRS score from baseline to Week 16		
Statistical Model	Primary estimand (hybrid): ANCOVA with MCMC-MI[b]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO + TCS	LEB 250 mg Q2W + TCS
	Number of participants (Nx)	63	139
	LSM (SE)	−35.5 (6.4)	−50.7 (4.5)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W vs PBO
	LSM difference (95% CI)		−15.2 (−27.7, −2.7)
	p-value		.017
Results and Analysis			
Analysis Description	**Major secondary endpoint:** Percentage of participants with a pruritus NRS score of ≥4 points at baseline who achieve both EASI 75 and a ≥4-point reduction in pruritus NRS score from baseline at Week 16		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO + TCS	LEB 250 mg Q2W + TCS
	Number of participants with baseline pruritus NRS score ≥4 (Nx)	57	130
	Response, n (%)	10 (16.8)	50 (38.3)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W vs PBO
	Common risk difference, n (95% CI)		21.6 (8.3, 35.0)
	p-value		0.005

Results and Analysis			
Analysis Description	**Major secondary endpoint:** CFB in DLQI at Week 16		
Statistical Model	Primary Estimand (hybrid): ANCOVA with MCMC-MI[b]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO + TCS	LEB 250 mg Q2W + TCS
	Number of participants (Nx)	51	109
	LSM (SE)	−6.5 (1.9)	−9.8 (1.8)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q2W vs PBO	
	LSM difference (95% CI)	−3.3 (−5.3, −1.3)	
	p-value	.001	

Results and Analysis			
Analysis Description	**Major secondary endpoint:** Percentage of participants with a DLQI total score of ≥4-points at baseline who achieve ≥4-point improvement in DLQI from baseline to Week 16		
Statistical Model	Primary estimand (hybrid): CMH with MCMC-MI[a]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO + TCS	LEB 250 mg Q2W + TCS
	Number of participants with baseline DLQI score ≥4 (Nx)	48	105
	Response, n (%)	28 (58.7)	81 (77.4)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q2W vs PBO	
	Common risk difference (95% CI)	17.2 (0.1, 34.3)	
	p-value	.036	

Results and Analysis			
Analysis Description	**Major secondary endpoint:** CFB in Sleep-Loss Scale score at Week 16		
Statistical Model	Primary estimand (hybrid): ANCOVA with MCMC-MI[b]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO + TCS	LEB 250 mg Q2W + TCS
	Number of participants (Nx)	63	139
	LSM (SE)	−0.8 (0.1)	−1.1 (0.1)
	Comparison groups	LEB 250 mg Q2W vs PBO	

Effect Estimate per Comparison	LSM difference (95% CI)		−0.3 (−0.6, −0.0)
	p-value		.025
Results and Analysis			
Analysis Description	**Other secondary endpoint:** CFB in POEM at Week 16		
Statistical Model	Supportive estimand for continuous endpoints (hypothetical): MMRM[c]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO + TCS	LEB 250 mg Q2W + TCS
	Number of participants (Nx)	64	135
	LSM (SE)	−6.2 (1.0)	−10.2 (07)
Effect Estimate per Comparison	Comparison groups		LEB 250 mg Q2W vs PBO
	LSM difference (SE)		−4.0 (1.1)
	p-value		<.001
Analyses			

[a] Primary estimand (hybrid), CMH-MCMC-MI: Participants who received high potency topical or systemic rescue medication, or discontinued treatment due to lack of efficacy had values set to their baseline value after this time through Week 16; MCMC-MI was used to handle the remaining missing data. CMH test stratified by geographic region, age group, and baseline IGA.

[b] Primary estimand (hybrid), ANCOVA with MCMC-MI: Participants who received high potency topical or systemic rescue medication, or discontinued treatment due to lack of efficacy had values set to their baseline value after this time through Week 16; MCMC-MI was used to handle the remaining missing data. ANCOVA model adjusted for treatment group, baseline value, geographic region, age group, and baseline IGA.

[c] Supportive estimand (hypothetical), MMRM: Data after high potency topical or systemic rescue medication or treatment discontinuation were treated as missing and missing data were handled by MMRM. The MMRM model includes treatment, baseline value, visit, the interaction of the baseline value-by-visit, the interaction of treatment-by-visit, and the stratification factors as fixed factors.

Abbreviations: ANCOVA = analysis of covariance; CFB =change from baseline; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI 75 = at least 75% reduction in EASI; EASI 90 = at least 90% reduction in EASI; IGA = Investigator's Global Assessment; LEB = lebrikizumab; LSM = least squares mean; MCMC-MI = Markov Chain Monte Carlo Multiple Imputation; MMRM = Mixed Model Repeated Measures; N = total number of participants; n = calculated number of participants experiencing endpoint; NRS = Numerical Rating Scale; NSD = needle safety device; Nx = number of participants in the analysis population; PBO = placebo; PCFB = percentage change from baseline; PFS= pre-filled syringe; POEM = Patient Oriented Eczema Measure; Q2W = every 2 weeks; SE = standard error; TCS = topical corticosteroid; vs = versus; W = week.

2.6.5.4. Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	102/1600	22/1600	4/1600
Non Controlled trials	5/294	4/294	1/294

Study KGAE (J2T-DM-KGAE or ADore)

KGAE was a 52 week, open-label, single-arm study to assess the safety and efficacy of lebrikizumab in adolescent patients (≥12 years to less than 18 years, weighing ≥40 kg) with moderate-to-severe AD. The patients were to have a chronic AD for at least 1 year and key inclusion criteria included EASI ≥16, IGA score ≥3, BSA ≥10% and been a candidate for systemic therapy.

At baseline and Week 2, all patients were administered subcutaneously a loading dose of 500 mg lebrikizumab. From Week 4 onwards, all patients were administered 250 mg lebrikizumab Q2W through Week 52 subcutaneously.

The use of any potency TCS, TCIs and PDE4 inhibitors were permitted to be used as add-on rescue treatment when a patient experienced clinical worsening of symptoms that were intolerable. Patients who required short-term systemic treatment for symptoms of AD were assessed on a case-by-case basis by the investigator. Patients who required long-term systemic treatment for symptoms of AD (e.g., non-responders) were discontinued from the study as per the protocol requirements.

A posttreatment follow-up visit was conducted approximately 12 weeks after the last injection of the study drug for patients who had discontinued early from the study or completed participation in the Open-Label Treatment Period and did not wish to enter the long-term extension study (KGAA).

Efficacy results

Altogether 206 received study treatment. All efficacy measures were included as secondary endpoints in the Study KGAE study design. The results are summarised below (Table 54).

Table 54: Secondary Endpoints and Summary of Efficacy Results (Safety Population)

Endpoints	LEB 250 mg Q2W N = 206
Percentage of participants with an IGA score of 0 or 1 and a reduction ≥2 points from baseline at Week 52; % (MCMC-MI analysis)	62.6
Percentage of participants achieving EASI 75 at Week 52; % (MCMC-MI analysis)	81.9
Percentage of participants achieving EASI 50 at Week 52; % (MCMC-MI analysis)	94.4
Percentage of participants achieving EASI 90 at Week 52; % (MCMC-MI analysis)	61.4
Percentage change from baseline in EASI at Week 52; Mean (SE) (MCMC-MI analysis)	-86.0 (1.6)
Change from baseline in BSA at Week 52; Mean (SD) (as-observed analysis)	-37.6 (21.1)
Change from baseline in PROMIS Anxiety and Depression scores at Week 52; mean (SD) (as-observed analysis)	
Change from baseline in PROMIS Anxiety scores	*-6.3 (10.0)*
Change from baseline in PROMIS Depression scores	*-3.4 (9.1)*
Change from baseline in DLQI total score at Week 52; mean (SE) (MCMC-MI analysis)	-8.9 (0.9)
Percentage of participants with a DLQI Total Score of ≥4 points at baseline who reported ≥4-point improvement in DLQI from baseline to Week 52; % (MCMC-MI analysis)	91.4
Percentage of participants with baseline DLQI Score >1 reporting a score of 0 or 1 at Week 52; % (MCMC-MI analysis)	36.9
Change from baseline in CDLQI total score at Week 52; mean (SE) (MCMC-MI analysis)	-6.5 (0.5)
Percentage of participants reporting a CDLQI score of 0 or 1 at Week 52; % (MCMC-MI analysis)	37.2

Abbreviations: BSA = body surface area; CDLQI = Children's Dermatology Life Quality Index; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI 50 = 50% reduction in EASI; EASI 75 = 75% reduction in EASI; EASI 90 = 90% reduction in EASI; IGA = Investigator's Global Assessment; LEB = lebrikizumab; MCMC-MI = Markov Chain Monte Carlo Multiple Imputation; N = number of participants in the analysis population; PROMIS = Patient-Reported Outcomes Measurement Information System; Q2W = every 2 weeks; SD = standard deviation; SE = standard error.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

According to the Applicant, data from study KGAB and KGAC was pooled when applicable. The key pooled efficacy data from Studies KGAB and KGAC Maintenance Period is summarised in Table 55 and discussed in section 2.6.6.

Table 55: Summary of Efficacy for Maintenance Period: Pooled Data for Studies KGAB and KGAC

Maintenance Period – Pooled Studies KGAB and KGAC				
Analysis Description	**Maintenance major secondary endpoint:** Percentage of participants maintaining IGA 0, 1 at Week 52 LEB responders with IGA 0,1 at Week 16			
Statistical Model	Maintenance Primary Estimand (hybrid): CMH with MCMC-MI[a]			
Descriptive Statistics and Estimate Variability	Treatment group	PBO (LEB withdrawal)	LEB 250 mg Q4W	LEB 250 mg Q2W
	W16 LEB-responders with IGA 0,1 (Nx)	38	77	77
	Maintained response at W52, n (%)	18 (47.9)	59 (76.9)	55 (71.2)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q4W vs PBO	LEB 250 mg Q2W vs PBO	
	Common risk difference n, (95% CI)	29.9 (10.5, 49.3)	22.6 (3.2, 42.0)	
	p-value	.003	.022	
Maintenance Period – Pooled Studies KGAB and KGAC				
Analysis Description	**Maintenance major secondary endpoint:** Percentage of participants maintaining EASI 75 at Week 52 LEB-Responders			
Statistical Model	Maintenance primary estimand (hybrid): CMH with MCMC-MI[a]			
Descriptive Statistics and Estimate Variability	Treatment group	PBO (LEB withdrawal)	LEB 250 mg Q4W	LEB 250 mg Q2W
	EASI 75 Responders at W16, (Nx)	57	115	112
	Maintained response at W52, n (%)	38 (66.4)	94 (81.7)	88 (78.4)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q4W vs PBO	LEB 250 mg Q2W vs PBO	
	Common risk difference n, (95% CI)	15.5 (0.3, 30.8)	11.6 (−4.5, 27.6)	
	p-value	.038	.147	

Maintenance Period – Pooled Studies KGAB and KGAC				
Analysis Description	**Other endpoint:** Percentage of participants with EASI 90 at Week 16 and Week 52 Week 16 LEB responders			
Statistical Model	Maintenance primary estimand (hybrid): CMH with MCMC-MI[a]			
Descriptive Statistics and Estimate Variability	Treatment group	PBO (LEB withdrawal)	LEB 250 mg Q4W	LEB 250 mg Q2W
	EASI-75 responders at W16, (Nx)	57	115	112
	EASI-75 responders with EASI 90 at W16, n (%)	36 (63.2)	69 (60.0)	69 (61.6)
	EASI-75 responders with EASI 90 at W52, n (%)	24 (41.9)	76 (66.4)	72 (64.0)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q4W vs PBO	LEB 250 mg Q2W vs PBO	
	Common risk difference n, (95% CI)	24.8 (8.4, 41.1)	21.6 (4.9, 38.4)	
	p-value	.004	.012	

Maintenance Period – Pooled Studies KGAB and KGAC				
Analysis Description	**Maintenance major secondary endpoint:** Percentage of participants maintaining pruritus NRS 4-point improvement at Week 52 and Week 16 in LEB responders			
Statistical Model	Maintenance primary estimand (hybrid): CMH with MCMC-MI[a]			
Descriptive Statistics and Estimate Variability	Treatment group	PBO (LEB withdrawal)	LEB 250 mg Q4W	LEB 250 mg Q2W
	Participants with pruritus NRS 4-point improvement at W16, (Nx)	28	65	61
	Maintained response at W52, n (%)	19 (66.3)	55 (84.7)	52 (84.6)
Effect Estimate per Comparison	Comparison groups	LEB 250 mg Q4W vs PBO	LEB 250 mg Q2W vs PBO	
	Common risk difference n, (95% CI)	17.7 (−3.1, 38.6)	18.1 (−1.7, 37.9)	
	p-value	.077	.058	

Maintenance Week 16 Escape Population Pooled Studies KGAB and KGAC – IGA 0,1 and 2-Point Improvement			
Analysis Description	**Other endpoint:** Proportion of participants achieving IGA 0,1 at Week 52 among Maintenance Week 16 Escape Population who are nonresponders at Week 16		
Statistical Model	Escape supportive estimand (hybrid): MCMC-MI[b]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO nonresponders to LEB 250 mg Q2W	LEB nonresponders to LEB 250 mg Q2W
	Number of participants (Nx)	158	147
	Response, n (%)	86 (43.2)	61 (28.4)
	95% CI	(36.2, 50.2)	(22.0, 34.9)
Maintenance Week 16 Escape Population Pooled Studies KGAB and KGAC – EASI 75			
Analysis Description	**Other endpoint:** Proportion of participants achieving EASI 75 at Week 52 among Maintenance Week 16 Escape Population who are nonresponders at Week 16		
Statistical Model	Escape supportive estimand (hybrid): MCMC-MI[b]		
Descriptive Statistics and Estimate Variability	Treatment group	PBO nonresponders to LEB 250 mg Q2W	LEB nonresponders to LEB 250 mg Q2W
	Number of participants (Nx)	159	147
	Response, n (%)	139 (69.4)	124 (57.7)
	95% CI	(62.8, 76.0)	(50.9, 64.6)
Analyses			
[a] Maintenance primary estimand (hybrid), CMH-MCMC-MI: Participants who received systemic rescue medication, discontinued treatment due to lack of efficacy, or transferred to escape arm had values set to their baseline value after this time through Week 52; participants who received topical rescue medication or discontinued treatment due to other reasons had values set to missing; MCMC-MI was used to handle the remaining missing data. CMH test stratified by geographic region. Pooled analysis is additionally stratified for study factor. [b] Escape supportive estimand (hybrid), MCMC-MI: Participants who discontinued treatment due to lack of efficacy had values set to their baseline value after this time through Week 52. Data were treated as missing after treatment discontinuation due to any other reasons. MCMC-MI was used to handle the remaining missing data.		

Abbreviations: CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EASI = Eczema Area and Severity Index; EASI 75 = at least 75% reduction in EASI; EASI 90 = at least 90% reduction in EASI; IGA = Investigator's Global Assessment; LEB = lebrikizumab; MCMC-MI = Markov Chain Monte Carlo Multiple Imputation; n = calculated number of participants experiencing endpoint; Nx = number of participants in the analysis population; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; vs = versus; W = week.

2.6.5.6. Supportive study(ies)

An overview of the supportive studies is provided in Table 56.

Table 56: Supportive Clinical Studies in AD

	Study KGAA (LTE Study) (KGAD Participants in Study KGAA[a])	Study KGAE	Study KGAG	Study KGAH	Study KGAF
	Phase 3	Phase 3	Phase 2	Phase 2	Phase 2b
N	86	206	209	55	280
Participants	Adults and adolescents[b]	Adolescents[b]	Adults	Adults	Adults
Monotherapy or combination	Combination w/ TCS	Monotherapy[c]	Combination w/ TCS	Monotherapy	Monotherapy
Treatment duration	100 weeks	52 weeks	12 weeks	12 weeks	16 weeks
Treatment	• LEB 250mg Q2W + TCS • LEB 250mg Q4W + TCS	• LEB 250mg Q2W	• PBO Q4W + TCS • LEB 250mg, single dose + TCS • LEB 125mg, single dose + TCS • LEB 125mg Q4W + TCS	• TCS • LEB 125mg Q4W	• PBO Q2W • LEB 125mg Q4W[d] • LEB 250mg Q4W[d] • LEB 250mg Q2W [d]
Randomization ratio	2:1	Single-arm open-label	1:1:1:1	1:1	2:3:3:3
Location of study	Canada, Germany, Poland, US	Australia, Canada, Poland, US	Australia, Canada, Czech Republic, Finland, France, Germany, Netherlands, Poland, South Korea, Spain, Switzerland, Taiwan, UK, US	Canada, US	US
Study status	Ongoing (data cutoff date: 06 June 2022)	Complete	Complete	Complete	Complete

Abbreviations: CSE = clinical summary of efficacy; EASI 75 = at least 75% improvement from Baseline in Eczema Area and Severity Index score; IGA = Investigator's Global Assessment; LEB = lebrikizumab; LTE = long-term extension; N = number of participants included in efficacy analyses; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; TCS = topical corticosteroids; UK = United Kingdom; US = United States; w/ = with.

a Study KGAE results reported in this CSE are only for those participants originating from Study KGAD who achieved an IGA 0 or 1 or EASI 75 at Week 16 without receiving rescue therapy, while treated with LEB 250 mg in Study KGAD.

b Adults (≥18 years); Adolescents (12 to <18 years weighing ≥40 kg)

c Participants were permitted to use TCS throughout Study KGAE but were not required to use them at any time during the study.

d Participants randomly assigned to LEB 125 mg Q4W received 250-mg loading dose at Week 0. Those assigned to LEB 250 mg Q4W received a 500-mg loading dose at Week 0. Participants assigned to LEB 250 mg Q2W received 500-mg loading doses at Week 0 and Week 2.

Study KGAA (J2T-DM-KGAA or ADjoin)

KGAA is an ongoing long-term extension study which will provide data over 100 weeks when complete and will include patients from KGAB, KGAC, KGAD, KGAE and KGAK studies. The CRS is anticipated to become available by February 2025.

Key interim results for patients enrolling from Study KGAD

Results in the initial MAA are reported from the 86 lebrikizumab responders from KGAD study who were re-randomised to treatment with lebrikizumab 250 mg Q2W or Q4W.

IGA

Among lebrikizumab-treated patients who were responders at week 16, 67.6% and 71.7% in the lebrikizumab 250 mg Q4W and QW2 groups, respectively, maintained IGA 0 or 1 in Study KGAA after 56 weeks of continued treatment. Table 57 shows the proportions of lebrikizumab-responders who maintained IGA 0,1, with a 2-point or greater improvement from Baseline (Study KGAD Week 0) after 56 weeks of continued treatment.

Table 57: Proportion of Patients Maintaining IGA 0,1 Induction Period Response at 56 Weeks of Treatment (MCMC-MI)

	LEB 250mg Q4W + TCS N = 29	LEB 250mg Q2W + TCS N = 57
LEB-Responders with IGA 0,1 (Nx)	**16**	**37**
Maintained response, n (%)	14 (86.8)	28 (75.4)
95% CI	69.7, 103.8	60.8, 89.9

Abbreviations: CI = confidence interval; CSE = clinical summary of efficacy; IGA = Investigator's Global Assessment; IGA 0,1 = IGA score of 0 or 1, with a 2-point or greater reduction from Baseline; LEB = lebrikizumab; MCMC-MI = Markov Chain Monte Carlo multiple imputation; PBO = placebo; N = total number of participants in the treatment arm; n = number of participants in the specified category; Nx = number of participants in analysis population; Q2W = every 2 weeks; Q4W = every 4 weeks; TCS = topical corticosteroids.
Note: 56 weeks of treatment corresponds to Week 40 of Study KGAA.

EASI 75

Among lebrikizumab-treated patients who were responders at week 16, 81.2% and 85.9% in the lebrikizumab 250 mg Q4W and QW2 groups, respectively, maintained EASI 75 in Study KGAA after 56 weeks of continued treatment. Table 58 shows the proportions of Study KGAD lebrikizumab-responders who maintained EASI 75 after 56 weeks of continued treatment.

Table 58: Proportion of Patients Maintaining EASI 75 at 56 Weeks of Treatment (MCMC-MI)

	LEB 250mg Q4W + TCS N = 29	LEB 250mg Q2W + TCS N = 57
LEB-responders with EASI 75 (Nx)	**29**	**56**
Maintained response, n (%)	24 (81.2)	48 (85.6)
95% CI	66.5, 96.0	75.6, 95.7

Abbreviations: CI = confidence interval; CSE = clinical summary of efficacy; EASI = Eczema Area and Severity Index; EASI 75 = 75% improvement from Baseline in EASI; LEB = lebrikizumab; MCMC-MI = Markov Chain Monte Carlo multiple imputation; N = total number of participants; n = number of participants in the specified category; Nx = number of participants in analysis population; Q2W = every 2 weeks; Q4W = every 4 weeks; TCS = topical corticosteroids.
Note: 56 weeks of treatment corresponds to Week 40 of Study KGAA.

Study KGAG (GS29250 or J2T-DM-KGAG or TREBLE) and Study KGAH (J2T-DM-KGAH or ARBAN)

Study KGAG and KGAH were phase 2 studies that provided initial effectiveness of lebrikizumab in AD. These studies are summarised in Table 59.

Study KGAE (J2T-DM-KGAE or ADore)

See section 2.6.5.4

Study KGAF (J2T-DM-KGAF)

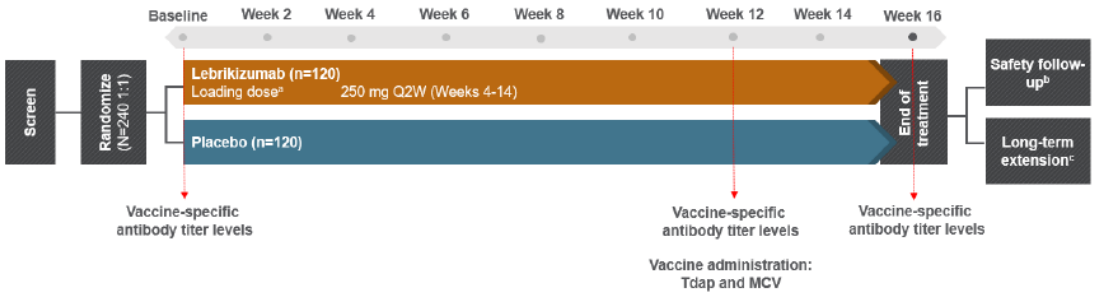
See section 2.6.5.1

Study KGAK (J2T-MC-KGAK)

The study was a 16-week, randomised, double-blind, placebo-controlled, parallel-group study designed to assess the impact of lebrikizumab on vaccine immune responses in adult patients (aged 18 to 55 years) with moderate-to-severe atopic dermatitis.

Participants were randomly assigned in a 1:1 ratio to receive either lebrikizumab (a loading dose of 500 mg administered at baseline and Week 2, and 250 mg Q2W thereafter through Week 14) or placebo. At Week 12, after the predose blood sample vaccine titres were withdrawn, 1 dose of each of the following 2 commercially available vaccines were administered to all participants still on study drug: Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi) (Tdap), and Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GlaxoSmithKline) (MCV). The antibody titres were determined 4 weeks later (Figure 18).

Figure 18: Study design for study KGAK



Abbreviations: MCV = Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GlaxoSmithKline); Q2W = once every 2 weeks; Tdap = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi).

[a] Lebrikizumab loading dose of 500 mg was administered at Baseline and Week 2

[b] The safety follow-up occurred at Week 26 (or approximately 12 weeks after last study drug injection).

[c] If eligible, participants continued to the long-term extension study (DRM06-AD07/J2T-DM-KGAA).

The results of the primary endpoints are shown in Table 59.

Table 59: Results of Primary Endpoints (Per Protocol Set Population)

Primary Endpoints	PBO N = 81	LEB 250mg Q2W N = 107	Difference (90%) CI vs. PBO [b]
The percentage of participants who develop a booster response [a] to tetanus toxoid 4 weeks after the administration of the Tdap vaccine at Week 16, *n (%)*	58 (73.4)	78 (73.6)	0.3 (-10.2, 11.2)
The percentage of participants who have positive antibody response [a] to Meningococcus C antigen of the MCV 4 weeks after the administration of the vaccine at Week 16, *n (%)*	60 (75.0)	86 (86.9)	12.2 (2.5, 22.0)

Abbreviations: CI = confidence interval; IGA = Investigator's Global Assessment; LEB = lebrikizumab; MCV = Meningococcal (Groups A, C, Y, and W-135) Oligosaccharide Diphtheria CRM197 Conjugate Vaccine (GlaxoSmithKline); N = number of participants in the analysis population; n = number of participants in the specified category; PBO = placebo; Q2W= every 2 weeks; Tdap = Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Sanofi).

[a] The definitions of booster response to tetanus toxoid and positive antibody response to MCV are specified in Section 3 of Protocol J2T-MC-KGAK/DRM06-AD18.

[b] Two-sided 90% confidence interval for the difference between treatment arms using the stratified (by baseline IGA severity) Newcombe approach.

Usability of the autoinjector and PFS-NSD – Human factor studies

For the autoinjector a use-related risk assessment, usability studies and HF validation testing was performed. The HFE of PFS-NSD presentation of lebrikizumab included an exploratory human factors study and a threshold analysis.

The Applicant also conducted a known problems analysis to identify use-related problems that have occurred with products that are comparable to the lebrikizumab autoinjector and PFS-NSD. Findings were identified and compiled from multiple sources, including device constituent manufacturer known use problems, clinical evaluation reports, complaint data from clinical trials, engineering evaluation of returned products, risk analyses, and predicate device human factors studies.

The lebrikizumab autoinjector was found to fulfil the usability needs of the intended users and the study results supported the safe and effective use of the PFP. All use problems observed were already identified in the use-related risk analysis and are known use problems. No new or unanticipated use problems were observed.

Based on the results of the Final Formative Human Factors Study #2 (RTP-814408) and the validation protocol advice from FDA the Applicant decided to exclude adolescent patients from the group of intended users for self-injection in the human factors study and stated that the adolescent patients must receive injections from a caregiver or HCP. This was because untrained adolescent user (without assistance from a guardian) represented a high-risk scenario and also overdosing errors were made by three adolescents in the formative studies. However, the PI texts in and PL differ from this stating that it is only recommended that lebrikizumab is administered by or under supervision of an adult and the healthcare professional determines if self-injection is appropriate. The Applicant has adequately justified that the commercial settings differ from the human factor study settings and adolescent patients or their caregivers will receive instructions on the dose regimen and training in the use of the device by a healthcare provider prior to use. Therefore it is reasonable to assume that adolescents will be able to appropriately administer the drug under adult supervision.

The Applicant has adequately assessed the use-related risk of the lebrikizumab PFS-NSD through the HFE process and was found to fulfil the usability needs of the intended users.

The IFU contains step by step instructions on how to inject with the lebrikizumab autoinjector and lebrikizumab PSF-NSD along with graphic representations of what each step looks like.

2.6.6. Discussion on clinical efficacy

The clinical program of lebrikizumab in moderate-to-severe AD consists of 3 pivotal studies, evaluating efficacy of lebrikizumab as monotherapy (studies KGAB and KGAC) or in combination with TCS (study KGAD).

The finally agreed indication for lebrikizumab is as follows: **"Lebrikizumab is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older with a body weight of at least 40 kg who are candidates for systemic therapy"**. SmPC further states that lebrikizumab can be used with or without TCS or TCI: "Lebrikizumab can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas". The initially proposed indication did not include body weight restriction, but was later modified upon CHMP's request, as there was no clinical data in patients with a body weight < 40 kg.

The Applicant sought SA from EMA initially in 2013 (EMA/CHMP/15140/2013) and follow-up SA in 2016 (EMA/CHMP/24061/2017). At the time of the initial advice in 2013, no studies in AD had been conducted and e.g. protocol(s) for Phase 3 studies were not available. After the initial EMA SA, the Applicant's plans evolved substantially. Further, at the time of the follow-up SA (EMA/CHMP/24061/2017), only results from the initial Phase 2 studies KGAG (TREBLE) and KGAH (URBAN) were available, and the plans of the Phase 3 pivotal studies were further modified after completion of the Phase 2b dose-range finding study (KGAF). In general, however, it can be concluded that no discrepancies between the EMA SA and the conducted Phase 3 studies are identified that would be critical for an adequate assessment of the efficacy of lebrikizumab in moderate-to-severe AD.

Overall, the extent of the clinical program seems adequate for evaluation of efficacy of lebrikizumab in moderate-to-severe AD in adults and adolescents.

Design and conduct of clinical studies

<u>Pivotal studies KGAB KGAC and KGAD</u>

Study design and treatments

KGAB and KGAC studies were similar in design and consisted of 16-week induction period where subjects were randomly assigned 2:1 to lebrikizumab 250 mg Q2W (with a loading dose of 500 mg at baseline and week 2) or placebo, and 36-week maintenance treatment period where the responders from the 16-week induction period (i.e. patients achieving IGA score of 0 or 1, or EASI 75, and not receiving any rescue treatment) were re-randomised 2:2:1 to lebrikizumab 250 mg Q2W, 250 mg Q4W or placebo (maintenance blinded period). Non-responders or subjects who required rescue medication during the induction period, were enrolled into escape arm receiving open-label lebrikizumab 250 mg Q2W until week 52 (maintenance escape period). Rescue medication during induction period included any topical or systemic medication. TCSs were prohibited during the induction period (unless used as a rescue therapy) but permitted intermittently during the maintenance period. Patients using TCS as a rescue therapy during the induction period could continue using study drug until Week 16 but were then assigned to Escape arm. On the other hand, patients using systemic rescue therapy during the Induction period, discontinued the study drug, but could enter the Escape arm after appropriate washout.

In KGAD study, patients were randomised 2:1 to receive lebrikizumab 250 mg (with a loading dose of 500 mg at baseline and week 2) + TCS or placebo + TCS for 16 weeks. Low- and mid-potency TCS was

provided to be used as needed. The use of low potency TCI also permitted in sensitive areas, but not supplied by the study site.

Overall, the study designs for the 3 pivotal studies were appropriate. In terms of lebrikizumab doses in the pivotal studies, the data from the 16-week Phase 2b study KGAF supported selection of the lebrikizumab 250 mg Q2W (with the 500 mg loading doses at weeks 0 and week 2) as the induction dose (weeks 0-16) for the Phase 3 studies. The results of the primary efficacy analysis showed a dose-dependent, statistically significant reduction in EASI scores from baseline to Week 16. The reductions, i.e. LS mean percentage change (SD) in EASI, were observed in the 250 mg Q2W −72.09% (37.229%), 250 mg Q4W −69.21% (38.282%) and in 125 mg Q4W −62.34% (37.266%). Given the fact that the 250 mg Q4W dose (with baseline loading dose of 500 mg) demonstrated statistically significant efficacy in terms of the primary and several secondary endpoints, the Applicant selected both 250 mg Q2W and Q4W as maintenance doses in Phase 3 to determine whether a lower dosing frequency was adequate once response was achieved, or whether the induction dosing frequency should be continued, which seems well justified. Despite the lack of active comparator, the design of the pivotal study is considered acceptable by CHMP to characterise the efficacy profile of lebrikizumab in AD.

In terms of concomitant medications, e.g. use of anti-histamines, the complete list of permitted concomitant treatments was initially not found in the submitted dossier. Upon CHMP's request, the Applicant provided the full list. It seemed that many participants used the prohibited, rescue or intermittent corticosteroid treatments during induction and maintenance periods of the studies KGAB and KGAC. Upon request, the Applicant further confirmed that the protocols were strictly followed, i.e. that concomitant treatments were recorded as protocol deviations or that the study drug was discontinued per protocol where applicable.

Study population

The eligibility criteria for the KGAB and KGAC studies were identical. The enrolled patients were adults or adolescents ≥12 to <18 years of age and weighing ≥40 kg with chronic AD that had been present for ≥1 year (according to American Academy of Dermatology Consensus Criteria), and been a candidate for systemic therapy. The AD was defined as moderate-to-severe at baseline by EASI score ≥16, IGA score ≥3 and ≥10% BSA of AD involvement, which can be supported. The patients were to apply a stable dose of non-medicated topical moisturiser daily throughout the study. Overall, the inclusion criteria were appropriate for an AD study. The enrolled patients were to have a history of inadequate response to treatment with topical medications; or determination that topical treatments are otherwise medically inadvisable. In terms of the key exclusion criteria, patients using topical medication, including TCSs, TCIs, PDE4 inhibitors or prescription moisturisers, as well as systemic medication, e.g. immunosuppressive/immunomodulating agents, phototherapy/photochemotherapy or biologics were excluded from the study. Otherwise, the exclusion criteria were mostly related to safety of the patients.

Overall, the eligibility criteria in the KGAB and KGAC studies are acceptable. Some of the inclusion and exclusion criteria were amended during the study. However, the changes were mostly minor clarifications, and it seems unlikely that the changes had relevant impact on the study conduct.

The eligibility criteria for the KGAD study were identical to the KGAB and KGAC studies in terms of patient population (adults and adolescents) and criteria of moderate-to-severe AD (chronic AD present for at least 1 year (according to American Academy of Dermatology Consensus Criteria), EASI score ≥16, IGA score ≥3 and ≥10% BSA), as well as most of the other criteria. In the KGAD study, however, patients with prior exposure to dupilumab could enter the study after 8 weeks washout. Further, some eligibility criteria due to the concomitant use of TCS in the KGAD study differed from the monotherapy studies, e.g. patients with important side effects to TCS were excluded from the study.

Endpoints

The co-primary endpoints of all three pivotal phase 3 studies KGAB, KGAC and KGAD were percentage of patients with an IGA score of 0 or 1 and a reduction ≥2 points from baseline to Week 16, and patients achieving EASI 75 at Week 16. These endpoints measure the same domain (improvement in extent of AD on skin), are widely used, aligned with the CHMP SA and acceptable. Both measures are dichotomised derivatives of the actual scales used, IGA and EASI.

Several key secondary, as well as other (secondary) efficacy endpoints were included in the studies. These endpoints can be considered relevant efficacy endpoints for AD, including the used patient-reported outcome measures, i.e., DLQI, POEM and PROMIS.

Two new PROs to provide additional daily data on symptoms of AD were incorporated into the studies, i.e., Pruritus NRS and Sleep-Loss Scale. The former asks about worst itching during the last 24 hours on a scale from 0 to 10, while Sleep-Loss Scale concerns the level of interference of itching on sleep last night on a likert scale: 0= not at all, 1= a little, 2= moderately, 3= quite a bit, and 4= unable to sleep. The psychometric validation of these assessments has been completed and is described in separate PRO dossiers. Both measures are single-item and included in the daily electronic diary. The validation work based on the Phase 2b trial as well as the data analysis in Phase 3 studies is based on weekly average scores that are calculated if data from at least 1 of the 7 prior days was provided by the subject.

Sample size

The sample size assumptions were informed by the results of the Phase 2b dose-ranging and well applicable to the then planned phase 3 studies. For KGAD, reasonable adjustments were made the expected response rates due to the concomitant use of TCS. Each of the studies were more than sufficiently powered for detecting a clinically relevant difference in efficacy of the induction treatment. The chosen sample size was driven by the need to collect sufficient safety data and to ensure sufficient responders for the Maintenance Period which is acceptable.

Randomisation

Randomisation by strata defined by three factors representing geography, a demographic factor (adolescent patients 12 to <18 years versus adults ≥18 years) and disease severity (IGA 3 versus 4) is conventional and acceptable. The three factors generate 3 x 2 x 2 = 12 randomisation lists and, inevitably, few subjects will enter a study from some of the strata. As such the procedure is acceptable if the stratification information is adequately taken into account in the data analysis. The primary analyses for the dichotomised co-primary endpoints are fully stratified such that comparisons are performed within each of the 12 strata and then combined with a specified weighing method. According to the protocol, the quantitative variables were to be analysed somewhat analogously by including each stratification strata in an ANCOVA model, however, this was turned into a conventional data modelling approach including a main effect for each stratification level in the model. While model used appears to deviate somewhat from the model that was pre-stated, it is conventional and in accordance with the EMA Guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013).

Blinding

The standard double-blind, placebo-controlled experimental setting applied in all of the three main studies is considered adequate for isolating the pharmacological effect of the IMP on signs and symptoms of AD. The active and placebo PFS's were identical in appearance. Furthermore, lebrikizumab was not associated with immediate side-effects that would risk the blinding.

In studies KGAB and KGAC, during the maintenance period, patients that reached EASI 75 or IGA 0,1 response at Week 16, were re-randomised to placebo (withdrawal) or lebrikizumab at Q2W or Q4W dosing frequency. Blinding to the treatment assignments during the initial 16 weeks and that during the

maintenance period was ensured by using placebo dummies as needed: to mimic loading doses and to mask the difference between withdrawal, reduced dosing frequency (Q4W) and continued Q2W during the maintenance period. Also, for those that entered the Escape arm at Week 16 or later, blinding of the previous treatment assignment was ensured by using, as applicable, dummy loading doses. However, the escape treatment of lebrikizumab Q2W was known.

The blinding was opened following database locks for induction and maintenance periods separately.

Overall, the blinding procedures are considered appropriate to avoid bias in individual patient assessments and in the statistical analysis and reporting. Specifically, blinding was ensured for the assessments relevant to the two main types of questions: efficacy during induction treatment and efficacy during maintenance among lebrikizumab responders at Week 16.

Statistical methods

In the three pivotal studies, the comparability of the treatment arms with respect to the pharmacological effect is distorted by intercurrent events: treatment discontinuation and the allowance/use of rescue medications. The Applicant describes the primary estimand of each of the Phase 3 trials as "*the difference between treatment conditions, i.e., Lebrikizumab vs Placebo, in the target patient population, in successful responses or means after 16 weeks achieved without use of rescue medication and if all patients continued with treatment except those who discontinued due to lack of efficacy*". Indeed, ideally the treatment effect would have been assessed without use of rescue medication among treatment compliant patients, and the fact these intercurrent events did happen should not be allowed to lead to anticonservative analyses.

Applicant's primary estimand and supportive estimand both consider any use of such rescue medication as a treatment failure. The supportive estimand for dichotomous variables also consider any treatment discontinuation as a treatment failure. This approach may not be conservative and may lead to overestimation of treatment effect especially for endpoints that are not closely related with the decision to initiate rescue medication or discontinue study treatment due to lack of efficacy. Upon CHMP's request, the Applicant provided descriptive analyses of disease activity and HRQoL (IGA, EASI, Pruritus NRS and DLQI) before and after initiation of rescue medication to allow comparison of the outcome trajectories that tended to precede rescue medication as compared with those that did not. Based on these analyses, although participants who used rescue medication generally had higher disease activity than those who did not, extensive overlap was noted in outcome profiles within the same treatment group. It was also noted that few patients continued efficacy assessment after premature discontinuation of study medication. These analyses further questioned the necessity of declaring "nonresponse" solely based on rescue medication and highlighted the need to evaluate treatment effect as per treatment policy strategy.

The Applicant was requested to analyse the primary and key secondary endpoints in accordance with ITT principle, i.e., treatment policy estimand for which data are used regardless of any intercurrent events. Furthermore, should rescue medication or treatment discontinuation also lead to missing data, any imputation models was to account for what is known about the subjects status with respect to these intercurrent events. Still, the analyses provided by the Applicant imputed any missing data with MCMC-MI which, in practice, implies a hypothetical scenario where the patients with missing data had used randomised treatment and rescue medication in a similar manner with those that provided data. Despite this caveat, these analyses supported the existence of robust treatment effects even if rescue medications were allowed, whether measured in terms of difference in proportion of responders or mean change from baseline. As compared with the prespecified primary estimand, these analyses that used data regardless of rescue medication, however, attenuated treatment effect considerably for DLQI which could have been expected. This endpoint may be less driven by the factors that drive the decision to initiate rescue treatment.

Upon CHMP's request, the Applicant clarified that for estimation of treatment-arm specific LSmeans, the default covariate weights of the respective SAS procedure were used. These imply a target population where a third of patients are from each region, half are adolescents and half have IGA of 3. As was expected based on theoretical grounds, use of covariate weights that correspond to study population improved the precision of estimation of LS means: The difference in SE was the greatest for DLQI: the SEs of the LSmeans reported in CSR were 2-3 -fold greater in comparison with SEs estimated using covariate weights that correspond to the study population. The LS mean point estimates happened to differ only little depending on whether the default covariate weights or covariates weights proportional to the study population were used. Also noting that no choice of covariate weights could impact the estimate of treatment effect, the issue was not pursued further.

Protocol amendments

Substantial changes in the pivotal trials were described in the initial MAA and further clarified upon CHMP's request. It can be concluded that these changes did not have relevant impact on the study outcomes.

Protocol deviations and other GCP issues

Following primary outcome database lock in study KGAD (Week 16), a site audit triggered by statistically implausible data at one study site resulted in a critical finding. Due to this GCP non-compliance at 1 study site, 35 patients were excluded from the mITT population, 18 from Study KGAC and 17 from Study KGAD. According to the Applicant, any efficacy analyses performed on the data of these patients would have led to inconclusive and unreliable results due to the unreliable baseline AD values. For this reason, efficacy analyses in this population were not performed. Based on further details upon CHMP's request, the use of using the mITT population as the primary analysis population appeared justified and the findings do not change the overall conclusion on the B/R.

16.3% and 15.5% of the patients during the Induction Period and 8.6 % and 7.9% of the patients during the Maintenance Period were identified to have at least 1 important protocol deviation in the KGAB and KGAC studies, respectively. Upon CHMP's request, the Applicant provided further discussion on the impact of important protocol deviations on participants' safety and overall assessment of study results. It can be concluded that participants' safety was ensured and that no major impact on assessment of results is expected.

In KGAD study, altogether 52.6% of the patients were identified with at least 1 important protocol deviation. Although this is can be considered a high number, a majority were in the category "study procedure/missing safety assessments", which are unlikely to affect assessment of efficacy. The 18 patients in KGAC study and 17 patients in the KGAD study were included in the important protocol deviations in the category "inclusion/exclusion".

All pivotal studies were conducted during the COVID-19 pandemic and altogether 10.8%, 10.3% and 7.9% of the patients in the KGAB, KGAC and KGAD studies reported at least 1 protocol deviation related to the COVID-19 pandemic. According to the Applicant, however, the primary, coprimary, and all key secondary endpoints were not impacted.

Efficacy data and additional analyses

Participant flow

Altogether 424 patients were randomised in the KGAB study, 283 to the lebrikizumab 250 Q2W group and 141 to placebo group. 157 (55.5%) of the patients lebrikizumab group were considered as responders (vs. 17% in the placebo group), were re-randomised into the maintenance blinded period and received either placebo, lebrikizumab (n=32), lebrikizumab 250 mg Q4W (n=63) or lebrikizumab 250 mg Q2W (n=48), out of which 68.8%, 85.7% and 77.4% of patients completed the 52-week study,

respectively. Altogether 106 patients (37.5%) receiving lebrikizumab during the induction period were classified as non-responders and were enrolled into the escape arm, and 20 patients (7.1%) discontinued the study prior to week 16.

A total of 445 patients were randomised into the KGAC study. Following findings of a site audit, data from all 18 participants at a specific site were excluded, creating an mITT Population of 427 participants, 281 in the lebrikizumab 250 Q2W group and 146 in the placebo group. 134 (47.7%) of the patients lebrikizumab group were considered as responders (vs. 15.1% in the placebo group), were re-randomised into the maintenance blinded period and received either placebo, lebrikizumab (n=28), lebrikizumab 250 mg Q4W (n=55) or lebrikizumab 250 mg Q2W (n=51), out of which 78.6%, 92.7% and 80.4% of the patients completed the 52-week study, respectively. Altogether 125 patients (44.5%) receiving lebrikizumab during the induction period were classified as non-responders and were enrolled into the escape arm, and 22 patients (7.8%) discontinued the study prior to week 16.

Percentages of screen failures were approximately 21% in KGAB and 27% in KGAC study, being in the range presented for the pivotal studies for mAbs approved in moderate to severe AD indication. Upon CHMP's request, the Applicant provided further details on the reasons for screen failures and no external validity issues arose.

In the KGAD study, 228 participants were randomly assigned to treatment groups. mITT population comprised of 211 participants (145 in the lebrikizumab 250 Q2W + TCS group and 66 in the placebo +TCS group). Altogether 134 patients (92.4%) in the lebrikizumab 250 Q2W + TCS group and 58 patients (87.9%) in the placebo +TCS group completed the 16-week treatment. Percentage of screen failures was approximately 27%, being roughly similar as for add-on study for mAb approved in moderate to severe AD indication. The Applicant provided reasons for screen failures. No external validity issues arose.

Demographic and other baseline characteristics

Overall, the demographic and baseline characteristics were well balanced between the study groups in the KGAB, KGAC and KGAD studies in terms of age, percentage of adolescent patients, gender, weight/BMI and duration since the AD onset. Across the 3 pivotal studies, 49.7% were females, so both genders were equally represented. Overall, patients from the EU represented 27.3% of the total population; more specifically 32.5% in study KGAB, 26.7% in study KGAC and 18.0% in study 18.0%.

Overall, 61.5% of patients had a baseline IGA of 3 (moderate atopic dermatitis), 38.5% of patients had a baseline IGA of 4 (severe atopic dermatitis), and 54.8% of patients had received prior systemic treatment. The mean baseline EASI was 29.6, the mean baseline Pruritus NRS was 7.2 and the mean baseline DLQI was 15.5.

In terms of prior AD therapies, the study groups were well balanced in all pivotal studies. Almost all reported prior use of TCS and depending on the study prior TCI use was reported by 33.6-43.4% of patients. Approximately half of patients reported use of prior systemic treatment in pivotal studies. Unlike in KGAB and KGAC studies, prior use of dupilumab was allowed in KGAD study and was reported by 13.7% of the patients (13.8% in the lebrikizumab 250 mg Q2W + TCS group and 13.6% in the placebo + TCS group). In KGAD study, previous tralokinumab use was reported by 1 patient in each group.

Primary endpoints results (Weeks 0 to 16)

Lebrikizumab demonstrated a statistically significant and clinically relevant improvements over placebo when used as monotherapy (KGAB and KGAC) or in combination with TCS (KGAD) and the co-primary endpoints, i.e. proportion of patients achieving EASI 75 and IGA 0,1 (with ≥2 point reduction from baseline) at Week 16 were met in all 3 pivotal studies.

IGA 0,1

Based on the primary analysis using the "hybrid" estimand, 43.1% and 33.2% of patients treated with lebrikizumab and 12.7% and 10.8% of patients treated with placebo achieved IGA 0,1 with ≥2-point reduction in the KGAB and KGAC studies at Week 16. This translated into a 29.7% (95% CI 21.6, 37.8, p<0.001) and 21.9% (95% CI 14.2, 29.6, p<0.001) difference from placebo in the KGAB and KGAC studies, respectively.

In KGAD, 41.2% of patients treated with lebrikizumab + TCS and 22.1% of patients treated with placebo + TCS achieved IGA 0,1 with ≥2-point reduction at Week 16. This translated into a 18.3% (95% CI 5.1, 31.5, p=0.011) difference from placebo.

EASI 75

In KGAB and KGAC, 58.8% and 52.1% of patients treated with lebrikizumab and 16.2% and 18.1% of patients treated with placebo achieved EASI 75 at Week 16. This translated into a 42% (95% CI 33.3, 50.6, p<0.001) and 33.3% (95% CI 24.4, 42.2, p<0.001) difference from placebo in the KGAB and KGAC studies, respectively.

In KGAD, 69.5% of patients treated with lebrikizumab + TCS and 42.2% of patients treated with placebo + TCS achieved EASI 75 at Week 16. This translated into a 26.4% (95% CI 12.1, 40.8, p<0.001) difference from placebo.

The supportive "composite" estimand yielded similar results to the primary analysis of the co-primary endpoints, with statistically significant differences and clinically relevant improvements with lebrikizumab over placebo when used either as monotherapy (KGAB and KGAC) or in combination with TCS (KGAD).

Unlike in KGAB and KGAC studies, prior use of dupilumab was allowed in KGAD study and was reported by 13.7% of the patients (13.8% in the lebrikizumab 250 mg Q2W + TCS group and 13.6% in the placebo + TCS group). Subgroup analyses of the primary and key secondary endpoints suggest that lebrikizumab shows benefit also in patients previously exposed to dupilumab. However, the number of these patients is too small to make any firm conclusions.

Key secondary endpoints (Weeks 0 to 16)

For the Induction Period, the key secondary endpoints in studies KGAB and KGAC supported the effects seen in the co-primary endpoints. In KGAB and KGAC, 38.3% and 30.7% of patients treated with lebrikizumab achieved EASI 90 at Week 16 compared to 9.0% and 9.5% of participants treated with placebo. The treatment difference between lebrikizumab and placebo was higher in KGAB compared to KGAC: 28.8 (95% CI 21.3, 36.3) vs 20.7 (95% CI 13.3, 28.1).

In KGAB and KGAC, 45.9% and 39.8% of patients treated with lebrikizumab achieved pruritus NRS score ≥4 point improvement at Week 16 compared to 13.0% and 11.5% of participants treated with placebo. The treatment difference between lebrikizumab and placebo was slightly higher in KGAB compared to KGAC: 32.9 (95% CI 24.6, 41.3) vs 28.3 (95% CI 20.0, 36.5).

Overall, for the secondary endpoints under multiplicity adjustment, statistically significant improvements (i.e. p<0.05) in lebrikizumab group vs. placebo group were seen in all endpoints, except for "Percentage of patients with a Pruritus NRS of ≥4 points at Baseline who achieve a ≥4-point reduction from Baseline to Week 2" in KGAC study.

Similarly to the KGAB and KGAC studies, the key secondary endpoints in the KGAD study supported the effects seen in the co-primary endpoints. 41.2% of patients treated with lebrikizumab + TSC achieved EASI 90 at Week 16 compared to 21.7% of participants treated with placebo + TSC. The treatment difference between lebrikizumab + TSC and placebo + TSC was 18.9 (95% CI 6.1, 31.7). 50.6% of patients treated with lebrikizumab + TSC achieved pruritus NRS score ≥4 point improvement at Week

16 compared to 31.9% of participants treated with placebo + TSC. The treatment difference between lebrikizumab and placebo was 19.2 (95% CI 4.3, 34.1). Overall, for all key secondary endpoints under multiplicity adjustment, a statistically significant improvements were seen in lebrikizumab group vs. placebo group.

Other secondary endpoints (Weeks 0 to 16)

In addition to the co-primary and several major secondary efficacy endpoints, the pivotal Phase 3 studies included an extensive list of other secondary endpoints. Only selected secondary endpoints are presented by the Applicant. Overall, lebrikizumab demonstrated an improvement over placebo in several of these secondary endpoints, whether used as monotherapy or in combination with TCS.

Maintenance Treatment period (KGAB and KGAC)

Regarding the key secondary endpoints specific for maintenance period, in lebrikizumab-responders re-randomised to the Maintenance Blinded Period, the maintenance of EASI 75 response, IGA 0,1 (with a ≥2 point improvement from Baseline), Pruritus NRS 4-Point Improvement and percentage improvement in EASI was higher in patients re-randomised to lebrikizumab vs. placebo. In general, the maintenance of responses from week 16 to week 52 was similar in patients re-randomised to lebrikizumab Q2W and Q4W, or even somewhat better in the lebrikizumab Q4W group, supporting the proposed Q4W dosing after the Induction Period. It is noted that a relatively large proportion of patients that were re-randomised to placebo after receiving lebrikizumab during the Induction Period (lebrikizumab withdrawal), maintained the treatment responses i.e. in the pooled analysis of KGAB and KGAC studies 66.4% maintained EASI 75 response, 47.9% maintained IGA 0,1 (with a ≥2 point improvement from Baseline) and 66.3% maintained Pruritus NRS 4-Point Improvement at Week 52.

Simulation data suggested that patients with adequate initial response may continue to maintain response with 250 mg QXW dosing but there is no clinical data to confirm this. It is therefore recommended that the Applicant conducts a clinical study that compares Q4W vs. QXW dosing during the maintenance period in subjects who are initial responders at week 16.

Maintenance Week 16 Escape Population Results (KGAB and KGAC)

Among the patients who were treated with placebo and lebrikizumab during the Induction Period and received open-label lebrikizumab 250 mg Q2W (Maintenance Week 16 Escape Population), 52.5% and 40% achieved IGA 0,1 and 83.9% and 76.9% achieved EASI 75 at Week 52. The responses were slightly higher in patients that received placebo during the Induction Period, but this group also received two loading doses of lebrikizumab when entering the Escape Arm and used somewhat more rescue therapy, i.e. 42.2% of patients that received placebo vs. 28.6% vs. those that received lebrikizumab during Induction Period, respectively, received any rescue therapy during Weeks 16 to 52.

The proposed Posology Section of the SmPC states that "Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment". Given that part of the lebrikizumab non-responders during the Induction Period achieved clinically relevant responses (e.g. EASI 75, IGA 0,1) during continued treatment, the optimal time point for lebrikizumab discontinuation in non-responders was inconclusive. Upon CHMP's request, the Applicant provided further analysis on patients that were partial responders at week 16, showing that some patients could benefit if the induction dosing is continued until week 24. Consequently, the SmPC was revised to include the option to continue Q2W up to week 24 in patients with initial partial response.

Rescue therapy

During the Induction Period in KGAB and KGAC studies, the use of rescue medications was clearly more frequent in the placebo group vs. lebrikizumab group. TCS was the most common rescue treatment, used by 29.8% vs. 8.5% of the patients (KGAB), and 37% vs. 16.7% (KGAC) of the patients in the

placebo and lebrikizumab groups, respectively. Systemic rescue treatment was used by 7.8% vs. 2.5% of the patients (KGAB), and 6.2% vs. 2.8% (KGAC) of the patients in the placebo and lebrikizumab groups, respectively. During the Induction period, patients in the lebrikizumab group demonstrated a 73% and 65% reduction in the risk of initiating rescue therapy vs. placebo in the KGAB study (HR: 0.27, 95% CI: 0.17 to 0.42) and KGAC study (HR: 0.35, 95% CI: 0.24 to 0.52), respectively. In pooled analysis for the KGAB and KGAC study, altogether 105 (36.6%) placebo-treated patients vs. 83 (14.7%) lebrikizumab-treated patients required at least 1 rescue therapy before Week 16.

During the Maintenance Period of the KGAB and KGAC studies, there were less differences in the use of rescue medications between groups. In the pooled analysis, 18.3%, 16.1% and 12.4% of patients in the placebo group (lebrikizumab withdrawal), lebrikizumab 250 mg Q4W and Q2W, respectively, used any rescue medication. High-potency topical rescue therapy was used somewhat more in the placebo group (lebrikizumab withdrawal), i.e. by 10% of the patients vs. 5.1% and 4.4% of the patients in the lebrikizumab 250 mg Q4W and Q2W groups, respectively.

Overall, rescue therapy use was comparable for all treatment groups during the Maintenance Period. Use of high-potency topical rescue therapy was highest for patients re-randomised to placebo (lebrikizumab withdrawal). Use of systemic rescue therapy was low for all treatment groups.

In study KGAD, use of low-to-mid-potency TCS and TCI was allowed to be used and not regarded as rescue therapy and therefore the overall use of rescue therapy was lower compared to the KGAB and KGAC monotherapy studies. Nevertheless, the use of rescue therapy was higher in the placebo + TCS group vs. lebrikizumab + TCS group. 10.6% of patients in the placebo + TCS group used at least 1 rescue therapy during the study compared to 4.1% in the lebrikizumab + TCS group, mostly high potency TCS (4.5% vs. 1.4%), and systemic treatment (7.6% vs. 3.4%).

In the pooled analysis for the Week 16 Escape Arm of the KGAB and KGAC study where all patients received open label lebrikizumab 250 mg Q2W (Week 16 to 52), any rescue therapy was used slightly more in patients that received placebo (42.2%) vs. patients that received lebrikizumab during the induction period (28.6%).

Subgroup analysis

Based on the subgroup analysis of pooled data from the Induction Periods of Studies KGAB and KGAC, and data from Study KGAD at Week 16, the treatment effect in subgroups were generally consistent with the overall study population, although in the pooled data from KGAB and KGAC studies, the proportion of patients achieving IGA 0,1, EASI 75 and EASI 90 was somewhat lower in patients in the weight group ≥100 kg vs. weight group ≤60 kg. For the Maintenance Period, the responses in the weight group ≥100 kg were somewhat higher with Q2W dosing vs. Q4W dosing. However, the number of patients in the ≥100 kg subgroup was too low to make further conclusions based on these results. In summary, the proposed Q4W dosing in subjects ≥100 kg is acceptable, as the overall benefit-risk balance of Q4W dosing is considered positive also in these subjects.

Adolescents

A subgroup analysis was performed for the adolescent population from the pivotal Phase 3 studies KGAB, KGAC and KGAD. In the pooled analysis of the KGAB and KGAC studies, 46.6% vs. 14.3% of the adolescent patients achieved IGA 0,1 and 62.0% vs. 17.3% achieved EASI 75 at Week 16 in lebrikizumab vs. placebo groups, respectively. In KGAD study, 57.3% vs. 28.6% of the of the adolescent patients achieved IGA 0,1 and 88.0% vs. 57.1% achieved EASI 75 at Week 16 in lebrikizumab vs. placebo groups, respectively. Furthermore, 16-week results were presented separately for the KGAE study, which enrolled only adolescent patients. Altogether, these analyses provided evidence that lebrikizumab has similar or somewhat better efficacy in adolescent population compared to adult population.

KGAE study was an open label 52-week study, with the aim to evaluate the safety and efficacy of lebrikizumab in adolescent patients (from 12 years to <18 years weighing ≥40 kg). The eligibility criteria were similar as in the Ph3 studies KGAB and KGAC in terms of moderate to severe AD, i.e. all patients had EASI≥16, IGA score≥ and BSA≥10%, and were candidate for systemic therapy. Altogether 206 patients were evaluated for efficacy (MCMC-MI analysis). At week 52, 62.6% had an IGA score of 0 or 1 and a reduction of ≥2 points from baseline, and 81.9% achieved EASI 75. It is noted that the lebrikizumab dose used in the study (after the 500 mg loading doses at week 0 and 2) was 250 mg Q2W from Week 4 through Week 52, which differs from the proposed maintenance dose of 250 mg Q4W after Week 16 in the SmPC. Nevertheless, the study provided supportive long-term efficacy data in adolescents and provided additional safety exposure data in this population.

Supportive studies

In addition to the pivotal studies, the clinical program in AD includes a long-term extension study (LTE) up to 100 weeks (KGAA), a separate 52-week study in adolescents (KGAE) (see above) and supportive Phase 2 studies (KGAG, KGAH and KGAF). At the time of the initial MAA, the LTE study and a study to evaluate the effect of lebrikizumab on vaccine responses (KGAK) were ongoing. The CSR of the KGAK study was submitted as part of the second round of assessment. Whereas immune responses to Tdap were not affected by lebrikizumab, significantly higher immune responses to MCV vaccine were seen in lebrikizumab-treated subjects vs. placebo-treated subjects. Upon request, the Applicant provided further discussion on the higher responses to the MCV vaccination in the lebrikizumab-treated group vs. placebo group. Although no clear root cause was identified, it is reassuring that the response rates to MCV in the lebrikizumab group was within the range reported in other studies, e.g. with dupilumab and tralokinumab. Therefore, it can be concluded that the antibody responses to both non-live vaccines were not negatively impacted by the concomitant lebrikizumab treatment. The results of the effect of lebrikizumab on vaccine responses is reflected in section 4.5 of the SmPC.

KGAA study

In terms of the LTE study KGAA, the initial MAA included data for 86 lebrikizumab-responders from KGAD study, who were re-randomised 2:1 to receive lebrikizumab 250 mg Q2W or Q4W. Out of the lebrikizumab-responders at week 16 of the KGAD study, 71.7% and 67.6% of the patients had IGA 0,1 response, and 85.9% and 81.2% had EASI 75 response after 56 weeks of continuous treatment in the lebrikizumab 250 mg Q2W and Q4W groups, respectively. Out of the lebrikizumab-responders who had IGA 0,1 or EASI 75 response at week 16, 75.4% and 86.8% maintained IGA 0,1 and 85.9% and 81.2% maintained EASI 75 in lebrikizumab 250 mg Q2W and Q4W groups, respectively after 56 weeks in KGAA study. The patients were allowed to use low to moderate potency TCS as needed, and over 70% of the patients used TCS. Rescue therapy, including high potency TCS and systemic rescue therapy, was used by 7.0% and 13.8% of the patients in the lebrikizumab 250 mg Q2W and Q4W groups, respectively. Overall, the efficacy results were similar in the lebrikizumab 250 mg Q2W and Q4W groups, which support the Q4W dosing in the long-term treatment.

2.6.7. Conclusions on the clinical efficacy

Lebrikizumab demonstrated a statistically significant and clinically relevant improvements over placebo when used as monotherapy or in combination with TCS in adolescent and adult patients with moderate to severe AD who are candidate for systemic therapy. The co-primary endpoints were met in all 3 pivotal studies, supported by several key secondary efficacy endpoints. The proposed posology for the induction period is 500 mg at week 0 and week 2 followed by 250 mg every other week until week 16. For the maintenance period, the proposed posology is 250 mg every four weeks. The posology is endorsed by CHMP. The CHMP concluded that the efficacy data supports the following indication: "Ebglyss is indicated

for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older with a body weight of at least 40 kg who are candidates for systemic therapy".

2.6.8. Clinical safety

The safety of lebrikizumab in the treatment of adults and adolescents with AD is supported by data from 13 studies included in the clinical development program for AD (6 phase 1, 3 phase 2 and 4 phase 3 studies). Placebo-controlled safety data in AD patients treated with the intended dose for 16 weeks was available from studies KGAB, KGAC, KGAD and KGAF. Long term safety data up to 52/56 weeks was available from studies KGAB, KGAC and KGAA (an extension study). Adolescents were included in studies KGAB, KGAC and KGAD. In addition, an open-label single arm study KGAE provided safety data in only adolescents.

Safety data are presented separately for 4 periods: the induction period, the maintenance period, combined induction and maintenance period and any exposure to lebrikizumab. To evaluate safety for the mentioned periods, 6 different analysis sets were defined. In the **induction period,** 3 different analysis sets were defined: AD ALL PC Weeks 0 to 16 (also referred to as LEB with or without TCS), AD Mono PC Weeks 0 to 16 (also referred to as LEB monotherapy) and AD TCS PC Weeks 0 to 16 (from a single study - KGAD, also referred to as LEB+TCS). The **maintenance period** is evaluated in the AD Mono PC Weeks 16 to 52 set (Maintenance Period Placebo-Controlled Analysis Set; includes lebrikizumab responders during the induction period who were re-randomised to LEB Q2W, LEB Q4W or placebo during the maintenance period; of note: patients treated with placebo during induction could also be re-randomised to one of the 3 arms in maintenance). The **combined induction and maintenance period** are evaluated in the AD Mono/TCS Weeks 0 to 52/56 set (Combined Induction and Maintenance Periods Analysis Set), while **any exposure** to lebrikizumab is evaluated in the AD All LEB set.

The safety population used in this application is the **modified safety population**, which includes all participants receiving at least 1 dose of study drug minus 38 participants (from studies KGAD, KGAC and KGAA; 36 lebrikizumab-treated and 2 placebo-treated patients) who were excluded due to unreliable data from one centre discovered during a site audit. Data for the concerned 38 participants are however available in the Dossier.

The most important analysis set is that which allows for assessment of causality between the treatment and safety outcome. This analysis set (AD ALL PC Weeks 0-16) includes the 16-week safety profile of lebrikizumab 250 mg Q2W in three placebo-controlled monotherapy studies (KGAF, KGAB, KGAC) and one placebo-controlled combo study (KGAD). Data from this pooled analysis set were used to report ADRs and frequencies in the product information.

Safety data for indications other than AD were provided as supportive safety data but these data were not integrated into the AD safety database due to differences in disease states and comorbid conditions, dose level and regimen, and drug product and process change.

Supportive safety data was also provided from a study to evaluate the effect of lebrikizumab on vaccine responses in patients with AD (KGAK). The study was ongoing at the time of data cut-off and safety results were not pooled in the integrated analysis set but are presented separately.

2.6.8.1. Patient exposure

As of the data cutoff date of 06 June 2022, the AD safety database included 1720 participants (372 adolescents) exposed to lebrikizumab at any dose. Overall exposure was 1637.02 patient-years.

Of the 1720 participants with moderate-to-severe AD, 891 participants (270 adolescents) were exposed to lebrikizumab for at least 1 year, 744 participants (246 adolescents) were treated with Q2W only, and 132 participants (23 adolescents) were treated Q2W followed by Q4W for at least 1 year.

Table 60: Total Exposure to Lebrikizumab in the AD All LEB Integrated Analysis Set

	AD All LEB				
	Any LEB **N = 1720**	**Any LEB Q2W Exposure[a]** **N =1367**	**Any LEB Q4W Exposure** **N = 245**	**LEB 250mg Q2W Only[b]** **N = 1218**	**LEB 250mg Q2W Induction, Q4W Maintenance** **N = 147**
Patient days of exposure, mean (SD)	347.6 (194.12)	347.8 (189.66)	341.5 (188.98)	375.7 (181.54)	537.0 (170.75)
Weeks of exposure n (%)					
≥1 day	1720 (100)	1367 (100)	245 (100)	1218 (100)	147 (100)
≥16 weeks	1567 (91.1)	1228 (89.8)	217 (88.6)	1108 (91.0)	147 (100)
≥24 weeks	1301 (75.6)	1040 (76.1)	204 (83.3)	1034 (84.9)	146 (99.3)
≥40 weeks	998 (58.0)	850 (62.2)	138 (56.3)	848 (69.6)	134 (91.2)
≥52[c] weeks	**891** (51.8)	745 (54.5)	115 (46.9)	**744** (61.1)	**132** (89.8)
≥78 weeks	269 (15.6)	197 (14.4)	31 (12.7)	196 (16.1)	68 (46.3)
≥104 weeks	59 (3.4)	34 (2.5)	9 (3.7)	34 (2.8)	23 (15.6)
Total patient-years[d]	**1637.02**	**1301.67**	**229.08**	**1252.97**	**216.11**

Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; N = number of patients in the safety analysis set; n = number of patients in specified category; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation.

[a] Includes all patients who received lebrikizumab 250 mg Q2W treatment at any time. Only the time on lebrikizumab 250 mg Q2W was included, time on other lebrikizumab dose/frequency or placebo was not included.

[b] Includes patients who received LEB 250 mg Q2W as their only lebrikizumab treatment. Only the time on lebrikizumab 250 mg Q2W was included, time on placebo was not included.

[c] Includes participants treated for at least 360 days (consistent with the minimum protocol window of 5 days). One-year exposures are bolded for emphasis.

[d] Total patient-years is calculated as sum of duration of exposure in days for all patients in dosing regimen/365.25.

Table 61: Summary of Lebrikizumab Exposure from the Placebo-Controlled Induction Period Analysis Sets

	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS Weeks 0-16 (ADhere)	
	PBO	LEB 250mg Q2W	PBO	LEB 250mg Q2W	PBO+TCS	LEB 250mg Q2W+TCS
	N = 404	N = 783	N = 338	N = 638	N = 66	N = 145
Patient days of exposure (SD)	102.8 (26.59)	108.8 (17.77)	102.2 (26.84)	108.4 (18.15)	106.3 (25.14)	110.4 (15.96)
Weeks of exposure, n (%)						
≥1 day	404 (100)	783 (100)	338 (100)	638 (100)	66 (100.0)	145 (100.0)
≥16 weeks	266 (65.8)	571 (72.9)	218 (64.5)	452 (70.8)	48 (72.7)	119 (82.1)
Total patient-years[a]	113.76	233.26	94.55	189.43	19.21	43.82

Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; N = number of patients in the safety analysis set; n = number of patients in the specified category; PBO = placebo; PC = placebo-controlled; Q2W = every 2 weeks; Q4W = every 4 weeks; SD = standard deviation; TCS = topical corticosteroids.

[a] Total patient-years is calculated as sum of duration of exposure in days for all patients in dosing regimen/365.25.

Of the 1720 participants with moderate-to-severe AD exposed to any dose of lebrikizumab,

- 372 (21.6%) were 12 to less than 18 years of age
- 1225 (71.2%) were 18 to less than 65 years of age
- 94 (5.5%) were 65 to less than 75 years of age
- 123 (7.2%) were 65 or more years of age, and
- 29 (1.7%) were 75 or more years of age.

2.6.8.2. Adverse events

2.6.8.2.1. Overview of Adverse Events

Table 62 and Table 63 provide an overview of adverse events for the different analysis sets during induction and maintenance treatment.

Induction period (placebo-controlled Weeks 0 to 16)

During the induction phase, the frequencies of SAEs were similar in the lebrikizumab and placebo groups. Most TEAEs were mild or moderate in severity. A higher proportion of participants discontinued treatment due to an AE in the lebrikizumab group (2.3%) compared to placebo (1.4%), with the most notable difference coming from the AD TCS analysis set. TEAE related to study treatment were more common in the lebrikizumab group (42 (10.4%) vs. 131 (16.8%) for PBO vs LEB respectively).

The frequencies of SAEs, TEAEs, and AEs leading to discontinuation were similar between lebrikizumab-treated subjects regardless of TCS.

Table 62: Overview of Adverse Events in the Placebo-Controlled Induction Period

	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS Weeks 0-16 (ADhere)	
	PBO N = 404 PYE = 113.8 n (adj %) [adj IR [a]]	LEB 250mg Q2W N = 783 PYE = 233.3 n (adj %) [adj IR [a]]	PBO N = 338 PYE = 94.6 n (adj %) [adj IR [a]]	LEB 250mg Q2W N = 638 PYE = 189.4 n (adj %) [adj IR [a]]	PBO+TCS N = 66 PYE = 19.2 n (%) [IR [a]]	LEB 250mg Q2W+TCS N = 145 PYE = 43.8 n (%) [IR [a]]
Deaths	1 (0.2)	0	1 (0.3)	0	0	0
SAE	8 (1.9) [7.0]	10 (1.3) [4.3]	7 (2.0) [7.4]	8 (1.2) [4.2]	1 (1.5) [5.2]	2 (1.4) [4.6]
TEAE	215 (53.1) [307.0]	384 (49.2) [247.3]	192 (57.1) [342.5]	321 (50.4) [257.8]	23 (34.8) [147.0]	63 (43.4) [199.8]
Mild	98 (24.2)	201 (25.7)	86 (25.5)	169 (26.4)	12 (18.2)	32 (22.1)
Moderate	99 (24.6)	165 (21.2)	89 (26.6)	137 (21.6)	10 (15.2)	28 (19.3)
Severe	18 (4.4)	18 (2.3)	17 (5.0)	15 (2.4)	1 (1.5)	3 (2.1)
TEAE related to study treatment[b]	42 (10.4)	131 (16.8)	39 (11.7)	114 (17.9)	3 (4.5)	17 (11.7)
DC from study drug due to AE	6 (1.4) [5.1]	18 (2.3) [7.9]	6 (1.8) [6.3]	15 (2.4) [8.1]	0	3 (2.1) [6.9]

Abbreviations: AD = atopic dermatitis; AE = adverse event; adj % = adjusted percentage; DC = discontinuation; IR = incidence rate; LEB = lebrikizumab; Mono = monotherapy; n = number of patients in the specified category; N = number of patients in the analysis population; PBO = placebo; PC = placebo-controlled; PY = patient-year; PYE = patient-years of exposure; Q2W = every 2 weeks; SAE = serious adverse event; TCS = topical corticosteroids; TEAE = treatment-emergent adverse event.

[a] Events per 100 PY.

[b] Relationship to study treatment is assessed by the investigator.

Combined induction and maintenance period (AD Mono/TCS Weeks 0 to 52/56)

The exposure adjusted incidence rates (events per 100 PY) of SAEs in the lebrikizumab-treated participants through Weeks 52/56 (3.9 for LEB 250 mg Q2W only and 3.6 for LEB 250 mg Q2W/Q4W only) were similar compared to the LEB 250 mg Q2W group of the induction period (4.3) and lower compared to placebo (6.6).

The IRs per 100 PY for TEAEs in the lebrikizumab-treated participants through Weeks 52/56 (159.4 for LEB 250 mg Q2W only and 119.7 for LEB 250 mg Q2W/Q4W only) were lower compared to the LEB 250 mg Q2W group of the placebo-controlled induction period (247.3).

Table 63: Overview of Adverse Events in the Maintenance Period, Combined Induction and Maintenance Period, and AD All LEB Analyses Sets

	AD Mono PC Weeks 16-52			AD Mono/TCS Weeks 0-52/56			AD All LEB		
	PBO (LEB Withdrawal) N = 60 PYE = 37.0 n (adj %) [adj IR[a]]	LEB 250mg Q2W N = 113 PYE = 71.1 n (adj %) [adj IR[a]]	LEB 250mg Q4W N = 118 PYE = 77.4 n (adj %) [adj IR[a]]	PBO N = 352 PYE = 106.8 n (%) [IR[a]]	LEB 250mg Q2W only N = 844 PYE = 622.3 n (%) [IR[a]]	LEB 250mg Q2W/Q4W only N = 147 PYE = 143.8 n (%) [IR[a]]	Any LEB 250mg Q2W N = 1367 PYE = 1301.7 n (%) [IR[a]]	Any LEB 250mg Q4W N = 245 PYE = 229.1 n (%) [IR[a]]	Any LEB N = 1720 PYE = 1637.0 n (%) [IR[a]]
Deaths	0	0	0	1 (0.3)	1 (0.1)	0	3 (0.2)	0	3 (0.2)
SAE	1 (1.6) [2.7]	2 (1.8) [3.0]	2 (1.7) [2.7]	7 (2.0) [6.6]	24 (2.8) [3.9]	5 (3.4) [3.6]	45 (3.3) [3.5]	5 (2.0) [2.2]	56 (3.3) [3.5]
TEAE	30 (50.0) [117.5]	56 (49.7) [121.1]	61 (51.7) [124.4]	194 (55.1) [286.9]	524 (62.1) [159.4]	93 (63.3) [119.7]	866 (63.4) [135.6]	129 (52.7) [94.1]	1106 (64.3) [137.9]
Mild	15 (25.0)	35 (31.0)	24 (20.4)	86 (24.4)	250 (29.6)	43 (29.3)	396 (29.0)	54 (22.0)	505 (29.4)
Moderate	15 (25.0)	17 (15.2)	31 (26.2)	93 (26.4)	242 (28.7)	42 (28.6)	407 (29.8)	66 (26.9)	510 (29.7)
Severe	0	4 (3.5)	6 (5.1)	15 (4.3)	32 (3.8)	8 (5.4)	63 (4.6)	9 (3.7)	91 (5.3)
TEAE related to study treatment[b]	7 (11.6)	12 (10.7)	22 (18.6)	39 (11.1)	187 (22.2)	42 (28.6)	301 (22.0)	44 (18.0)	372 (21.6)
DC from study drug due to AE	0	1 (0.9) [1.4]	2 (1.7) [2.6]	5 (1.4) [4.7]	32 (3.8) [5.2]	3 (2.0) [2.1]	62 (4.5) [4.8]	6 (2.4) [2.6]	73 (4.2) [4.5]

Abbreviations: AD = atopic dermatitis; adj % = adjusted percentage; AE = adverse event; DC = discontinuation; IR = incidence rate; LEB = lebrikizumab; Mono = monotherapy; n = number of patients in the specified category; N = number of patients in the analysis population; PBO = placebo; PC = placebo-controlled; PY = patient-years; PYE = patient years of exposure; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TCS = topical corticosteroids; TEAE = treatment-emergent adverse event.

[a] Events per 100 PY.

[b] Relationship to study treatment is judged by the investigator.

2.6.8.2.2. Common Treatment-Emergent Adverse Events

Common TEAEs are those reported at a frequency of greater than or equal to 1% before rounding in the lebrikizumab-treated group.

Induction period (Placebo-controlled Weeks 0 to 16)

Across all analysis sets in the placebo-controlled induction period, the following preferred terms were reported more frequently in the lebrikizumab group compared to placebo:

- conjunctivitis (6.5% in the LEB 250 mg Q2W group versus 1.8% in the placebo group)

- nasopharyngitis (4.4% in the LEB 250 mg Q2W group versus 3.2% in the placebo group)
- headache (4.4% in the LEB 250 mg Q2W group versus 2.9% in the placebo group)
- conjunctivitis allergic (1.8% in the LEB 250 mg Q2W group versus 0.7% in the placebo group)
- dry eye (1.4% in the LEB 250 mg Q2W group versus 0.9% in the placebo group), and
- rhinitis allergic (1.0% in the LEB 250 mg Q2W group versus 0.2% in the placebo group).

Table 64: Treatment-Emergent Adverse Events Occurring in at Least 1% of Lebrikizumab-Treated Participants from the Induction Period Placebo-Controlled Analysis Sets

	AD ALL PC Weeks 0-16		**AD Mono PC Weeks 0-16**		**AD TCS Weeks 0-16 (ADhere)**	
Preferred Term	**PBO** **N = 404** **PYE = 113.8** **n (adj %)** **[adj IR[a]]**	**LEB 250mg Q2W** **N = 783** **PYE = 233.3** **n (adj %)** **[adj IR[a]]**	**PBO** **N = 338** **PYE = 94.6** **n (adj %)** **[adj IR[a]]**	**LEB 250mg Q2W** **N = 638** **PYE = 189.4** **n (adj %)** **[adj IR[a]]**	**PBO +TCS** **N = 66** **PYE = 19.2** **n (%)** **[IR[a]]**	**LEB 250mg Q2W+TCS** **N = 145** **PYE = 43.8** **n (%)** **[IR[a]]**
Patients with at least 1 TEAE	215 (53.1) [307.0]	384 (49.2) [247.3]	192 (57.1) [342.5]	321 (50.4) [257.8]	23 (34.8) [147.0]	63 (43.4) [199.8]
Conjunctivitis	7 (1.8) [6.2]	51 (6.5) [22.8]	7 (2.1) [7.6]	44 (6.8) [24.2]	0	7 (4.8) [16.5]
Dermatitis atopic	74 (18.4) [76.9]	47 (6.0) [21.2]	71 (21.4) [90.3]	44 (6.8) [24.3]	3 (4.5) [16.1]	3 (2.1) [6.9]
Nasopharyngitis	13 (3.2) [11.8]	34 (4.4) [15.2]	9 (2.6) [9.6]	31 (4.9) [17.0]	4 (6.1) [21.7]	3 (2.1) [7.0]
Headache	12 (2.9) [10.5]	34 (4.4) [15.0]	11 (3.2) [11.7]	27 (4.3) [14.7]	1 (1.5) [5.2]	7 (4.8) [16.4]
Oral herpes	9 (2.3) [8.1]	15 (1.9) [6.5]	8 (2.4) [8.8]	13 (2.0) [6.9]	1 (1.5) [5.2]	2 (1.4) [4.6]
Conjunctivitis allergic	3 (0.7) [2.6]	14 (1.8) [6.1]	3 (0.9) [3.2]	14 (2.2) [7.5]	0	0
Dry eye	4 (0.9) [3.4]	11 (1.4) [4.8]	4 (1.1) [4.2]	8 (1.2) [4.3]	0	3 (2.1) [7.0]
Pruritis	7 (1.8) [6.4]	9 (1.2) [3.9]	7 (2.1) [7.8]	9 (1.4) [4.8]	0	0
COVID-19	5 (1.3) [4.4]	9 (1.1) [3.8]	5 (1.5) [5.4]	7 (1.1) [3.7]	0	2 (1.4) [4.6]
Hypertension	4 (1.0) [3.6]	9 (1.1) [3.8]	3 (0.9) [3.2]	5 (0.8) [2.6]	1 (1.5) [5.2]	4 (2.8) [9.3]
Rhinitis allergic	1 (0.2) [0.9]	8 (1.0) [3.5]	1 (0.3) [1.1]	7 (1.1) [3.7]	0	1 (0.7) [2.3]
Injection site pain	4 (1.0) [3.5]	7 (1.0) [3.2]	4 (1.2) [4.2]	7 (1.2) [3.9]	0	0
Herpes zoster	0	5 (0.6) [2.1]	0	3 (0.5) [1.6]	0	2 (1.4) [4.6]
Impetigo	6 (1.5) [5.4]	6 (0.8) [2.6]	5 (1.5) [5.4]	4 (0.6) [2.1]	1 (1.5) [5.3]	2 (1.4) [4.6]
Urinary tract infection	2 (0.5) [1.7]	5 (0.6) [2.1]	2 (0.6) [2.1]	3 (0.5) [1.6]	0	2 (1.4) [4.6]
Fall	1 (0.2)	3 (0.4)	1 (0.3)	1 (0.2)	0	2 (1.4)

	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS Weeks 0-16 (ADhere)	
	PBO	LEB 250mg Q2W	PBO	LEB 250mg Q2W	PBO +TCS	LEB 250mg Q2W+TCS
Preferred Term	N = 404 PYE = 113.8 n (adj %) [adj IR[a]]	N = 783 PYE = 233.3 n (adj %) [adj IR[a]]	N = 338 PYE = 94.6 n (adj %) [adj IR[a]]	N = 638 PYE = 189.4 n (adj %) [adj IR[a]]	N = 66 PYE = 19.2 n (%) [IR[a]]	N = 145 PYE = 43.8 n (%) [IR[a]]
	[0.8]	[1.3]	[1.0]	[0.5]		[4.6]
Type 2 diabetes mellitus	0	2 (0.2) [0.8]	0	0	0	2 (1.4) [4.6]
Nausea	2 (0.5) [1.8]	6 (0.8) [2.6]	2 (0.6) [2.0]	4 (0.6) [2.2]	0	2 (1.4) [4.6]
Vomiting	1 (0.3) [0.9]	4 (0.5) [1.7]	1 (0.3) [1.1]	2 (0.3) [1.1]	0	2 (1.4) [4.6]
Thrombocytopenia	0	4 (0.5) [1.7]	0	2 (0.3) [1.0]	0	2 (1.4) [4.6]
Injection site rash	0	3 (0.4) [1.3]	0	1 (0.2) [0.6]	0	2 (1.4) [4.6]
Injection site reaction	1 (0.3) [1.0]	5 (0.6) [2.1]	0	3 (0.5) [1.6]	1 (1.5) [5.3]	2 (1.4) [4.6]

Abbreviations: AD = atopic dermatitis; adj % = adjusted percentage; COVID-19 = coronavirus disease 2019; IR = incidence rate; LEB = lebrikizumab; n = number of patients in the specified category; N = number of patients in the safety analysis set; PC = placebo-controlled; PY = patient-years; PYE = patient-years of exposure; Q2W = every 2 weeks; TCS = topical corticosteroids; TEAE = treatment-emergent adverse event.

[a] Events per 100 PY.

Maintenance period (AD Mono PC Weeks 16 to 52)

In the maintenance period, the frequencies of common TEAEs were similar between the LEB 250 mg Q2W and placebo groups, except for folliculitis which was reported more frequently in the LEB 250 Q2W group (3 subjects, 2.7%) compared to placebo (0 subjects).

The following TEAEs were more frequently reported in the LEB 250 mg Q4W group compared to placebo

- COVID-19
- nasopharyngitis
- headache
- folliculitis
- conjunctivitis allergic, and
- oral herpes.

The following TEAEs were more frequently reported in the LEB 250 mg Q4W group compared to the LEB 250 mg Q2W group

- COVID-19
- nasopharyngitis
- conjunctivitis allergic

- headache
- conjunctivitis, and
- oral herpes.

Combined induction and maintenance period (AD Mono/TCS Weeks 0 to 52/56)

In addition to common TEAEs reported in the placebo-controlled period, the following TEAEs were reported by at least 1% of lebrikizumab-treated participant through Weeks 52/56 and with higher frequency with lebrikizumab compared to placebo.

- vaccination complication
- folliculitis
- URTI
- back pain
- vaccination site pain
- herpes dermatitis
- acne
- asthma
- arthralgia
- dizziness
- eye pruritus
- fatigue, and
- blepharitis.

The IRs of common TEAEs were similar in the lebrikizumab groups compared to the LEB 250 mg Q2W group from the placebo-controlled induction period, except for COVID-19.

Any AD lebrikizumab exposure (AD All LEB)

In addition to the previously reported common TEAEs, the following TEAEs were reported by at least 1% of participants in the Any LEB group: alanine aminotransferase increased, anxiety, cough, diarrhea, and eosinophilia.

Table 65: Treatment-Emergent Adverse Events Occurring in at Least 1% of Lebrikizumab-Treated Participants from the Maintenance Period, Combined Induction and Maintenance Period, or AD All LEB Analysis Sets

	AD Mono PC Weeks 16-52			AD Mono/TCS Weeks 0-52/56			AD All LEB		
Preferred Term	PBO N = 60 PYE = 37.0 n (adj %) [adj IR[a]]	LEB 250mg Q2W N = 113 PYE = 71.1 n (adj %) [adj IR[a]]	LEB 250mg Q4W N = 118 PYE = 77.4 n (adj %) [adj IR[a]]	PBO N = 352 PYE = 106.8 n (%) [IR[a]]	LEB 250mg Q2W Only N = 844 PYE = 622.3 n (%) [IR[a]]	LEB 250mg Q2W/Q4W Only N = 147 PYE = 143.8 n (%) [IR[a]]	Any LEB 250mg Q2W N = 1367 PYE = 1301.7 n (%) [IR[a]]	Any LEB 250mg Q4W N = 245 PYE = 229.1 n (%) [IR[a]]	Any LEB N = 1720 PYE = 1637.0 n (%) [IR[a]]
Patients with at least 1 TEAE	30 (50.0) [117.5]	56 (49.7) [121.1]	61 (51.7) [124.4]	194 (55.1) [286.9]	524 (62.1) [159.4]	93 (63.3) [119.7]	866 (63.4) [135.6]	129 (52.7) [94.1]	1106 (64.3) [137.9]
COVID-19	2 (3.3) [5.5]	3 (2.6) [4.2]	11 (9.4) [14.9]	5 (1.4) [4.7]	39 (4.6) [6.4]	13 (8.8) [9.3]	111 (8.1) [8.8]	22 (9.0) [10.1]	133 (7.7) [8.4]
Nasopharyngitis	3 (5.0) [8.3]	4 (3.5) [5.8]	9 (7.6) [12.2]	11 (3.1) [10.5]	55 (6.5) [9.2]	19 (12.9) [14.2]	116 (8.5) [9.4]	19 (7.8) [8.6]	157 (9.1) [10.2]
Dermatitis atopic	7 (11.7) [19.8]	5 (4.4) [7.2]	7 (5.9) [9.3]	73 (20.7) [79.4]	68 (8.1) [11.6]	10 (6.8) [7.2]	110 (8.0) [9.0]	14 (5.7) [6.3]	128 (7.4) [8.3]
Conjunctivitis allergic	2 (3.3) [5.5]	2 (1.8) [2.9]	7 (5.9) [9.4]	3 (0.9) [2.8]	42 (5.0) [7.0]	9 (6.1) [6.5]	54 (4.0) [4.3]	9 (3.7) [4.0]	70 (4.1) [4.4]
Vaccination complication	2 (3.3) [5.4]	3 (2.7) [4.5]	3 (2.5) [3.9]	0	17 (2.0) [2.8]	3 (2.0) [2.1]	22 (1.6) [1.7]	3 (1.2) [1.3]	25 (1.5) [1.5]
Folliculitis	0	3 (2.7) [4.4]	3 (2.5) [3.9]	4 (1.1) [3.8]	13 (1.5) [2.1]	4 (2.7) [2.8]	16 (1.2) [1.2]	4 (1.6) [1.8]	21 (1.2) [1.3]
Headache	1 (1.6) [2.7]	1 (0.9) [1.5]	5 (4.2) [6.5]	10 (2.8) [9.5]	35 (4.1) [5.8]	10 (6.8) [7.3]	62 (4.5) [4.9]	8 (3.3) [3.6]	81 (4.7) [5.1]
Conjunctivitis	3 (5.0) [8.4]	0	6 (5.0) [8.1]	7 (2.0) [6.6]	60 (7.1) [10.2]	18 (12.2) [13.6]	98 (7.2) [8.0]	9 (3.7) [4.0]	112 (6.5) [7.2]
Oral herpes	1 (1.6) [2.7]	1 (0.9) [1.4]	4 (3.4) [5.2]	9 (2.6) [8.6]	21 (2.5) [3.4]	7 (4.8) [5.1]	45 (3.3) [3.5]	7 (2.9) [3.1]	50 (2.9) [3.1]

	AD Mono PC Weeks 16-52			AD Mono/TCS Weeks 0-52/56			AD All LEB		
Preferred Term	**PBO** **N = 60** **PYE = 37.0** **n (adj %)** **[adj IR[a]]**	**LEB 250mg Q2W** **N = 113** **PYE = 71.1** **n (adj %)** **[adj IR[a]]**	**LEB 250mg Q4W** **N = 118** **PYE = 77.4** **n (adj %)** **[adj IR[a]]**	**PBO** **N = 352** **PYE = 106.8** **n (%)** **[IR[a]]**	**LEB 250mg Q2W Only** **N = 844** **PYE = 622.3** **n (%)** **[IR[a]]**	**LEB 250mg Q2W/Q4W Only** **N = 147** **PYE = 143.8** **n (%)** **[IR[a]]**	**Any LEB 250mg Q2W** **N = 1367** **PYE = 1301.7** **n (%)** **[IR[a]]**	**Any LEB 250mg Q4W** **N = 245** **PYE = 229.1** **n (%)** **[IR[a]]**	**Any LEB** **N = 1720** **PYE = 1637.0** **n (%)** **[IR[a]]**
Upper respiratory tract infection	3 (5.1) [8.8]	2 (1.8) [2.9]	2 (1.7) [2.6]	6 (1.7) [5.7]	13 (1.5) [2.1]	3 (2.0) [2.1]	39 (2.9) [3.0]	9 (3.7) [4.0]	66 (3.8) [4.1]
Back pain	1 (1.7) [2.8]	2 (1.8) [3.0]	2 (1.7) [2.6]	2 (0.6) [1.9]	7 (0.8) [1.1]	3 (2.0) [2.1]	12 (0.9) [0.9]	2 (0.8) [0.9]	17 (1.0) [1.0]
Vaccination site pain	0	2 (1.8) [3.0]	2 (1.7) [2.6]	1 (0.3) [0.9]	9 (1.1) [1.5]	2 (1.4) [1.4]	14 (1.0) [1.1]	2 (0.8) [0.9]	16 (0.9) [1.0]
Food allergy	0	1 (0.9) [1.5]	3 (2.5) [3.9]	1 (0.3) [0.9]	1 (0.1) [0.2]	3 (2.0) [2.1]	3 (0.2) [0.2]	3 (1.2) [1.3]	7 (0.4) [0.4]
Herpes dermatitis	0	1 (0.9) [1.4]	3 (2.5) [3.9]	2 (0.6) [1.9]	8 (0.9) [1.3]	3 (2.0) [2.1]	14 (1.0) [1.1]	4 (1.6) [1.8]	18 (1.0) [1.1]
Acne	1 (1.6) [2.7]	1 (0.9) [1.5]	2 (1.7) [2.6]	3 (0.9) [2.8]	12 (1.4) [1.9]	2 (1.4) [1.4]	22 (1.6) [1.7]	2 (0.8) [0.9]	26 (1.5) [1.6]
Aspartate aminotransferase increased	0	1 (0.9) [1.4]	2 (1.7) [2.6]	0	5 (0.6) [0.8]	2 (1.4) [1.4]	10 (0.7) [0.8]	3 (1.2) [1.3]	13 (0.8) [0.8]
Contusion	0	1 (0.9) [1.5]	2 (1.7) [2.7]	2 (0.6) [1.9]	4 (0.5) [0.6]	2 (1.4) [1.4]	5 (0.4) [0.4]	2 (0.8) [0.9]	8 (0.5) [0.5]
Erythema	0	1 (0.9) [1.4]	2 (1.7) [2.6]	0	4 (0.5) [0.6]	2 (1.4) [1.4]	6 (0.4) [0.5]	2 (0.8) [0.9]	9 (0.5) [0.6]
Ligament sprain	0	1 (0.9) [1.5]	2 (1.7) [2.6]	1 (0.3) [0.9]	6 (0.7) [1.0]	2 (1.4) [1.4]	10 (0.7) [0.8]	3 (1.2) [1.3]	14 (0.8) [0.9]
Weight increased	0	1 (0.9) [1.4]	2 (1.7) [2.6]	0	3 (0.4) [0.5]	2 (1.4) [1.4]	3 (0.2) [0.2]	2 (0.8) [0.9]	5 (0.3) [0.3]

	AD Mono PC Weeks 16-52			AD Mono/TCS Weeks 0-52/56			AD All LEB		
	PBO	LEB 250mg Q2W	LEB 250mg Q4W	PBO	LEB 250mg Q2W Only	LEB 250mg Q2W/Q4W Only	Any LEB 250mg Q2W	Any LEB 250mg Q4W	Any LEB
Preferred Term	N = 60 PYE = 37.0 n (adj %) [adj IR[a]]	N = 113 PYE = 71.1 n (adj %) [adj IR[a]]	N = 118 PYE = 77.4 n (adj %) [adj IR[a]]	N = 352 PYE = 106.8 n (%) [IR[a]]	N = 844 PYE = 622.3 n (%) [IR[a]]	N = 147 PYE = 143.8 n (%) [IR[a]]	N = 1367 PYE = 1301.7 n (%) [IR[a]]	N = 245 PYE = 229.1 n (%) [IR[a]]	N = 1720 PYE = 1637.0 n (%) [IR[a]]
Dry eye	0	1 (0.9) [1.4]	1 (0.8) [1.3]	2 (0.6) [1.9]	17 (2.0) [2.8]	2 (1.4) [1.4]	19 (1.4) [1.5]	1 (0.4) [0.4]	25 (1.5) [1.5]
Rhinitis allergic	0	0	0	1 (0.3) [0.9]	15 (1.8) [2.4]	0	17 (1.2) [1.3]	0	18 (1.0) [1.1]
Hypertension	1 (1.6) [2.7]	2 (1.7) [2.8]	0	4 (1.1) [3.8]	13 (1.5) [2.1]	2 (1.4) [1.4]	26 (1.9) [2.0]	1 (0.4) [0.4]	31 (1.8) [1.9]
Urinary tract infection	2 (3.4) [5.7]	0	1 (0.9) [1.3]	1 (0.3) [0.9]	13 (1.5) [2.1]	1 (0.7) [0.7]	27 (2.0) [2.1]	3 (1.2) [1.3]	32 (1.9) [2.0]
Asthma	0	0	1 (0.8) [1.3]	1 (0.3) [0.9]	12 (1.4) [1.9]	2 (1.4) [1.4]	15 (1.1) [1.2]	1 (0.4) [0.4]	21 (1.2) [1.3]
Arthralgia	0	1 (0.9) [1.5]	0	1 (0.3) [0.9]	11 (1.3) [1.8]	1 (0.7) [0.7]	19 (1.4) [1.5]	4 (1.6) [1.8]	27 (1.6) [1.7]
Pruritus	0	1 (0.9) [1.5]	1 (0.9) [1.3]	7 (2.0) [6.6]	10 (1.2) [1.6]	3 (2.0) [2.1]	20 (1.5) [1.6]	3 (1.2) [1.3]	33 (1.9) [2.0]
Injection site reaction	0	0	0	1 (0.3) [0.9]	12 (1.4) [1.9]	1 (0.7) [0.7]	18 (1.3) [1.4]	1 (0.4) [0.4]	20 (1.2) [1.2]
Dizziness	0	0	0	1 (0.3) [0.9]	10 (1.2) [1.6]	0	11 (0.8) [0.9]	0	14 (0.8) [0.9]
Eye pruritus	0	0	1 (0.8) [1.3]	0	9 (1.1) [1.5]	1 (0.7) [0.7]	11 (0.8) [0.8]	3 (1.2) [1.3]	16 (0.9) [1.0]
Fatigue	1 (1.7) [2.8]	0	0	3 (0.9) [2.8]	8 (0.9) [1.3]	2 (1.4) [1.4]	18 (1.3) [1.4]	5 (2.0) [2.2]	25 (1.5) [1.5]
Blepharitis	0	1 (0.9) [1.4]	0	1 (0.3) [0.9]	7 (0.8) [1.1]	3 (2.0) [2.1]	10 (0.7) [0.8]	0	11 (0.6) [0.7]

	AD Mono PC Weeks 16-52			AD Mono/TCS Weeks 0-52/56			AD All LEB		
Preferred Term	**PBO** **N = 60** **PYE = 37.0** **n (adj %)** **[adj IR[a]]**	**LEB 250mg Q2W** **N = 113** **PYE = 71.1** **n (adj %)** **[adj IR[a]]**	**LEB 250mg Q4W** **N = 118** **PYE = 77.4** **n (adj %)** **[adj IR[a]]**	**PBO** **N = 352** **PYE = 106.8** **n (%)** **[IR[a]]**	**LEB 250mg Q2W Only** **N = 844** **PYE = 622.3** **n (%)** **[IR[a]]**	**LEB 250mg Q2W/Q4W Only** **N = 147** **PYE = 143.8** **n (%)** **[IR[a]]**	**Any LEB 250mg Q2W** **N = 1367** **PYE = 1301.7** **n (%)** **[IR[a]]**	**Any LEB 250mg Q4W** **N = 245** **PYE = 229.1** **n (%)** **[IR[a]]**	**Any LEB** **N = 1720** **PYE = 1637.0** **n (%)** **[IR[a]]**
Abdominal pain	0	1 (0.9) [1.4]	1 (0.8) [1.3]	0	4 (0.5) [0.6]	3 (2.0) [2.1]	14 (1.0) [1.1]	1 (0.4) [0.4]	17 (1.0) [1.0]
Anxiety	2 (3.3) [5.6]	1 (0.9) [1.4]	1 (0.8) [1.3]	3 (0.9) [2.8]	4 (0.5) [0.6]	3 (2.0) [2.1]	14 (1.0) [1.1]	2 (0.8) [0.9]	23 (1.3) [1.4]
Cough	0	0	2 (1.7) [2.6]	1 (0.3) [0.9]	4 (0.5) [0.6]	3 (2.0) [2.1]	19 (1.4) [1.5]	2 (0.8) [0.9]	27 (1.6) [1.7]
Diarrhea	2 (3.3) [5.5]	0	0	1 (0.3) [0.9]	7 (0.8) [1.1]	0	18 (1.3) [1.4]	4 (1.6) [1.8]	29 (1.7) [1.8]
Nausea	1 (1.6) [2.7]	0	0	2 (0.6) [1.9]	7 (0.8) [1.1]	1 (0.7) [0.7]	18 (1.3) [1.4]	1 (0.4) [0.4]	21 (1.2) 1.3]
Alanine aminotransferase increased	1 (1.6) [2.6]	0	1 (0.9) [1.3]	0	4 (0.5) [0.6]	1 (0.7) [0.7]	16 (1.2) [1.2]	3 (1.2) [1.3]	21 (1.2) [1.3]
Eosinophilia	0	0	0	2 (0.6) [1.9]	8 (0.9) [1.3]	0	17 (1.2) [1.3]	0	20 (1.2) [1.2]

Abbreviations: AD = atopic dermatitis; adj % = adjusted percentage; COVID-19 = coronavirus disease 2019; IR = incidence rate; LEB = lebrikizumab; n = number of patients in the specified category; N = number of patients in the safety analysis set; PY = patient-years; PYE = patient-years of exposure; Q2W = every 2 weeks; Q4W = every 4 weeks; TCS = topical corticosteroids; TEAE = treatment-emergent adverse event.

[a] Events per 100 PY.

2.6.8.2.3. Other Treatment-Emergent Adverse Events by SOC

TEAEs were analysed by SOC to assist in identification of AEs that may be apparent only when all effects on a given organ system are evaluated in aggregate.

Induction period (Placebo-controlled Weeks 0 to 16)

LEB with or without TCS (AD ALL PC)

The most frequently reported SOCs for lebrikizumab-treated participants compared to placebo-treated participants were

- Infections and infestations
    - 21.2% in the LEB 250 mg Q2W group versus 18.9% in the placebo group (primarily driven by the PTs conjunctivitis and nasopharyngitis)
- Eye disorders
    - 6.6% in the LEB 250 mg Q2W group versus 4.4% in the placebo group (primarily driven by the PTs conjunctivitis allergic and dry eye)
- Nervous system disorders
    - 6.3% in the LEB 250 mg Q2W group versus 4.6% in the placebo group, and
- General disorders and administration site conditions
    - 5.1% in the LEB 250 mg Q2W group versus 3.9% in the placebo group.

Odds ratios for the frequencies of TEAEs within SOCs were presented in appended tables (not shown here for brevity). In addition to the common TEAEs presented above, the following less common TEAEs were more than twice as frequent with LEB than with PBO (odds ratio ≥2) in the induction phase:

Within the SOC Infections and infestations: gastroenteritis.
Within the SOC Eye disorders: blepharitis.
Within the SOC Nervous system disorders: dizziness.
Within the SOC General disorders and administration site conditions: injection site erythema and injection site reaction.
Within the SOC Respiratory, thoracic and mediastinal disorders: asthma, cough, oropharyngeal pain and sinus congestion.
Within the SOC Gastrointestinal disorders: diarrhoea.
Within the SOC Musculoskeletal and connective tissue disorders: Pain in extremity

Maintenance period (AD Mono PC Weeks 16 to 52)

The frequencies of TEAEs within the following SOCs were higher in the LEB 250 mg Q4W group compared to the placebo (LEB withdrawal) group.

- Infections and infestations
    - 30.5% in the LEB 250 mg Q4W group versus 21.0% in the placebo (LEB withdrawal) group
- Eye disorders

- 9.3% in the LEB 250 mg Q4W group versus 5.0% in the placebo (LEB withdrawal) group (primarily driven by the PT Conjunctivitis allergic)

- Nervous system disorders
  - 7.6% in the LEB 250 mg Q4W group versus 3.3% in the placebo (LEB withdrawal) group (primarily driven by the PT Headache), and
- Musculoskeletal and connective tissue disorders
  - 3.4% in the LEB 250 mg Q4W group versus 1.7% in the placebo (LEB withdrawal) group (primarily driven by 2 events of Back pain).

Combined induction and maintenance period (AD Mono/TCS Weeks 0 to 52/56)

The frequencies of TEAEs in the following SOCs were higher in the lebrikizumab-treated groups through Weeks 0 to 52/56 compared to the LEB 250 mg Q2W group of the placebo-controlled induction period. This was not unexpected based on longer exposure to lebrikizumab.

The frequencies of these SOCs were

- Infections and infestations
  - 30.1% in the LEB 250 mg Q2W only group
  - 44.9% in the LEB 250 mg Q2W/Q4W only group, and
  - 19.0% in the placebo group.
- Eye disorders
  - 11.5% in the LEB 250 mg Q2W only group
  - 12.9% in the LEB 250 mg Q2W/Q4W only group, and
  - 4.5% in the placebo group.
- Respiratory, thoracic and mediastinal disorders
  - 6.6% in the LEB 250 mg Q2W only group
  - 6.1% in the LEB 250 mg Q2W/Q4W only group, and
  - 2.6% in the placebo group.
- Musculoskeletal and connective tissue disorders
  - 6.0% in the LEB 250 mg Q2W only group
  - 5.4% in the LEB 250 mg Q2W/Q4W only group, and
  - 3.4% in the placebo group.

2.6.8.2.4. Adverse events of special interest

Conjunctivitis

In the SmPC, the term Conjunctivitis includes the PTs of Conjunctivitis and Conjunctivitis bacterial. The PT of Conjunctivitis allergic is listed as a separate ADR.

In the induction phase the frequency of conjunctivitis events was 6.9%% in the LEB 250 mg Q2W group versus 1.8% in the placebo group. During maintenance, the frequency of conjunctivitis was 5.0% in the LEB 250 mg Q4W group and 5.9% in the placebo (LEB withdrawal) group. 14.2% of patients experienced Conjunctivitis or Conjunctivitis bacterial during one year of treatment with the intended dose. Overall, events within the conjunctivitis, keratitis, ocular symptoms, and dry eye clusters and PT of blepharitis were reported in 17.7% of patients treated with the intended dose for one year.

All events reported within conjunctivitis, keratitis, ocular symptom, and dry eye clusters were nonserious and mild or moderate in severity. One lebrikizumab-treated participant reported a severe event of blepharitis.

Table 66: Summary of Conjunctivitis from the Induction Period Placebo-Controlled Analysis Sets

	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS Weeks 0-16 (KGAD)	
Participants with ≥1 TEAE Event cluster Preferred Term	PBO N = 404 PYE = 113.8 n (adj %) [adj IR[a]]	LEB 250mg Q2W N = 783 PYE = 233.3 n (adj %) [adj IR[a]]	PBO N = 338 PYE = 94.6 n (adj %) [adj IR[a]]	LEB 250mg Q2W N = 638 PYE = 189.4 n (adj %) [adj IR[a]]	PBO+TCS N = 66 PYE = 19.2 n (%) [IR[a]]	LEB 250mg Q2W+TCS N = 145 PYE = 43.8 n (%) [IR[a]]
Conjunctivitis cluster	10 (2.5) [8.9]	67 (8.5) [30.6]	10 (3.0) [10.9]	60 (9.3) [33.7]	0	7 (4.8) [16.5]
Conjunctivitis	7 (1.8) [6.2]	51 (6.5) [22.8]	7 (2.1) [7.6]	44 (6.8) [24.2]	0	7 (4.8) [16.5]
Conjunctivitis allergic	3 (0.7) [2.6]	14 (1.8) [6.1]	3 (0.9) [3.2]	14 (2.2) [7.5]	0	0
Conjunctivitis bacterial	0	3 (0.4) [1.3]	0	3 (0.5) [1.6]	0	0
Keratitis cluster	1 (0.3) [0.9]	5 (0.6) [2.2]	1 (0.3) [1.1]	4 (0.6) [2.1]	0	1 (0.7) [2.3]
Keratitis	1 (0.3) [0.9]	1 (0.1) [0.4]	1 (0.3) [1.1]	1 (0.2) [0.5]	0	0
Vernal keratoconjunctivitis	0	2 (0.2) [0.8]	0	1 (0.2) [0.5]	0	1 (0.7) [2.3]
Atopic keratoconjunctivitis	0	2 (0.3) [0.9]	0	2 (0.3) [1.1]	0	0
Ocular symptoms cluster	1 (0.2) [0.9]	9 (1.1) [3.9]	1 (0.3) [1.1]	7 (1.1) [3.7]	0	2 (1.4) [4.6]
Dry Eye cluster	4 (0.9) [3.4]	12 (1.5) [5.2]	4 (1.1) [4.2]	8 (1.2) [4.3]	0	4 (2.8) [9.3]
Blepharitis	1 (0.2) [0.9]	6 (0.8) [2.6]	1 (0.3) [1.1]	5 (0.8) [2.6]	0	1 (0.7) [2.3]

Abbreviations: AD = atopic dermatitis; adj % = study size adjusted percentage; adj IR = study size adjusted incidence rate; LEB = lebrikizumab; Mono = monotherapy; N = number of patients in the analysis set; n = number of patients in the specified category; PBO = placebo; PC = placebo-controlled; PY = patient-years; PYE = patient-years of exposure; Q2W = every 2 weeks; TCS = topical corticosteroids; TEAE = treatment-emergent adverse event.

[a] Events per 100 PY.

Note: Conjunctivitis as identified in this table refers broadly to several ocular symptoms and disorders including blepharitis, conjunctivitis of various etiologies (that is, bacterial, viral, allergic), and dry eye.

Infections, including herpes infections, relevant parasitic infections, and opportunistic infections

The incidence of the Infections and infestations SOC was higher in lebrikizumab-treated participants versus placebo-treated participants.

The most frequently reported events within this SOC and reported with higher frequency in the lebrikizumab group compared to placebo were nasopharyngitis (4.4% in the lebrikizumab group and 3.2% in the placebo group) and Herpes zoster (0.6% in the lebrikizumab group and 0 events in the placebo group). No confirmed opportunistic infections were reported. A lower frequency of skin infections was reported in the lebrikizumab-treated participants (2.2%) during the placebo-controlled period compared to placebo (5.9%). One helminth-parasitic infection was reported by a participant who received LEB 250 mg Q2W during induction and LEB 250 mg Q4W during maintenance in the AD Mono/TCS Weeks 0 to 52/56 analysis set.

In the induction phase, all herpes infections combined were balanced across treatment groups (2.9% in the lebrikizumab group and 3.7% in the placebo group). However, Herpes zoster events were reported only in the lebrikizumab group (0.6%) during induction, therefore, Herpes zoster is included as an ADR in proposed labeling.

The incidence of serious infections was low; 1 case of severe infectious colitis, two cases of COVID-19, one case of acarodermatitis and erysipelas and one case of pneumonia in the combined induction and maintenance phases in patients treated with lebrikizumab. All events were recovered/resolved and did not lead to treatment discontinuation.

These findings were consistent when participants were treated with lebrikizumab with or without TCS. No clinically meaningful differences were observed between different dosing regimens of LEB 250 mg Q2W and LEB 250 mg Q4W.

Eosinophilia and eosinophil-related disorders

From baseline to Week 16 the frequency of participants with increased blood eosinophils at any time point post-baseline was higher in lebrikizumab-treated participants (20.3%) compared to placebo-treated participants (11.7%). Mean increases in eosinophil from baseline to Week 16 for the LEB 250 mg Q2W group was 0.11 x 109 cells/L while the mean increases from baseline for the placebo group was 0. Overall, mean increases were small and did not lead to eosinophil-related disorders. Eosinophilia (greater than 5000 cells/mm3) is included as an ADR in proposed labeling.

Hypersensitivity reactions

During the placebo-controlled induction period, no clinically significant imbalance in the frequency of hypersensitivity events was reported with lebrikizumab compared to placebo. No specific pattern of PTs

was observed besides Dermatitis atopic (as most events were related to the underlying disease). No serious events of immediate hypersensitivity or anaphylaxis were reported.

Injection site reactions

ISRs were reported in a numerically higher frequency in the lebrikizumab-treated group (n=20, 2.6%) compared to placebo (n=6, 1.5%) during the induction period with or without TCS. A total of 53 participants reported an ISR TEAE during the one-year follow-up. The majority of participants reported ISR TEAEs within Week 0 to 16 (n = 38) and Weeks 16 to 32 (n = 15).

No dose related differences were reported. Most events were mild or moderate in severity and none were serious. ISR is included as an ADR in proposed labeling.

Atopic dermatitis exacerbation

Events representing AD exacerbation, specifically dermatitis atopic, were reported with a lower frequency in the lebrikizumab-treated group (6.4%) compared to the placebo-treated group (18.9%) during the induction period with or without TCS. The majority of events were nonserious, mild or moderate in severity, and did not lead to treatment discontinuation. The IR of AD exacerbations in lebrikizumab-treated participants was lower in the AD All LEB group (8.8 per 100 PY) compared to lebrikizumab-treated participants during the placebo-controlled period (22.3 per 100 PY).

Hepatic safety

Based on the hepatic disorders SMQ (narrow terms), the percentage of participants that reported at least 1 TE hepatic disorder during the induction period was 1.1% (n = 8) in the lebrikizumab group, and 0 in the placebo group.

Shifts to high serum AST and ALT were more common in participants receiving lebrikizumab during the induction period. During induction, a shift to high serum alanine aminotransferase is noted in LEB 250mg Q2w (54 events, 7.8%) compared to placebo (12 events, 3.6%). A shift to high serum aspartate aminotransferase is noted in LEB 250mg Q2W (31 events, 4.2%) compared to placebo (11 events, 3.1%). Of note, the frequencies were calculated among patients with normal baseline values and ata least one post-baseline measure. During maintenance, a TE shift to high in serum alanine aminotransferase has been observed in LEB 250mg Q4W arm (7 events, 6.8%) and LEB 250mg Q2w (8 events, 8.4%) compared to placebo (2 events, 4.3%). A shift to high aspartate aminotransferase has been recorded in 4 participants (7.5%) in placebo, 3 (2.8%) in LEB Q4W and 5 (5%) in LEB Q2W.

The frequency of hepatic TEAEs through Weeks 52/56 (in the combined induction and maintenance set, ie. AD Mono/TCS Weeks 0 to 52/56) were: 17 (2.0%) in the LEB 250 mg Q2W only group; 4 (2.7%) in the LEB 250 mg Q2W/Q4W only group, and 0 in the placebo group. The most frequently PTs reported across all treatment groups were AST increased, ALT increased, and GGT increased.

The frequency of participants reporting at least 1 hepatic TEAE any AD lebrikizumab exposure set (ie. AD All LEB) were: 48 (2.8%) in the Any LEB group; 34 (2.5%) in the Any LEB Q2W group, and 10 (4.1%) in the Any LEB Q4W group.

In any lebrikizumab exposure set, participants with elevated transaminase (and normal bilirubin) were recorded. ALT values ≥5x ULN (and normal bilirubin) were recorded in 3 (0.2%) additional participants. Narratives of those patients are provided, however follow-up laboratory data could not be obtained for any of the 3 patients after peak ALT values were recorded. AST values ≥5x ULN (and normal bilirubin)

were recorded in 1 (0.1%) additional participant (in any lebrikizumab exposure set). The participant's narrative provides a plausible alternative explanation for the observed lab values and myopathy (extreme weightlifting). One participant with AST value at least 10x ULN and normal TBL was identified. According to the participant's narrative, the study drug was not interrupted despite a significant rise in enzymes on Day 525 (AST 11,2xULN, GGT 12.5xULN, ALT 4.3xULN, ALP 1.7xULN) but no more data is available.

Suicide/self-injury

Two (0.1%) events of suicidal ideation within the suicide/self-injury standardised MedDRA query were reported across the entire AD program. One event was reported during the induction period and 1 SAE was reported during the long-term extension study associated with an acute stressor. No events led to treatment discontinuation.

An adult female participant with history of anxiety and depression and treated with lebrikizumab during induction period reported a nonserious moderate event of suicidal ideation on Study Day 66. Patient recovered on the same day.

An adult female participant with no medical history of depression reported a SAE of major depression with suicidal ideation following a major traumatic life event on Study Day 449. She was treated with escitalopram and therapy visits. The event recovered on Study Day 503 and did not lead to study discontinuation.Given that the prevalence of clinical depression in adults with AD is around 15% (Patel et al. 2019) and that suicidal ideation is common in severe depression, and that there is no specific signal of increased risk of suicide by blocking IL-13, it is agreed that the data do not suggest an increased risk of suicide/self-injury among those treated with lebrikizumab.

Malignancies

Overall, 13 lebrikizumab-treated participants (0.8%) reported 20 malignancy events after any exposure to lebrikizumab during 0-52/56 weeks of follow-up. During the placebo-controlled period, nonmelanoma skin cancer (NMSC) events were reported in 2 patients (0.3%) in the lebrikizumab group and 2 patients (0.5%) in the placebo group. No malignancies other than NMSC were reported during the placebo-controlled induction period. NMSC events were generally unremarkable, localised, and a similar frequency was reported across treatment groups. All NMSC events were nonserious, mild or moderate in severity, and did not lead to treatment discontinuation.

Seven participants reported malignancies other than NMSC in the Any AD Lebrikizumab Exposure analysis set. One participant died from pancreatic carcinoma with metastases to liver and bone during the Study KGAC maintenance escape period. For brevity, only narratives of malignancies in younger participants will be presented here.

An adult female with no pertinent medical history reported a neuroendocrine tumor of the appendix on Study Day 245 in the open-label arm of Study KGAA and received lebrikizumab 250 mg Q2W. The SAE was not resolved during the study period and led to study discontinuation on Study Day 282.

An adolescent male with a history of AD and lower lip epidermoid cysts treated with LEB 250 mg Q2W on Study Day 1 reported a mild nonserious event of cutaneous T-cell lymphoma (mycosis fungoides). Investigator could not confirm the diagnosis of mycosis fungoides due to the participant's age and

immunohistochemical stains required for a definitive diagnosis was pending. Participant discontinued from the study.

An adult male participant reported a moderate nonserious event of cutaneous T-cell lymphoma during the maintenance period on Study Day 149. The event was not recovered. Participant discontinued from the study due to physician decision.

An adult female participant reported a moderate and nonserious event of left ovarian teratoma. The event recovered and did not lead to treatment discontinuation.

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths in the AD Program

There were 4 deaths in the lebrikizumab AD clinical programme.

- 1 death due to myocardial infarction was reported in the placebo group during the 16-week induction period of Study KGAC, and
- 3 deaths were reported in participants treated with lebrikizumab 250 mg Q2W
    - 1 death due to pancreatic cancer was reported in the maintenance escape period of Study KGAC
    - 1 death due to natural causes was reported in the long-term extension Study KGAA after rolling over from Study KGA
    - 1 death due to cardiac arrest was reported in the open-label period of Study KGAE.

The available information indicate no apparent relation to study drug. However, two events with very limited data available are described in more detail below.

An adult male participant was enrolledin Study KGAD and laterentered the long-term extension Study KGAA. During the long-term extension Study KGAA, the participant died of natural causes, as reported by the investigator. The participant had a medical history of hypertension, cardiac ablation, AD, insomnia, and gastroesophageal reflux disease. The investigator assessed the event to be unrelated to study treatment.

During the open-label Study KGAE, an adolescentmale participant died of cardiac arrest , as reported by the investigator. The participant tested positive for COVID-19 in the hospital emergency room as part of screening. The investigator reported the cardiac arrest was likely due to COVID-19. The investigator assessed the event to be unrelated to study treatment.

Deaths in the Asthma Program

To support safety evaluations for the AD submission, an integrated database with all studies (Phases 1 to 3) conducted in participants with asthma was created to form an Asthma ALL Lebrikizumab Exposure Analysis Set (Asthma ALL Lebrikizumab). This is an uncontrolled dataset and included studies with various treatment regimens and doses. Only descriptive statistics are provided for this analysis set.

Treatment doses for asthma studies were lower than for AD studies. In Phase 2, doses studied varied and included 37.5 mg, 125 mg, or 250 mg Q4W, and in some studies participants were dosed at 0.3 mg/kg to 5 mg/kg. In Phase 3, doses studied included 37.5 mg or 125 mg administered Q4W.

There were 5 deaths in the Asthma ALL LEB analysis set reported for lebrikizumab-treated participants, 3 of which occurred in lebrikizumab-treated participants during the treatment period.

The provided narratives indicate no relation to study drug.

Other Serious Adverse Events

All SAEs in the placebo-controlled induction period were single cases. No clinically meaningful differences between treatment groups were noted for SAEs in either the induction or the maintenance phase. Frequencies of SAEs during the maintenance phase and IRs of SAEs in the AD All LEB analysis set did not suggest an increase with longer exposure.

Induction period (Placebo-controlled Weeks 0 to 16)

The frequency of participants reporting at least 1 SAE was similar in the lebrikizumab and placebo groups (Table 67). No single PT within a SOC was reported by more than 1 participant in each treatment group during induction.

Table 67: Summary of Serious Adverse Events by Preferred Term from the Induction Period Placebo-Controlled Analysis Sets

	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS Weeks 0-16 (Adhere)	
	PBO	LEB 250mg Q2W	PBO	LEB 250mg Q2W	PBO+TCS	LEB 250mg Q2W+TCS
Preferred Term	N = 404 PYE = 113.8 n (adj %) [adj IR[a]]	N = 783 PYE = 233.3 n (adj %) [adj IR[a]]	N = 338 PYE = 94.6 n (adj %) [adj IR[a]]	N = 638 PYE = 189.4 n (adj%) [adj IR[a]]	N = 66 PYE = 19.2 n (%) [adj IR[a]]	N = 145 PYE = 43.8 n (%) [adj IR[a]]
Patients with at least 1 SAE	8 (1.9) [7.0]	10 (1.3) [4.3]	7 (2.0) [7.4]	8 (1.2) [4.2]	1 (1.5) [5.2]	2 (1.4) [4.6]
Dermatitis atopic	1 (0.2) [0.9]	1 (0.1) [0.4]	1 (0.3) [1.1]	1 (0.2) [0.5]	0	0
Myocardial infarction	1 (0.2) [0.9]	1 (0.1) [0.4]	1 (0.3) [1.1]	1 (0.2) [0.5]	0	0
Edema peripheral	1 (0.2) [0.8]	1 (0.1) [0.4]	1 (0.3) [1.0]	1 (0.2) [0.5]	0	0
Accidental overdose	0	1 (0.1)[b] [0.4]	0	1 (0.2)[b] [0.5]	0	0
Arthralgia	0	1 (0.1) [0.4]	0	1 (0.2) [0.5]	0	0
Cardiac failure	0	1 (0.1) [0.4]	0	1 (0.2) [0.5]	0	0
Carpel tunnel syndrome	0	1 (0.1) [0.4]	0	1 (0.2) [0.5]	0	0
Cerebellar syndrome	0	1 (0.1) [0.4]	0	1 (0.2) [0.5]	0	0
Fall	0	1 (0.1) [0.4]	0	0	0	1 (0.7) [2.3]
Large intestine infection	0	1 (0.1) [0.4]	0	1 (0.2) [0.5]	0	0
Multiple injuries	0	1 (0.1) [0.4]	0	1 (0.2) [0.5]	0	0
Sinus node dysfunction	0	1 (0.1) [0.4]	0	0	0	1 (0.7) [2.3]
Synovitis	0	1 (0.1) [0.4]	0	1 (0.2) [0.5]	0	0
Uterine leiomyoma	1 (0.5) [1.7]	0	1 (0.6) [2.0]	0	0	0
Acute kidney injury	1 (0.3) [0.9]	0	0	0	1 (1.5) [5.2]	0
Cellulitis	1 (0.3) [0.9]	0	1 (0.3) [1.1]	0	0	0
Dehydration	1 (0.3) [0.9]	0	0	0	1 (1.5) [5.2]	0
Fibula fracture[c]	1 (0.2) [0.9]	0	1 (0.3) [1.1]	0	0	0
Tibia fracture[c]	1 (0.2) [0.9]	0	1 (0.3) [1.1]	0	0	0

	AD ALL PC Weeks 0-16		AD Mono PC Weeks 0-16		AD TCS Weeks 0-16 (Adhere)	
	PBO	LEB 250mg Q2W	PBO	LEB 250mg Q2W	PBO+TCS	LEB 250mg Q2W+TCS
Preferred Term	N = 404 PYE = 113.8 n (adj %) [adj IR[a]]	N = 783 PYE = 233.3 n (adj %) [adj IR[a]]	N = 338 PYE = 94.6 n (adj %) [adj IR[a]]	N = 638 PYE = 189.4 n (adj%) [adj IR[a]]	N = 66 PYE = 19.2 n (%) [adj IR[a]]	N = 145 PYE = 43.8 n (%) [adj IR[a]]
Pulmonary embolism	1 (0.2) [0.8]	0	1 (0.3) [1.0]	0	0	0
Sepsis	1 (0.3) [0.9]	0	1 (0.3) [1.1]	0	0	0

Abbreviations: AD = atopic dermatitis; adj % = adjusted percentage; IR = incidence rate; LEB = lebrikizumab; Mono = monotherapy; n = number of patients in the specified category; N = number of patients in the analysis population; PY = patient-years; PC = placebo-controlled; PYE = patient-years of exposure; Q2W = every 2 weeks; SAE = serious adverse event; TCS = topical corticosteroids.

[a] Events per 100 PY.

[b] Accidental overdose was with Xanax.

[c] Fibula and tibia fracture occurred in the same patient.

Maintenance period (AD Mono PC Weeks 16 to 52)

The frequencies of participants with at least 1 SAE were similar for both lebrikizumab groups and placebo (LEB withdrawal).

The frequencies of participants reporting SAEs were

- 1.8% in the LEB 250 mg Q2W group
- 1.7% in the LEB 250 mg Q4W group, and
- 1.6% in the placebo (LEB withdrawal) group.

No SAE was reported by more than 1 participant.

Combined induction and maintenance period (AD Mono/TCS Weeks 0 to 52/56)

The IRs per 100 PY of SAEs were

- 3.9 in the LEB 250 mg Q2W only group
- 3.6 in the LEB 250 mg Q2W/Q4W only group, and
- 6.6 in the placebo group.

These IRs for lebrikizumab-treated participants were similar to those reported in the LEB 250 mg Q2W group in the placebo-controlled induction period.

Any AD lebrikizumab exposure (AD All LEB)

The IRs per 100 PY of SAEs were

- 3.5 in the Any LEB group
- 3.5 in the Any LEB 250 mg Q2W group, and
- 2.2 in the Any LEB 250 mg Q4W group.

These IRs for any lebrikizumab-treated participant were similar to those reported in the LEB 250 mg Q2W group in the placebo-controlled induction period.

2.6.8.4. Laboratory findings

Chemistry analytes where numerical differences were observed between lebrikizumab and placebo groups and which were not yet addressed in safety topics of special interest include:

- Blood urea nitrogen (BUN)
- potassium
- sodium
- chloride
- phosphate
- urate

Based on assessment of the provided data, the observed differences were not considered clinically meaningful.

There were no clinically meaningful differences observed for changes in haematology and chemistry analytes for lebrikizumab-treated participants compared to those treated with placebo. In some of the analytes, differences in prevalence of "high", "low", or "abnormal" haematology findings were observed; however, mean changes from baseline were small and not clinically meaningful.

Weight

This section describes weight changes in adult participants. Weight in adolescents is discussed separately.

Induction period (Placebo-controlled Weeks 0 to 16)

LEB with or without TCS (AD ALL PC)

The frequency of adult participants with weight gain defined as at least a 7% increase at any time postbaseline was higher in the LEB 250 mg Q2W group (5.1%) compared with placebo (1.8%). Box plots with changes up to Week 16 illustrate that these frequencies were influenced by a few participants with higher values.

The frequency of adult participants with weight loss defined as at least a 7% decrease at any time postbaseline was 3.3% in the LEB 250 mg Q2W group compared to 5.2% in the placebo group.

Overall, in the induction period the mean and median changes in weight from last baseline to last postbaseline in adults were

- LEB 250 mg Q2W (n = 657)
  - Mean (SD): 0.57 (3.22) kg
  - Median: 0.40 kg
  - minimum: -17.6 kg
  - maximum: 20.0 kg
- Placebo (n = 336)
  - Mean (SD): -0.18 (3.86) kg
  - Median: 0.25 kg
  - minimum: -24.3kg

- maximum: 26.9 kg

Combined induction and maintenance period (AD Mono/TCS Weeks 0 to 52/56)

The frequencies of participants with weight gain at any time were

- 9.7% in the LEB 250 mg Q2W only group
- 18.3% in the LEB 250 mg Q2W/Q4W only group, and
- 2.1% in the placebo group.

These frequencies of participants with weight gain (at least 7%) in any lebrikizumab-treated participant through Weeks 0 to 52/56 were higher than the LEB 250 mg Q2W group in the placebo-controlled induction period (5.2%).

The frequencies of participants with weight loss at any time were

- 5.7% in the LEB 250 mg Q2W only group
- 11.7% in the LEB 250 mg Q2W/Q4W only group, and
- 5.5% in the placebo group.

The frequencies of participants with weight loss (at least 7%) at any time in any lebrikizumab-treated participant through Weeks 0 to 52/56 were higher than the LEB 250 mg Q2W group in the placebo-controlled induction period (3.3%).

2.6.8.5. Safety in special populations

2.6.8.5.1. Safety Analyses in the Adolescent Population

The AD safety database included 372 adolescents (12-18 years of age) exposed to lebrikizumab at any dose. 270 adolescents were exposed to lebrikizumab for at least 1 year. 246 adolescents were treated with Q2W only, and 23 adolescents were treated Q2W followed by Q4W for at least 1 year.

Induction period (Placebo-controlled Weeks 0 to 16)

LEB with or without TCS (AD ALL PC)

A total of 1187 participants (1040 adults and 147 adolescents) were included in the AD ALL PC analysis set.

In the adolescent population, TEAEs were reported at a lower frequency in the lebrikizumab (35.6%) group compared to the placebo (55.3%) group. All events were mild or moderate in severity. No deaths occurred in the placebo-controlled analysis set. One (1%) SAE of synovitis was reported in the lebrikizumab group compared to no events in the placebo group.

The most common TEAEs in adolescents (ages 12 to less than 18 years old) occurring more frequently in the lebrikizumab-treated adolescents compared to placebo were

- conjunctivitis
- nasopharyngitis
- dry eye, and
- rhinitis allergic

Although the sample size is small and frequencies are low, the reported numbers of the following PTs were numerically higher in the lebrikizumab-treated adolescent population compared to the lebrikizumab-treated adult population (at least 18 years of age)

- Dry eye (2.9% versus 1.2%)
- Pruritus (2.2% versus 1.0%), and
- Rhinitis allergic (2.2% versus 0.9%)

All other common PTs were reported with similar or numerically higher frequency in the adult population compared to adolescents.

Table 68: Overview of Adverse Events in Adolescent and Adult Participants in the Placebo-Controlled Induction Period from the AD ALL PC Analysis Set

	AD ALL PC			
	Adolescents		Adults	
	PBO N = 48 n (adj %)	LEB 250mg Q2W N = 99 n (adj %)	PBO N = 356 n (adj %)	LEB 250mg Q2W N = 684 n (adj %)
Deaths	0	0	1 (0.3)	0
SAE	0	1 (1.0)	8 (2.2)	9 (1.3)
TEAE	27 (55.3)	35 (35.6)	188 (52.8)	349 (51.1)
Mild	15 (30.8)	19 (19.4)	83 (23.3)	182 (26.6)
Moderate	11 (22.4)	16 (16.2)	88 (24.8)	149 (21.9)
Severe	1 (2.1)	0	17 (4.7)	18 (2.6)
Discontinuation from study treatment due to adverse events	0	0	6 (1.7)	18 (2.7)
TEAE within special safety topics				
Conjunctivitis cluster	2 (3.9)	6 (6.1)	8 (2.3)	61 (8.9)
Keratitis cluster	0	0	1 (0.3)	5 (0.7)
Infections	12 (24.5)	16 (16.3)	65 (18.1)	150 (21.9)
Potential opportunistic infections (broad)	0	0	3 (0.8)	8 (1.2)
Herpes infections	2 (3.9)	1 (1.0)	13 (3.7)	22 (3.2)
Parasitic infections	0	0	0	0
Skin infections	6 (12.3)	1 (1.0)	18 (5.0)	16 (2.4)
Eosinophilia and eosinophil-related disorders	0	1 (1.0)	3 (0.9)	4 (0.6)
Hypersensitivity				
Potential immediate events	6 (12.1)	3 (3.1)	19 (5.4)	19 (2.8)
Potential non-immediate events	6 (12.4)	7 (7.2)	63 (17.8)	70 (10.3)
Injection site reactions	1 (2.1)	0	5 (1.4)	20 (3.0)
Atopic dermatitis exacerbation	11 (22.6)	5 (5.2)	65 (18.4)	45 (6.5)
Hepatic events (broad)	0	0	0	8 (1.2)
Suicide/self-injury	0	0	0	1 (0.2)
Malignancies	0	0	2 (0.6)	2 (0.3)
NMSC	0	0	2 (0.6)	2 (0.3)
Malignancies excluding NMSC	0	0	0	0

Abbreviations: AD = atopic dermatitis; adj % = adjusted percentage; LEB = lebrikizumab; n = number of patients in the specified category; N = number of patients in the analysis population; NMSC = nonmelanoma skin cancer; PBO = placebo; PC = placebo-controlled; TEAE = treatment-emergent adverse event; Q2W = every 2 weeks.

No clinically meaningful differences between the lebrikizumab and placebo groups were observed for adolescent growth parameters (weight, height, and BMI).

Any lebrikizumab exposure (AD All LEB)

The long-term safety profile in all adolescents exposed to any dose of lebrikizumab was consistent with the safety profile in adults.

Table 69: Overview of Adverse Events in Adolescent and Adult Participants in the AD All LEB Analysis Set

	AD All LEB					
	Adolescents			Adults		
	Any LEB Q2W N = 371 n (%)	Any LEB Q4W N = 29 n (%)	Any LEB N = 372 n (%)	Any LEB Q2W N = 996 n (%)	Any LEB Q4W N = 216 n (%)	Any LEB N = 1348 n (%)
Deaths	1 (0.3)	0	1 (0.3)	2 (0.2)	0	2 (0.1)
SAE	7 (1.9)	1 (3.4)	8 (2.2)	38 (3.8)	4 (1.9)	48 (3.6)
TEAE	219 (59.0)	11 (37.9)	227 (61.0)	647 (65.0)	118 (54.6)	879 (65.2)
Mild	103 (27.8)	8 (27.6)	108 (29.0)	293 (29.4)	46 (21.3)	397 (29.5)
Moderate	108 (29.1)	3 (10.3)	111 (29.8)	299 (30.0)	63 (29.2)	399 (29.6)
Severe	8 (2.2)	0	8 (2.2)	55 (5.5)	9 (4.2)	83 (6.2)
Discontinuation from study treatment due to adverse events	10 (2.7)	1 (3.4)	11 (3.0)	52 (5.2)	5 (2.3)	62 (4.6)
TEAE within special safety topics						
Conjunctivitis cluster	28 (7.5)	3 (10.3)	31 (8.3)	125 (12.6)	15 (6.9)	152 (11.3)
Keratitis cluster	1 (0.3)	0	1 (0.3)	8 (0.8)	1 (0.5)	8 (0.6)
Infections	126 (34.0)	6 (20.7)	131 (35.2)	350 (35.1)	73 (33.8)	484 (35.9)
Potential opportunistic infections (broad)	7 (1.9)	0	7 (1.9)	18 (1.8)	2 (0.9)	24 (1.8)
Herpes infections	22 (5.9)	0	22 (5.9)	53 (5.3)	11 (5.1)	65 (4.8)
Parasitic infections	0	0	0	0	1 (0.5)	1 (0.1)
Skin infections	13 (3.5)	1 (3.4)	14 (3.8)	34 (3.4)	6 (2.8)	49 (3.6)
Eosinophilia and eosinophil-related disorders	12 (3.2)	0	12 (3.2)	9 (0.9)	1 (0.5)	15 (1.1)
Hypersensitivity						
Potential immediate events	12 (3.2)	0	12 (3.2)	38 (3.8)	4 (1.9)	43 (3.2)
Potential non-immediate events	53 (14.3)	6 (20.7)	59 (15.9)	141 (14.2)	22 (10.2)	178 (13.2)
Injection site reactions	7 (1.9)	0	7 (1.9)	37 (3.7)	6 (2.8)	46 (3.4)
Atopic dermatitis exacerbation	38 (10.2)	3 (10.3)	41 (11.0)	79 (7.9)	11 (5.1)	95 (7.0)
Hepatic events (broad)	9 (2.4)	0	9 (2.4)	26 (2.6)	10 (4.6)	40 (3.0)
Suicide/self-injury	0	0	0	2 (0.2)	0	2 (0.1)
Malignancies	1 (0.3)	0	1 (0.3)	12 (1.2)	0	12 (0.9)
NMSC	0	0	0	5 (0.5)	0	5 (0.4)

	AD All LEB					
	Adolescents			Adults		
	Any LEB Q2W N = 371 n (%)	Any LEB Q4W N = 29 n (%)	Any LEB N = 372 n (%)	Any LEB Q2W N = 996 n (%)	Any LEB Q4W N = 216 n (%)	Any LEB N = 1348 n (%)
Malignancies excluding NMSC	1 (0.3)	0	1 (0.3)	7 (0.7)	0	7 (0.5)

Abbreviations: AD = atopic dermatitis; LEB = lebrikizumab; n = number of patients in the specified category; N = number of patients in the analysis population; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Table 70: Number of events and frequencies of non-immediate hypersensitivity reactions

	AD All LEB			Induction		Maintenance		
	Q2W	Q4W	Any LEB	Q2W	PLAC	Q2W	Q4W	PLAC
Adolescents	53 (14.3%)	6 (20.7%)	59 (15.9%)	7 (7.2%)	6 (12.4%)	0	3 (17.6%)	1 (12.5%)
Adults	38 (14.2%)	3 (10.2%)	41 (13.2%)	70 (10.3%)	63 (17.8%)	8 (8%)	14 (13.9%)	7 (13.5%)

2.6.8.5.2. Elderly

The frequency of participants with at least 1 TEAE in the adult population was similar across age subgroups (adolescent, adult, elderly) The sample size for those older than 75 years of age was limited. Although numerical differences for individual PTs may show some variability across age groups, no treatment by age group interaction was identified.

Table 71: Treatment-Emergent Adverse Events Occurring in at Least 1% of Participants from the Placebo-Controlled Induction Period Stratified by Age Group

Preferred Term	Subgroup	PBO N = 404 n (%[a])	LEB 250mg Q2W N = 783 n (%[a])
Ns	Adolescents (12<18)	48	99
	Adults (≥18 - <65)	322	616
	(≥65 - <75)	28	53
	(>=75)	6	15
Participants with at least 1 TEAE	Adolescents (12<18)	27 (56.3)	35 (35.4)
	Adults (≥18 - <65)	172 (53.4)	321 (52.1)
	(≥65 - <75)	11 (39.3)	19 (35.8)
	(≥75)	5 (83.3)	9 (60.0)
Conjunctivitis	Adolescents (12<18)	1 (2.1)	4 (4.0)
	Adults (≥18 - <65)	5 (1.6)	47 (7.6)
	(≥65 - <75)	0	0
	(≥75)	1 (16.7)	0
Dermatitis atopic	Adolescents (12<18)	11 (22.9)	5 (5.1)
	Adults (≥18 - <65)	58 (18.0)	36 (5.8)

Preferred Term	Subgroup	PBO N = 404 n (%[a])	LEB 250mg Q2W N = 783 n (%[a])
	(≥65 - <75)	2 (7.1)	3 (5.7)
	(≥75)	3 (50.0)	3 (20.0)
Nasopharyngitis	Adolescents (12<18)	2 (4.2)	4 (4.0)
	Adults (≥18 - <65)	11 (3.4)	29 (4.7)
	(≥65 - <75)	0	1 (1.9)
	(≥75)	0	0
Headache	Adolescents (12<18)	3 (6.3)	3 (3.0)
	Adults (≥18 - <65)	8 (2.5)	29 (4.7)
	(≥65 - <75)	0	2 (3.8)
	(≥75)	1 (16.7)	0
Oral herpes	Adolescents (12<18)	1 (2.1)	1 (1.0)
	Adults (≥18 - <65)	6 (1.9)	14 (2.3)
	(≥65 - <75)	1 (3.6)	0
	(≥75)	1 (16.7)	0
Conjunctivitis allergic	Adolescents (12<18)	1 (2.1)	2 (2.0)
	Adults (≥18 - <65)	2 (0.6)	12 (1.9)
	(≥65 - <75)	0	0
	(≥75)	0	0
Dry eye	Adolescents (12<18)	0	3 (3.0)
	Adults (≥18 - <65)	4 (1.2)	8 (1.3)
	(≥65 - <75)	0	0
	(≥75)	0	0
Pruritis	Adolescents (12<18)	2 (4.2)	2 (2.0)
	Adults (≥18 - <65)	5 (1.6)	6 (1.0)
	(≥65 - <75)	0	1 (1.9)
	(≥75)	0	0
COVID-19	Adolescents (12<18)	1 (2.1)	0
	Adults (≥18 - <65)	4 (1.2)	8 (1.3)
	(≥65 - <75)	0	1 (1.9)
	(≥75)	0	0
Hypertension	Adolescents (12<18)	0	0
	Adults (≥18 - <65)	3 (0.9)	7 (1.1)
	(≥65 - <75)	1 (3.6)	2 (3.8)
	(≥75)	0	0
Rhinitis allergic	Adolescents (12<18)	0	2 (2.0)
	Adults (≥18 - <65)	1 (0.3)	6 (1.0)
	(≥65 - <75)	0	0
	(≥75)	0	0

Abbreviations: COVID-19 = coronavirus disease 2019; LEB = lebrikizumab; N = number of patients in the analysis population; n = number of patients in the specified category; Ns = number of patients for each subgroup; PBO = placebo; Q2W = every 2 weeks; TEAE = treatment-emergent adverse event.

A Crude percentages are presented as some subgroups are very small and not represented in all studies and all treatment groups, therefore, adjusted percentage could be misleading.

Table 72: Adverse Events by Age Group in Lebrikizumab-Treated Participants MedDRA Terms

	Age <65 Years N = 1597 n (%)	Age 65-74 Years N = 94 n (%)	Age 75-84 Years N = 24 n (%)	Age ≥85 Years N = 5 n (%)
Total TEAEs	1036 (64.9)	53 (56.4)	14 (58.3)	3 (60.0)
Serious AEs – Total	47 (2.9)	6 (6.4)	2 (8.3)	1 (20.2)
Fatal	2 (0.1)	1 (1.1)	0	0
Hospitalisation/prolong existing hospitalisation	34 (2.1)	5 (5.3)	2 (8.3)	0
Life-threatening	3 (0.2)	0	0	1 (20.0)
Disability/incapacity	1 (0.1)	0	0	0
Other (medically significant)	11 (0.7)	1 (1.1)	0	0
AEs leading to treatment discontinuation	59 (3.7)	8 (8.5)	5 (20.8)	1 (20.0)
Psychiatric disorders	57 (3.6)	1 (1.1)	0	0
Nervous system disorders	132 (8.3)	5 (5.3)	1 (4.2)	1 (20.0)
Accidents and injuries	94 (5.9)	8 (8.5)	1 (4.2)	0
Cardiac disorders	14 (0.9)	2 (2.1)	1 (4.2)	0
Vascular disorders	33 (2.1)	4 (4.3)	1 (4.2)	0
Cerebrovascular disorders	2 (0.1)	0	0	0
Infections and infestations	587 (36.8)	24 (25.5)	3 (12.5)	1 (20.0)
Anticholinergic syndrome	0	0	0	0
Quality of life decrease	0	0	0	0
Sum of postural hypotension, falls, blackouts, syncope, dizziness, ataxia, fractures	41 (2.6)	3 (3.2)	1 (4.2)	0

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in the analysis population; n = number of participants in the specified category; TEAE = treatment-emergent adverse event.

Supportive safety results from study KGAK

The most common AEs were COVID-19 (5.6%), nasopharyngitis (3.2%), headache (3.2%), dermatitis atopic (4.8%), and conjunctivitis (2.4%). No subjects in the placebo arm experienced conjunctivitis compared to 2.4% in the LEB arm. The frequency of hypersensitivity and injection site reactions was balanced across treatment arms an in line with previous studies. Other events of special interest (herpes infections, malignancies, self-injury, severe eosinophilia) did not occur in LEB treated patients during

this 16 week study. No new safety topics in terms of nature, frequency or severity of adverse events arose from the results of study KGAK.

The safety and immunogenicity profile in study KGAK is consistent with what has been observed in prior studies.

2.6.8.6. Immunological events

ADA frequencies in Phase 1 and phase 2 Trials

In the phase 1 trials, ADA were present in 0-10% of the healthy subjects post baseline.

In the phase 2 trials, 18-25% of AD patients were at some point post baseline positive for ADA after any dose of lebrikizumab. Persistent positive ADA results (i.e., positive for more than 2 post-baseline time points or positive at the last time point) were less frequent. Although most of the positive post-baseline ADA results were deemed to be treatment-emergent, most ADAs were transient (positive ADA detected in only one post baseline sampling timepoint).

ADA frequencies in Phase 3 Trials

In the phase 3 trials, immunogenicity was assessed using a newly developed immunogenicity assay, which was more sensitive, specific, and drug tolerant than the assays used for phase 1 and phase 2 trials.

A total of 822 participants randomly assigned to lebrikizumab 250 mg Q2W were evaluable for TE ADA. At baseline, the incidence of ADA was 72 (8.8%), (10.6% in KGAB, 8.5% in KGAC and 7.7% in KGAD).

Of the 822 evaluable participants in the lebrikizumab 250 mg Q2W only group through 1 year,

- 28 (3.4%) participants became TE ADA positive,
  - 21 (2.6%) participants were treatment-induced,
  - 7 (0.9%) participants were treatment boosted, and
- 24 (2.9%) participants were NAb positive.

Of the 145 evaluable participants who responded to lebrikizumab 250 mg Q2W and were re- randomised to lebrikizumab 250 mg Q4W through 1 year,

- 4 (2.8%) participants became TE ADA positive,
  - 2 (1.4%) participants were treatment-induced,
  - 2 (1.4%) participants were treatment boosted, and
- 4 (2.8%) participants were NAb positive.

Of the 330 evaluable participants treated with continuous placebo,

- 3 (0.9%) participants became TE ADA positive,
- 3 (0.9%) participants were treatment-induced, and
- 3 (0.9%) participants were NAb positive.

A vast majority of TE ADA positive participants (26 of 28, 92.9%) in the lebrikizumab 250 mg Q2W only treatment group had a maximum titre through the dosing period of 1:160 or less. The highest reported TE ADA titre in this treatment group was 1:640, and it was reported in only 1 patient.

A similar titre distribution was seen for TE ADA positive responder participants treated with lebrikizumab 250 mg Q2W followed by lebrikizumab 250 mg Q4W. Both treatment-induced participants had a maximum postbaseline titre of 1:20, and the 2 treatment-boosted participants had maximum titres of 1:40 and 1:160, respectively.

For TE ADA positive participants treated with only placebo, the highest maximum reported titre was 1:40.

Among participants treated at any time with any dose of lebrikizumab (Atopic Dermatitis All Lebrikizumab Exposure Integrated Immunogenicity Analysis Set, Studies KGAB, KGAC, KGAD, KGAE, and/or KGAA), 117 (9.2%) participants had ADA present at baseline. For all participants exposed to lebrikizumab across the 5 clinical studies, 1272 were evaluable for TE ADA.

- 49 (3.9%) participants became TE ADA positive,
    - 36 (2.8%) participants were treatment-induced,
    - 13 (1.0%) participants were treatment boosted,
- 43 (3.4%) participants were NAb positive, and
- 9 (0.7%) participants were TE ADA inconclusive.

A subset analysis of adolescent participants (ages 12 to less than 18 years) demonstrated similar immunogenicity incidence to the overall population.

Effect of Immunogenicity on Pharmacokinetics, Efficacy and safety

Phase 1 trials

In most of the phase 1 trials no or only few subjects were ADA positive at baseline or had TE ADA. Pharmacokinetics was comparable in TE ADA positive and TE ADA negative subjects in phase 1 trials.

Phase 2 trials

According to the clinical study reports (CSRs), concentrations of lebrikizumab were slightly reduced in ADA positive patients relative to ADA negative patients in studies KGAG and KGAH. One patient in study KGAG (100701) experienced a substantial drop in lebrikizumab serum concentrations from Week 4 onwards that was likely ADA-induced.

The Applicant confirmed that the presence of ADA was not found to impact PK in study KGAF. Persistent positive neutralizing ADA (NAb) was observed for a total of 3 patients, PK results for these 3 patients were generally consistent with overall findings for corresponding dose groups.

Phase 3 trials

The impact of baseline and TE ADA on the PK of lebrikizumab was evaluated using pooled phase 3 data from Week 0 to 52. Two datasets were used, one with Q2W maintenance dosing (data from studies KGAB, KGAC, KGAD, and KGAE) and the other for Q4W maintenance dosing (data from studies KGAB and KGAC). Graphical exploration indicated that patients who were ADA positive had lebrikizumab exposure that was consistent with patients who were ADA negative.

A summary of the effects of immunogenicity on the clinical outcomes of EASI75 and IGA (0,1), at Week 52 was provided. The percentage of responders at week 52 was equal or higher among patients who were TE ADA positive compared to patients who were TE ADA negative.

No summary on the association between TE ADA and treatment effect was provided for the week 16 timepoint, which was the time point for evaluation of primary efficacy.

The frequency of hypersensitivity reactions and ISRs was evaluated in patients who were TE ADA positive versus TE ADA negative using the AD combined induction and maintenance periods immunogenicity analysis set.

Using all narrow and broad search terms, the frequency of hypersensitivity reactions in the continuous lebrikizumab 250 mg Q2W treatment group was similar between TE ADA negative and TE ADA positive participants (208 of 792, 26.3% and 7 of 28, 25.0%, respectively). Using narrow search terms only, hypersensitivity reactions were reported with a higher numerical frequency in TE ADA negative participants compared to TE ADA positive participants (138 of 792, 17.4% and 4 of 28, 14.3% respectively). In the lebrikizumab 250 mg Q2W/Q4W treatment group, no TE ADA positive participants reported hypersensitivity reactions (broad and narrow terms) compared to 35 of 140, 25.0% of TE ADA negative participants. Similar results were seen for the continuous placebo treatment group.

The frequency of participants with at least 1 Injection site reaction high-level term (HLT) TEAE was higher in the LEB 250 mg Q2W only participants who were TE ADA positive (N = 28, n = 3, 10.7%) compared to those who were TE ADA negative (N = 792, n = 23, 2.9%). There was no temporal association with ISRs and development of TE ADA.

In both the LEB 250 mg Q2W/Q4W only treatment group and continuous placebo treatment group, no TE ADA positive participants had ISRs, compared to 3 of 140 (2.1%) and 5 of 327 (1.5%) of TE ADA negative participants in each treatment group, respectively.

No clinically meaningful association was found between TE ADA status and hypersensitivity events or ISRs.

2.6.8.7. Safety related to drug-drug interactions and other interactions

No formal studies have been conducted to examine the effect of lebrikizumab on the PK of other drugs. As a mAb, lebrikizumab is not anticipated to directly impact the PK of other drugs.

2.6.8.8. Discontinuation due to adverse events

In the induction phase 18 (2.3%) subjects in the LEB 250 mg Q2W group had at least 1 AE leading to discontinuation of study treatment, compared to 6 (1.4%) subjects in the PBO group.

In the maintenance phase, the frequencies of AEs leading to permanent discontinuation of study treatment were:

- 1 (0.9%) event of vernal keratoconjunctivitis in the LEB 250 mg Q2W group, and
- 2 (1.7%) events (1 event of conjunctivitis allergic and 1 event of conjunctivitis) in the LEB 250 mg Q4W group.

Events leading to discontinuation in the lebrikizumab treated patients were mostly related to the conjunctivitis cluster and to atopic dermatitis and other skin infestations which could be related to lack of efficacy. The number of subjects experiencing AEs leading to withdrawal was low, suggesting that lebrikizumab is well tolerated.

2.6.8.9. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

The clinical program designed to assess the safety of lebrikizumab is focused on adult and adolescent patients at least 12 years of age and ≥40kg with moderate-to-severe AD. To date, 1720 patients with moderate-to-severe AD have been exposed to lebrikizumab, 1228 patients have been treated with the intended induction dose for ≥16 weeks and 132 patients have been treated with the intended induction and maintenance posology for at least 1 year. The ICH E1 requirements on the size of the safety database and the degree of patient exposure are well exceeded.

Safety data for this application have been obtained from adult and adolescent participants with AD from 8 studies: 1 Phase 2, randomised open-label Study KGAH (ARBAN), 5 multi-centre, randomised, double-blind, placebo-controlled studies (including 2 Phase 2 Studies KGAG (TREBLE) and KGAF, and 3 phase 3 Studies KGAB (Advocate 1), KGAC (Advocate 2), and KGAD (Adhere)), 1 Phase 3, open-label, adolescent single arm Study KGAE (Adore), and 1 Phase 3 long-term safety Study KGAA (Adjoin). Phase 3 clinical study programme consists of studies KGAB and KGAC (replicative design: randomised, double-blind, placebo controlled), KGAD (randomised, double-blind, placebo controlled, lebrikizumab in combination with TCS), KGAE (open-label single arm study in adolescents) and KGAA (long-term extension study). The cut-off date was 06 June 2022.

There is one ongoing extension study (KGAA) listed as a Category 3 study of the RMP that will address the safety concern on long term safety. The final study report is anticipated for February 2025.

Proposed safety profile

No monitoring guidance is proposed in the SmPC. No dose adjustments are proposed for elderly, renal and hepatic impairment and body weight. No contraindications except for hypersensitivity is proposed. The warnings listed in section 4.3 of the SmPC include hypersensitivity, conjunctivitis, vaccinations, helminth infection and traceability. Lebrikizumab is to be avoided concurrently with live and live attenuated vaccines. These SmPC proposals are agreed by the CHMP.

Regarding the safety concerns in the Risk Management Plan (section 2.7.1), the Applicant does not propose any important identified risks, nor important potential risks. Proposed as missing information are long term safety and safety in pregnant and breastfeeding women.

Adverse events

The Applicant initially proposed to include conjunctivitis, herpes zoster, eosinophilia, keratitis and injection site reaction as ADRs in section 4.8 of the SmPC. Based on differences between lebrikizumab and placebo arms, and upon CHMP's request, dry eye and blepharitis were also included in SmPC section 4.8**.**

Despite the presence of long-term safety data and the intended continuous use of lebrikizumab, the Applicant chose to tabulate only TEAEs from the 16-week induction phase as ADRs in the product information. The safety profile of lebrikizumab during the induction period can be well characterised by comparison to placebo (lebrikizumab 250mg Q2W vs placebo). However, causality assessment of TEAEs in the maintenance period is difficult. Responders in trials KGAB and KGAC were re-randomised after week 16 (with no washout period), and a new posology arm (lebrikizumab 250mg Q4w) was introduced. Placebo arms used for comparison of TEAE incidences during maintenance were not true placebo but represented patients re-randomised to placebo after initial response to lebrikizumab (LEB). Moreover, the majority of data for the placebo arm in the combined induction and maintenance analysis set comes from the induction period which makes the treatment arms incomparable in terms of exposure time. Ultimately, only 6 patients completed 52 weeks of treatment receiving placebo throughout the whole period, limiting the soundness of comparison to placebo in the long-term setting. There is no comparator

in the Any exposure to lebrikizumab set. Taken together, true and 'clean' comparator data exists for only the first 16 weeks.

Despite these difficulties, the ADR list in section 4.8 should include all AEs from various sources for which a causal relationship is at least a reasonable possibility, as per the SmPC Guideline. Upon thorough reassessment of the data, no new ADRs were found during maintenance but all ADRs to be included were already seen during the placebo controlled 16-week induction.

Although the Applicant applied for the dosing regimen of lebrikizumab 250mg Q4W in the maintenance period, the dosing regimen of Q2W was also evaluated during the maintenance period. Many TEAEs occurred with a higher frequency in LEB Q4W compared to Q2W. However, as previously commented, these data are difficult to interpret in a meaningful way.

Common TEAEs

The most frequently reported SOCs for lebrikizumab-treated participants, occurring more often compared to placebo, were Infections and infestations (primarily driven by the PTs conjunctivitis and nasopharyngitis), Eye disorders (primarily driven by the PTs conjunctivitis allergic and dry eye), Nervous system disorders (primarily driven by the PT Headache) and General disorders and administration site conditions (injection site reactions).

Common TEAEs are those reported at a frequency of greater than or equal to 1% in the lebrikizumab-treated group. Common TAES reported more frequently in the lebrikizumab group compared to placebo in the induction phase were conjunctivitis (6.9%), nasopharyngitis (4.4%), headache (4.4%), conjunctivitis allergic (1.8%), dry eye (1.4%) and rhinitis allergic (1.0%).

Some TEAEs were reported more often with lebrikizumab than with placebo during induction but were not included as ADRs in the SmPC. The Applicant was requested to justify and clarify these decisions. Upon further scrutiny of the data it was concluded that headache, nasopharyngitis, herpes simplex, rhinitis allergic, high serum cholesterol, hepatic enzymes elevated and weight gain are not ADRs.

In the maintenance period, the most common TEAEs in lebrikizumab 250 mg Q4W were COVID-19 (9.4%), nasopharyngitis (7.6), conjunctivitis allergic (5.9%), conjunctivitis (5.0%), dermatitis atopic 5.9%), headache (4.2%), oral herpes (3.4%) and folliculitis (2.5%). All of these TEAEs, except for dermatitis atopic and conjunctivitis, were more frequent with LEB 250 mg Q4W compared to those in the LEB withdrawal placebo arm.

Despite higher frequencies in patients treated with LEB, based on the totality of data it was concluded that a plausible causal relationship was only present for the following TEAEs: Conjunctivitis, Herpes zoster, Eosinophilia, Conjunctivitis allergic, Keratitis, Dry eye, Blepharitis, and Injection site reaction.

Serious adverse events and deaths

The frequency of participants reporting at least 1 SAE was low and similar in the lebrikizumab and placebo groups during both the induction and maintenance period. During induction, frequencies of SAEs were similar for both treatment arms regardless of concomitant TCS.

All SAEs in the placebo-controlled induction period were single cases. No clinically meaningful differences between treatment groups were apparent for SAEs in either the induction or the maintenance phase. Frequencies and incidence rates of SAEs did not suggest an increase with longer exposure.

In total 4 deaths were recorded during the AD lebrikizumab clinical programme. One death occurred in placebo arm while 3 deaths occurred in patients receiving lebrikizumab 250 mg Q2W. Investigators assessed all deaths as unrelated to study drug treatments.

Adverse events of special interest

Conjunctivitis was an expected adverse event, as it has been commonly observed in AD patients treated with other drugs in the same drug class. The observed incidence rates (6.9% in the induction phase and 5.0% in the maintenance phase) were similar to those seen in AD patients treated with other mAbs acting on IL-13. Over the whole 52-week treatment, the overall incidence of conjunctivitis was 14.2% in the target population treated with the intended dose (LEB 250mg Q2W/Q4W). The frequencies of TEAEs from keratitis cluster, ocular symptoms cluster and blepharitis cluster are all increased in LEB compared to placebo arms, albeit with rather small numerical differences between treatment arms. The observed keratitis events were regarded as extensions of more severe forms of allergic conjunctivitis and were included as ADRs.

The majority of events in the conjunctivitis and keratitis clusters were nonserious, the majority of participants had 1 event, the majority of events resolved and almost all events required treatment with medications.

It appears that conjunctivitis is an ADR specific to AD patients as it was not seen in the asthma study program nor in monkeys. A higher proportion of lebrikizumab-treated participants who reported an AE of conjunctivitis, keratitis, ocular symptom, dry eye clusters, and blepharitis PTs had a medical history of conjunctivitis or facial dermatitis compared to participants who did not report conjunctivitis related AEs.

In both the induction and maintenance period, the frequency of participants who reported eosinophilia TEAEs was higher among participants receiving lebrikizumab compared to placebo. There were no events of eosinophil-related disorders. In total 8 patients treated with lebrikizumab across analyses sets experienced severe eosinophilia (3 in induction period, 3 additional in combined induction and maintenance period and 2 additional in any lebrikizumab exposure). In at least 2 participants the eosinophil level did not return to baseline and in 3 participants a lack of efficacy was observed. Eosinophilia is listed as an ADR which is endorsed. The eosinophilia frequency "uncommon" in the ADR table refers only to severe eosinophilia (>5000 cells/mm3). Given the clearly higher overall frequency of increased blood eosinophils in lebrikizumab-treated participants (20.3%) compared to placebo-treated participants (11.7%), the Applicant was requested to add this information to the SmPC section 4.8 under the description of selected adverse reactions sub-section.

Of note, in the supportive study KGAK, the frequency of mild eosinophil elevation was in line with findings in other studies which indicates that the event is causally related to the drug and the frequency of around 20% is not a chance finding.

In the induction period, the frequency of TEAE Infections and infestations is somewhat higher in LEB 250 mg Q2W arm compared to placebo (21.2% vs 18.6%).

Based on the presented data and the requested additional discussion it can be agreed that nasopharyngitis, gastroenteritis, diarrhoea, and herpes simplex are not ADRs with a reasonable possibility for causality although slightly higher frequencies were seen. Lack of biological mechanism and no dose-response pattern are the main reasons for this conclusion. For example, in the case of nasopharyngitis, the exposure adjusted incidence rate with LEB 250mg Q2W was lower than that with placebo, which makes it implausible that the lower dose of LEB 250mg Q4W would be causally linked to nasopharyngitis.

Although the incidence of herpes simplex was slightly higher with LEB during induction, there was no difference during maintenance and the number of subjects is very small. In addition, another manifestation of a herpes simplex infection, the eczema herpeticum was lower with LEB than placebo during maintenance. Therefore, causality between LEB and herpes simplex is not considered plausible.

No confirmed opportunistic infections were reported. A lower frequency of skin infections was reported in the lebrikizumab-treated participants (2.2%) during the placebo-controlled period compared to placebo (5.9%), reflecting the efficacy of lebrikizumab. The incidence of serious infections was low; 1 case of severe infectious colitis, two cases of COVID-19, one case of acarodermatitis and erysipelas and one case of pneumonia in the combined induction and maintenance phases in patients treated with lebrikizumab. All events were recovered/resolved and did not lead to treatment discontinuation.

No events of parasitic infections were reported in any treatment group in the induction nor in the maintenance period. One (0.7%) parasitic infection in the LEB 250 mg Q2W/Q4W only group (KGAD-6016-002) was reported in the combined induction and maintenance period. It was a case of mild enterobiasis and ascariasis that resolved after treatment.

In the induction period, frequency of immediate hypersensitivity reactions was lower in LEB 250mg Q2W (n=22, 2.8%) compared to placebo (n=25, 6.2%). All the events were nonserious, and only a small number of participants discontinued treatment (in those who did, the events were not true hypersensitivity reactions). In the maintenance period, the frequency of immediate hypersensitivity reactions was slightly higher in both lebrikizumab arms although the number of events is very small.

The frequencies of nonimmediate hypersensitivity events in the induction period were lower in the lebrikizumab group (n = 77, 9.9%) compared to placebo (n = 69, 17.1%), while in the maintenance period the frequencies were similar in LEB Q4W and placebo (n = 17, 14.4% and n = 8, 13.3%, respectively). The frequency of non-immediate hypersensitivity reactions in adolescents receiving LEB Q4W (17.6% in the maintenance period and 20.7% in any LEB exposure set) was higher compared to adults receiving the same dosing regimen (13.9% in maintenance and 10.2% in any LEB exposure) and higher compared to adolescents receiving placebo (12.5% in maintenance) or adolescents receiving LEB Q2W (0 in maintenance and 14.3% in any LEB exposure set). Upon request, the non-immediate hypersensitivity reactions were examined more closely, and the Applicant claims the reported PTs were not considered true nonimmediate hypersensitivity reactions (ie. dermatitis atopic, conjunctivitis allergic, dermatitis contact and rhinitis allergic). It is agreed that those reactions could be a manifestation of the underlying condition. The number of included adolescents is notably smaller compared to adults, which is a possible explanation for the difference in proportions among the two populations rather than a true difference in occurrence of these reactions. The observation of a higher frequency of these reactions in adolescents receiving LEB Q4W compared to LEB Q2W is likely due to a very small sample size in the LEB Q4W arm (29 adolescents in total).

In the induction period, the frequency of injection site reactions was higher in the lebrikizumab group (n = 20, 2.6%) compared to placebo (n = 6, 1.5%). The most frequently reported PTs in lebrikizumab-treated participants were injection site pain, injection site erythema and injection site reaction. Injection site reactions are listed as ADRs.

Regarding hepatic safety, the frequency of participants reporting at least 1 TE hepatic disorder in the induction period was higher in lebrikizumab compared to placebo group (8 participants (1.1%) compared to 0). In the maintenance period, the situation is similar, albeit with few events (3 participants (2.5%) in LEB Q4W; 1 participant (0.9%) in LEB Q2W and 1 participant (1.7%) in placebo). Also, in any lebrikizumab exposure set, an imbalance in the frequency of hepatic TEAEs is observed in participants receiving LEB 250 mg Q4W compared to Q2W (10 participants (4.1%) vs 34 participants (2.5%), respectively).

No participants with laboratory criteria for Hy's law were identified, neither in the induction nor in the maintenance period. In the Any AD lebrikizumab exposure set (AD All LEB), one participant meeting the criteria for potential Hy's law was identified. A narrative for this subject is provided which reveals self-reported drinking alcohol before drawing blood, thrombocytopenic at baseline, baseline GGT 4.7xULN, AST 2.3x ULN, AST:ALT ratio of 4:1. On Day 213 he developed jaundice and lab results showed GGT 5x

ULN, AST 153 (3.7x ULN), and TBL 92.3 umol/L (4.5x ULN). According to the narrative, the patient is most likely to have alcoholic liver disease. Moreover, since abnormal liver biochemistry was present at baseline, it would be more appropriate to replace the ULN with the pre-treatment baseline level (according to CIOMS on DILI: consensus report from 2020). According to this modification of the definition, the raise in AST was 1.6 times from the baseline level, which does not reach the Hy's law threshold of transaminase elevation.

In any lebrikizumab set, additional 3 participants were identified with ALT values ≥5x ULN (and normal bilirubin) and 1 additional patient with AST values ≥5x ULN (and normal bilirubin).

The Applicant argues that due to the lack of mechanistic plausibility, the low frequency of TEAEs and SAEs, low treatment discontinuations, the absence of DILI, and infrequent laboratory shifts, hepatic events were not deemed to be associated with lebrikizumab. Based on further scrutiny of the data and a detailed individual case review for participants with AST/ALT elevations above 3xULN, a reasonable possibility of a causal relationship cannot be unequivocally established at this time.

There seemed to be a difference in weight gain between treatment arms. However, weight fluctuations were not sustained over time and only seen among some BMI categories. Based upon the totality of the data, it was concluded that a causal relationship between lebrikizumab and weight gain is not likely.

Two events of suicidal ideation were reported in the AD program (both treated with LEB) and one event of completed suicide was reported in the asthma program with lower dose lebrikizumab. Given that the prevalence of clinical depression in adults with AD is around 15% (Patel et al. 2019) and that suicidal ideation is common in severe depression, and that there is also no specific signal of increased risk of suicide by blocking IL-13, it is agreed that the data do not suggest an increased risk of suicide/self-injury among those treated with lebrikizumab. This topic will continue to be routinely monitored and presented for discussion in PSURs as a topic of interest.

Regarding malignancies, there were no malignancy events other than NMSC reported during the placebo-controlled induction period. No malignancy was reported in the Weeks 16 to 52 maintenance period.

One death was reported during the combined induction and maintenance period in a 73-year-old male participant due to metastatic pancreatic carcinoma.

However, in any lebrikizumab exposure set 7 additional lebrikizumab-treated participants reporting malignancy (other than NMSC) were found. It is noted that out of these 7 additional cases, 4 occurred in younger patients (aged 17-30) and included 2 participants with cutaneous T-cell lymphoma, 1 participant with neuroendocrine tumour of the appendix and 1 participant with ovarian teratoma. There is limited information about these events; 3 participants (out of these 4) discontinued study participation and the outcome of the malignancy is unknown. This is potentially concerning. The Applicant has agreed to continue monitoring the occurrence of malignancies in patients receiving lebrikizumab as part of routine surveillance activities. Based on a comprehensive discussion provided, this approach is reasonable for the time being.

Immunogenicity

Characterisations of immunogenicity were conducted with data from seven clinical pharmacology studies, three Phase 2 AD studies and five Phase 3 AD studies. The focus of this assessment is on the Phase 3 AD studies as they are considered most relevant to the AD indication and the most adequate and up to date analytical method was used for ADA detection in these studies.

In the phase 1 trials, ADA were present in 0-10% of the healthy subjects post baseline. In the phase 2 trials, 18-25% of AD patients were at some point post baseline positive for ADA after any dose of lebrikizumab. However, most of the positive post-baseline ADA results were transient.

In the combined phase 3 Studies KGAB, KGAC and KGAD, 3.4% of participants treated with lebrikizumab 250 mg Q2W, 2.8% of participants treated with lebrikizumab 250 mg Q2W/Q4W, and 0.9% of participants treated with placebo developed treatment-emergent ADA over 12 months. Nearly all TE ADA positive participants were also positive for NAb to lebrikizumab but most ADAs were low titre. No association between TE ADA (including titre magnitude) and treatment effect at week 16 or 52 could be established. ADA/Nab frequencies and titres were similar in the adolescents compared to the overall population. Upon request, the Applicant provided supplementary information and confirmed that ADAs are not expected to have clinically relevant impact on exposure to lebrikizumab.

No clinically meaningful association was found between TE ADA status and hypersensitivity events or ISRs.

Safety in special populations

There were 53 participants older than 65 years of age exposed to lebrikizumab during the induction period. Only 15 participants older than 75 were exposed in the same period. The safety of elderly subjects is addressed in the SmPC according to QRD template. Based on the subgroup analyses provided, no special concern in the elderly is evident.

The AD safety database included 372 adolescents (12-18 years of age) exposed to lebrikizumab at any dose. 270 adolescents were exposed to lebrikizumab for at least 1 year. 246 adolescents were treated with Q2W only, and 23 adolescents were treated Q2W followed by Q4W for at least 1 year.

The overall safety profile in all adolescents exposed to any dose of lebrikizumab was consistent with the safety profile in adults in terms of frequency and nature of adverse events. In the induction period overall SAEs, TEAEs, discontinuations and TEAEs within special safety topics all occurred with lower frequency in adolescents compared to adults in both lebrikizumab and placebo groups.

The most common TEAEs in adolescents occurring more frequently in the lebrikizumab-treated adolescents compared to placebo were conjunctivitis, nasopharyngitis, dry eye, and rhinitis allergic.

In the induction phase, dry eye, pruritus and rhinitis allergic were PTs with numerically higher frequencies in the lebrikizumab-treated adolescent population compared to the lebrikizumab-treated adult population (at least 18 years of age). After any exposure to LEB the frequency of eosinophilia was higher in the LEB treated adolescents 12 (3.2%) compared to LEB treated adults 15 (1.1%). These small differences between frequencies of AEs in adolescents compared to adults are of no clinical importance and do not affect how ADRs are reported in the SmPC section 4.8.

Regarding weight, height and BMI in adolescents, no meaningful differences in growth parameters between placebo and lebrikizumab were observed based on the mean changes in any LEB group for Z-score close to 0 for all growth parameters. No particular patterns arise from the numerically small differences in common TEAEs in the induction period across age groups, for sex, weight, race, ethnicity and across geographical regions.

Additional safety data was obtained from a study to evaluate the effect of lebrikizumab on vaccine responses in patients with AD (KGAK). The study was ongoing at the time of data cut-off and safety results were not pooled in the integrated analysis set. The safety and immunogenicity profile in study KGAK was consistent with that in the pooled analysis set.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

No major safety issues are identified for patients with atopic dermatitis treated with lebrikizumab and the overall safety profile is manageable. The data suggest that most AEs occur within the first few months of drug treatment and that the AE pattern does not change over time. No clinically meaningful differences were observed between different lebrikizumab dosing regimens (Q2W vs. Q4W in the maintenance phase). No differences in AE pattern were seen between monotherapy and lebrikizumab + topical treatment. The overall safety profile in all adolescents exposed to any dose of lebrikizumab was consistent with the safety profile in adults in terms of frequency and nature of adverse events.

The frequency of treatment emergent anti-drug antibody formation was low, up to 2.8% of patients treated with 250 mg lebrikizumab developed ADAs. No clinically meaningful association was found between TE ADA status and PK, efficacy or safety.

The ongoing open-label long-term safety extension study KGAA listed as a Category 3 study of the RMP will provide further information to characterise long-term safety. In addition, an observational study listed as a Category 3 study will provide further information on the use of lebrikizumab during pregnancy.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnant and breastfeeding women Long-Term safety of lebrikizumab

2.7.2. Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Estimated Due Dates**
Category 3 - Required additional pharmacovigilance activities				
Post-marketing observational study of pregnancy and infant outcomes among women exposed to lebrikizumab during pregnancy in US-based Administrative Claims Data *Planned*	Objectives include: • to estimate occurrence of pregnancy and infant outcomes among women exposed to lebrikizumab in pregnancy. • If the sample size permits, to evaluate the relative risk of the adverse pregnancy and infant outcomes among women with AD exposed to lebrikizumab in pregnancy compared to women with AD unexposed to lebrikizumab in pregnancy.	*Missing information:* Use in pregnant women	*Protocol* *Final Study Report*	*Within 6 months of EC decision, anticipated 31 May 2024* *31 September 2031*
A long-term study to assess the safety and efficacy of lebrikizumab in patients with moderate-to-severe atopic dermatitis (J2T-DM-KGAA) *Ongoing*	To evaluate the long-term safety and efficacy of lebrikizumab in patients with moderate-to-severe AD.	*Missing information:* Long-term safety of lebrikizumab	*Final Study Report*	*February 2025*

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Estimated Due Dates
Category 3 - Required additional pharmacovigilance activities				
Long-term safety and efficacy of lebrikizumab in adult and adolescent patients with moderate-to-severe atopic dermatitis (M-17923-32)	To evaluate the long-term safety and efficacy of lebrikizumab in patients with moderate-to-severe AD.	*Missing information:* Long-term safety of lebrikizumab	*Protocol* *Final study report*	*05 April 2023 (first version approved by the Competent Authority)* *August 2026*

Abbreviation: AD = atopic dermatitis; AE=adverse event; FPFV=first patient, first visit; LPLV=last patient, last visit; Q4W=every 4 weeks.

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnant and breastfeeding women	Routine risk minimisation measures: SmPC Section 4.6 PL Section 2 Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None proposed. Additional pharmacovigilance activities (Pregnant woman): • Observational database study of pregnancy and infant outcomes among women exposed to lebrikizumab during pregnancy
Long-term safety of lebrikizumab	Routine risk minimisation: None Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None proposed Additional pharmacovigilance activities: • A long-term study to assess the safety and efficacy of lebrikizumab in patients with moderate-to-severe atopic dermatitis (J2T-DM-KGAA) • Long-term safety and efficacy of lebrikizumab in adult and adolescent patients with moderate-to-severe atopic dermatitis (M-17923-32)

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28.09.2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ebglyss (lebrikizumab) is included in the additional monitoring list as a new active substance.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication for lebrikizumab is: "treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older with a body weight of at least 40 kg who are candidates for systemic therapy."

Atopic dermatitis (AD) is a chronic and relapsing inflammatory disorder characterised by erythematous, pruritic, dry, scaly and often lichenified skin. Pruritus is a hallmark of AD and is responsible for much of the disease burden for patients and their families. Moderate to severe AD is associated with significant burden, impacting sleep, quality of life, and treatment needs.

The goals of therapy are to reduce pruritus and establish persistent disease control that is sufficient to enable patients to be fully functional at home, work and school. These goals typically require a multistep approach with interventions that are aimed at avoiding relevant triggers, improving the skin barrier, normalizing the skin dysbiosis and reducing inflammation.

3.1.2. Available therapies and unmet medical need

Topical therapies, e.g. moisturisers are the mainstay of therapy for patients with mild-to-moderate disease. TCS are used as the first-line anti-inflammatory treatment and reduce disease recurrence when used intermittently. Use of low-potency TCS bears low risk, but inappropriate use of high-potency TCS can cause local side effect such as skin thinning, purpura, striae and dyspigmentation.

Topical calcineurin inhibitors (TCIs) tacrolimus and pimecrolimus are alternative topical immunomodulators for the treatment of AD. Currently per EMA recommendations, these medicines should be only used in patients over the age of 2 years with mild or moderate disease (in the case of pimecrolimus) and moderate to severe disease (in the case of tacrolimus), when treatment with topical corticosteroids should not or cannot be used.

Other treatment options include short-term phototherapy if disease cannot be controlled with topical therapies and oral glucocorticoids. Systemic non-biologic immunomodulatory therapies, e.g. ciclosporin, azathioprine, methotrexate and mycophenolate mofetil are also used, often off-label. Other treatments options for moderate-to-severe AD include oral JAK inhibitors abrocitinib, baricitinib, upadacitinib. However, the use of JAK inhibitors has been associated with some serious side effects and should be used with caution.

Recently, two biological therapies have been approved by EMA for moderate-to-severe AD. Dupilumab is a mAb against IL-4Rα that inhibits IL-4 signalling via the Type I receptor (IL-4Rα/γc), and both IL-4 and IL-13 signalling through the Type II receptor (IL-4Rα/IL-13Rα). Tralokinumab is a mAb against IL-13 that neutralises the biological activity of IL-13 by blocking its interaction with the IL-13Rα1/IL-4Rα receptor complex.

Although several therapies have recently become available for the treatment of moderate-to-severe AD, new therapies that are effective and safe particularly in the long-term treatment of this chronic disease are needed.

3.1.3. Main clinical studies

The clinical development program supporting lebrikizumab for the treatment of moderate-to-severe AD in adults and adolescents 12 years of age and older with a body weight of at least 40 kg and who are candidates for systemic therapy, is primarily based on 3 pivotal trials:

- KGAB and KGAC studies were randomised, double-blind, placebo-controlled, parallel-group studies designed to confirm the safety and efficacy of lebrikizumab in adults and adolescents (12 to less than 18 years of age that weighted at least 40 kg) with moderate-to-severe AD. Both studies included Induction period (0-16 weeks) and Maintenance period (16-52 weeks).
- KGAD study was a 16-week randomised, double blind, placebo-controlled, parallel-group study designed to evaluate the safety and efficacy of lebrikizumab + TCS compared with placebo + TCS in adults and adolescents (12 to less than 18 years of age that weighted at least 40 kg) with moderate-to-severe AD.

The co-primary endpoints in all 3 pivotal studies were:

- Percentage of patients with an IGA score of 0 or 1 and a reduction ≥2 points from baseline to Week 16.
- Percentage of patients achieving EASI 75 (≥75% reduction from Baseline in EASI score) at Week 16

3.2. Favourable effects

Lebrikizumab demonstrated a statistically significant and clinically relevant improvements over placebo when used as monotherapy or in combination with TCS. The co-primary endpoints, i.e. proportion of patients achieving EASI 75 and IGA 0,1 (with ≥2 point reduction from baseline) at Week 16 were met in all 3 pivotal studies.

Based on the primary analysis using the "hybrid" estimand, 43.1% and 33.2% of patients treated with lebrikizumab and 12.7% and 10.8% of patients treated with placebo achieved IGA 0,1 in the KGAB and KGAC studies at Week 16. This translated into a 29.7% (95% CI 21.6, 37.8, p<0.001) and 21.9% (95% CI 14.2, 29.6, p<0.001) difference from placebo in the KGAB and KGAC studies, respectively. 58.8% and 52.1% of patients treated with lebrikizumab and 16.2% and 18.1% of patients treated with placebo

achieved EASI 75 in KGAB and KGAC studies at Week 16. This translated into a 42% (95% CI 33.3, 50.6, p<0.001) and 33.3% (95% CI 24.4, 42.2, p<0.001) difference from placebo in the KGAB and KGAC studies, respectively.

In KGAD, 41.2% of patients treated with lebrikizumab + TCS and 22.1% of patients treated with placebo + TCS achieved IGA 0,1 at Week 16. This translated into a 18.3% (95% CI 5.1, 31.5, p=0.011) difference from placebo. 69.5% of patients treated with lebrikizumab + TCS and 42.2% of patients treated with placebo + TCS achieved EASI 75 at Week 16. This translated into a 26.4% (95% CI 12.1, 40.8, p<0.001) difference from placebo.

The supportive "composite" estimand yielded similar results to the primary analysis of the co-primary endpoints.

For the Induction Period, the key secondary endpoints in studies KGAB and KGAC supported the effects seen in the co-primary endpoints with statistically significant differences over placebo e.g. in EASI 90, pruritus NRS ≥4 point improvement, sleep loss scale ≥2 improvement and DLQI ≥4 point improvement.

The pivotal studies included adults and adolescents 12 to less than 18 years of age that weighted at least 40 kg. The subgroup analysis in adolescent patients provided evidence that lebrikizumab has similar or somewhat better efficacy in adolescents compared to adult population. In the pooled analysis of the KGAB and KGAC studies, 46.6% vs. 14.3% of the adolescent patients achieved IGA 0,1 and 62.0% vs. 17.3% achieved EASI 75 at Week 16 in lebrikizumab vs. placebo groups, respectively. In KGAD study, 57.3% vs. 28.6% of the of the adolescent patients achieved IGA 0,1 and 88.0% vs. 57.1% achieved EASI 75 at Week 16 in lebrikizumab vs. placebo groups, respectively.

Among IGA 0,1 responders at Week 16 in KGAB and KGAC studies, high proportions in 250 mg Q4W and Q2W lebrikizumab groups maintained the response at Week 52 (74.2% and 75.8% in KGAB, 80.6% and 64.6% in KGAC). Of note, high proportions were observed in placebo (lebrikizumab withdrawal) group as well (46.5% in KGAB and 49.8% in KGAC).

Among EASI 75 responders at Week 16 in KGAB and KGAC studies, high proportions in 250 mg Q4W and Q2W lebrikizumab groups maintained the response at Week 52, i.e. in the Maintenance period (79.2% and 79.2% in KGAB, 84.7% and 77.4% in KGAC). Of note, high proportions were observed in placebo (lebrikizumab withdrawal) group as well (61.3% in KGAB and 72.0% in KGAC).

3.3. Uncertainties and limitations about favourable effects

Simulation data suggest that patients with adequate initial response may continue to maintain response with 250 mg QXW dosing but there is no clinical data to confirm this. It is therefore recommended that the Applicant conducts a clinical study that compares Q4W vs. QXW dosing during the maintenance period in subjects who are initial responders at week 16.

The efficacy and safety of lebrikizumab in adolescents weighing <40 kg has not been demonstrated but is being addressed in a clinical study according to the agreed PIP.

Long-term efficacy data are very limited. A LTE study with planned duration of 100 Weeks is ongoing.

3.4. Unfavourable effects

A total of 1720 participants (including 372 adolescents) with AD were exposed to any dose of lebrikizumab for 1637.02 PY. The dosing regimen proposed for marketing (lebrikizumab 250 mg Q2W during the first 16 weeks followed by lebrikizumab 250 mg Q4W) was administered to 147 participants (216.11 PY).

Induction period (weeks 0-16)

During induction, higher incidences of TEAEs were reported in the lebrikizumab treated subjects than in those on placebo in the following SOCs: Infections and infestations, Eye disorders, and Nervous system disorders. Common TAES reported more frequently in the lebrikizumab group compared to placebo in the induction period were conjunctivitis (6.9%), nasopharyngitis (4.4%), headache (4.4%), conjunctivitis allergic (1.8%), dry eye (1.4%) and rhinitis allergic (1.0%).

Maintenance period (weeks 16-52)

In the maintenance period (weeks 16-52), the same TEAEs were common and the frequencies were roughly similar to those seen in the induction period.

Events of special interest

The observed incidence rates of infectious conjunctivitis were 6.9% in the induction phase and 5.0% in the maintenance phase. Conjunctivitis allergic occurred in 1.8% of LEB treated subjects during induction and 5.9% during maintenance. All events of conjunctivitis were nonserious according to (ICH) E2A guidelines. Two (0.1%) events of conjunctivitis, and 4 (0.2%) events of conjunctivitis allergic were classified as severe (a severe event is defined as an event that prevents normal everyday activities). Most events of conjunctivitis (72.1%) were reported as recovered or resolved by the data cutoff date. Four events of conjunctivitis led to treatment discontinuation.

Of the 183 participants reporting events within the conjunctivitis cluster (conjunctivitis of various etiologies, that is, bacterial, viral, allergic), the majority occurred earlier in treatment but throughout the whole 52 weeks of treatment with the proposed posology (LEB 250 Q2W/Q4W) the total frequency of conjunctivitis was 14.2% and of conjunctivitis allergic was 6.1%.

Of the 1720 AD patients with any exposure to lebrikizumab 250 mg total of 9 (0.5%) participants reported 14 events within the keratitis cluster during the whole study period. Five of these events occurred during the induction period. One (0.9%) event of severe vernal keratoconjunctivitis in a LEB 250 mg Q2W participant led to treatment discontinuation. Eleven (0.6%) participants reported a total of 13 events of blepharitis. Seven of these events occurred during the induction period. One severe event of blepharitis was noted. None led to treatment discontinuation.

In the induction period, the frequency of TEAE Infections and infestations was higher in LEB 250 mg Q2W arm compared to placebo (21.2% vs 18.6%). This was primarily driven by conjunctivitis and nasopharyngitis. The exposure adjusted incidence rate with LEB 250mg Q2W was lower than that with placebo.

Although the combined incidence of all herpes infections was balanced between treatment groups, herpes zoster and herpes simplex infections were more common with lebrikizumab compared to placebo. Herpes zoster occurred in 5 (0.6%) patients treated with LEB compared to 0 patients in the placebo arm during induction. Herpes simplex occurred in 2 (0.3%) patients treated with LEB compared to 0 patients in the placebo arm during induction. No eczema herpeticum events were reported in the lebrikizumab group compared to 3 (0.7%) events in the placebo group. All herpes infection events were nonserious and none led to treatment discontinuation.

From baseline to Week 16, the frequency of participants with increased blood eosinophils at any time point post-baseline was higher in lebrikizumab-treated participants (20.3%) compared to placebo-treated participants (11.7%). TE eosinophilia AEs were reported at a similar frequency in the lebrikizumab group (0.6%) compared to placebo (0.8%). A shift to severely elevated eosinophil levels (greater than 5000 cells/mm^3) was detected in 3 lebrikizumab-treated participants (0.4%) and 0 placebo-treated participants during induction treatment. The eosinophilia was transient and did not result in discontinuation. No eosinophil-related disorder AEs were reported.

In the induction period, frequency of immediate hypersensitivity reactions was lower in LEB 250mg Q2W (n=22, 2.8%) compared to placebo (n=25, 6.2%). In the maintenance period, the frequency of immediate hypersensitivity reactions was slightly higher in both lebrikizumab arms although the number of events is very small. No serious events of immediate hypersensitivity or anaphylaxis were reported in the AD program.

As for nonimmediate hypersensitivity, in the induction period, the frequencies of nonimmediate hypersensitivity events were lower in the lebrikizumab group (n = 77, 9.9%) compared to placebo (n = 69, 17.1%), while in the maintenance period the frequencies were similar in LEB Q4W and placebo (n = 17, 14.4% and n = 8, 13.3%, respectively).

The frequency of non-immediate hypersensitivity reactions in adolescents receiving lebrikizumab Q4W is 17.6% in the maintenance period and 20.7% in any LEB exposure set compared to adults receiving the same dosing regimen (13.9% in maintenance and 10.2% in any LEB exposure) and higher compared to adolescents receiving placebo (12.5% in maintenance) or adolescents receiving LEB Q2W (0 in maintenance and 14.3% in any LEB exposure set).

The incidence of injection site reactions was higher in the lebrikizumab-treated group (n=20, 2.6%) compared to placebo (n=6, 1.5%) during the induction period but decreased over time and was similar between groups during maintenance. All events were nonserious. One (0.1%) event of injection site dermatitis which occurred within a month was severe and led to treatment discontinuation. Another participant discontinued treatment due to injection site rash, which occurred within 15 days of study drug administration.

Serious adverse events

In total 4 deaths were recorded during the AD lebrikizumab clinical programme. One death occurred in placebo arm while 3 deaths occurred in patients receiving lebrikizumab 250 mg Q2W. Investigators assessed all deaths as unrelated to study drug treatments.

The frequency of participants reporting at least 1 SAE was low and similar in the lebrikizumab and placebo groups during both the induction and maintenance period (below 2%). During induction, frequencies of SAEs were similar for both treatment arms regardless of concomitant TCS. No SAE was reported by more than 1 participant in each treatment group during induction.

Serious infections occurred in two patients during the induction period: one (0.2%) placebo-treated participant 2 serious events of cellulitis of the right extremity and sepsis and one (0.1%) lebrikizumab-treated participant reported a serious event of severe infectious colitis. Of the 1720 AD patients with any exposure to lebrikizumab 250 mg an additional two cases of COVID-19, one case of acarodermatitis and erysipelas and one case of pneumonia were classified as serious infections. All serious infections were recovered/resolved and did not lead to treatment discontinuation.

Immunogenicity

In the combined phase 3 Studies KGAB, KGAC and KGAD, 3.4% of participants treated with lebrikizumab 250 mg Q2W, 2.8% of participants treated with lebrikizumab 250 mg Q2W/Q4W, and 0.9% of participants treated with placebo developed treatment-emergent ADA over 12 months. Nearly all TE ADA positive participants were also positive for NAb to lebrikizumab but most ADAs were low titre (only 2 participants had maximum titres of 1:320 and 1:640, respectively). ADA/Nab frequencies and titres were similar in the adolescents compared to the overall population.

Special populations

There were 53 participants older than 65 and 15 participants older than 75 exposed to lebrikizumab during the induction period. There were 99 adolescents exposed to lebrikizumab during the induction period.

There were 270 adolescents exposed to any dose of lebrikizumab for at least 1 year. The total number of adolescents with AD exposed to any dose of lebrikizumab is 372. In the induction period overall SAEs, TEAEs, discontinuations and TEAEs within special safety topics all occurred with lower frequency in adolescents compared to adults in both lebrikizumab and placebo groups. Regarding weight, height and BMI in adolescents, the mean changes in any LEB group for Z-score was close to 0 for all growth parameters.

The overall safety profile in all adolescents exposed to any dose of lebrikizumab was consistent with the safety profile in adults in terms of frequency and nature of adverse events. The most common TEAEs in adolescents occurring more frequently in the lebrikizumab-treated adolescents compared to placebo were conjunctivitis, nasopharyngitis, dry eye, and rhinitis allergic.

There is limited amount of data from the use of lebrikizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of tralokinumab during pregnancy.

3.5. Uncertainties and limitations about unfavourable effects

The ADR list is generated based only on the first 16 weeks of treatment (the induction period). This is acceptable as only the induction period enabled comparison to true placebo and as no new information on the nature, frequency, severity or causal relationship of events is evident from the long-term data.

The long-term safety profile of lebrikizumab has not been fully characterised as long-term safety study in AD patients is ongoing. The M-17923-32 study on long-term safety and efficacy of lebrikizumab in adult and adolescent patients with moderate-to-severe atopic dermatitis will provide further long-term data. Long-term safety is listed as a missing information in the safety concerns in the RMP.

Lebrikizumab has not been studied in pregnant or breastfeeding women, and no information on the excretion of lebrikizumab in human milk or effects on the nursing infant is available. There is currently insufficient clinical data available to draw conclusions about the safety of using lebrikizumab during pregnancy. Animal studies have not shown any effects on male and female reproductive organs and on sperm count, motility, and morphology. As a precautionary measure, it is preferable to avoid the use of lebrikizumab during pregnancy (section 4.6 of SmPC). Use in pregnant and breastfeeding women has been added as a missing information in the list of safety concerns in the RMP. The safety of lebrikizumab us in pregnant and breastfeeding women will be monitored in an observational PASS.

3.6. Effects Table

Table 73: Effects Table for Lebrikizumab in AD

Effect	Short Description		Unit	LEB 250 mg (Q2W/Q4W)	Placebo	Uncertainties/ Strength of evidence	References
Favourable Effects							
IGA 0/1 at week 16	Achievement of IGA 0 or 1 and a reduction ≥2 points from baseline		%	250mg Q2W KGAB: 43.1 KGAC: 33.2 KGAD: 41.2	 12.7 10.8 22.1	Superiority to placebo shown as monotherapy (KGAB and KGAC) and in combination with TCS (KGAD)	CSRs
EASI 75 at week 16	Achievement of ≥75% reduction from baseline in EASI score		%	250mg Q2W KGAB: 58.8 KGAC: 52.1 KGAD: 69.5	 16.2 18.1 42.2	Superiority to placebo shown as monotherapy (KGAB and KGAC) and in combination with TCS (KGAD)	CSRs
IGA 0/1 at week 52	Maintained IGA 0 or 1		%	250mg Q2W/Q4W KGAB: 75.8/74.2 KGAC: 64.6/80.6 Pooled analysis: 71.2/76.9	 46.5 49.8 47.9	Q4W dose regimen as effective as Q2W in maintaining IGA 0 or 1 In pooled analysis (KGAB and KGAC), statistically significant difference vs. placebo with Q2W and Q4W	CSRs SCE for the pooled data
EASI 75 at week 52	Maintained EASI 75 after achieving EASI 75 at week 16		%	250mg Q2W/Q4W KGAB: 79.2/79.2 KGAC: 77.4/84.7 Pooled analysis: 78.4/81.7	 61.3 72.0 66.4	Q4W dose regimen as effective as Q2W in maintaining EASI 75 In pooled analysis (KGAB and KGAC), statistically significant difference vs. placebo with Q4W, but not with Q2W (p=0.147)	CSRs SCE for the pooled data
Unfavourable Effects							
Conjunctivitis/ conjunctivitis allergic/keratitis/ blepharitis	Incidence during 0-16 weeks induction		%	6.9/ 1.8/ 0.6/ 0.8	1.8/ 0.7/ 0.3/ 0.2	Incidence during 0-52/56 weeks was 14.2%/ 6.1%/ 0.7%/ 2% in lebrikizumab-treated participants.	SCS
Injection site reaction	Incidence during 0-16 weeks induction		%	2.6	1.5	Incidence during 0-52/56 weeks was 2.0% in lebrikizumab-treated participants.	SCS
Eosinophilia	Incidence of increase in blood eosinophils to >5000 per microliter during 0-16 weeks		%	0.4	0	The frequency of participants with increased blood eosinophils at any time point post-baseline (0 to Week 16) was 20.3% in lebrikizumab-treated participants and 11.7% in placebo-treated participants	SCS

Abbreviations:

Abbreviations: ADA= anti-drug antibody, ISI= integrated summary of immunogenicity, SCS=summary of clinical safety, LEB=lebrikizumab. PBO= placebo.
Notes: Conjunctivitis as identified in this table refers to conjunctivitis of various aetiologies (bacterial, viral, allergic).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Although several therapies have recently become available for the treatment of moderate-to-severe AD, new therapies that are effective and safe particularly in the long-term treatment setting of this chronic disease are needed.

In the current marketing authorisation application, the applicant has clearly demonstrated the beneficial treatment effect of lebrikizumab 250 mg Q2W (with loading doses) as monotherapy and in combination with TCS in patients with a chronic moderate-to-severe AD, whose disease is inadequately controlled with topical medication. The favourable effects seen in the co-primary endpoints were both statistically significant and clinically relevant in both adults and adolescent population studied.

Importantly, in addition to the investigator-assessed endpoints IGA 0,1 and EASI 75 that are to some extent overlapping measures, beneficial effects were also seen in patient-reported outcomes, including pruritus NRS, DLQI and sleep-loss scale that measures the interference of itch on sleep. Supportive evidence of effectiveness of lebrikizumab was provided by several other efficacy endpoints included in the pivotal studies.

In terms of long-term treatment, the beneficial effect of lebrikizumab was well maintained up to 52 weeks in patients that achieved IGA 0,1 and/or EASI 75 at week 16. Some patients with initial partial response at week 16 benefit from continuation of the induction dose Q2W up to week 24. The Q4W dosing seemed as effective as Q2W dosing after induction period and appears to be the preferred dosing in long-term treatment.

In relation to safety, the number and total exposure of AD patients treated with the intended dose of lebrikizumab is sufficient and thus, the safety profile has been sufficiently characterised. Lebrikizumab was well tolerated and has a similar safety profile in both adults and adolescents ≥12 years of age and ≥40kg.

Overall, the safety profile for lebrikizumab is manageable. No clinically meaningful differences in safety were observed between different lebrikizumab dosing regimens (Q2W vs. Q4W in the maintenance phase). No differences in AE pattern were seen between monotherapy and lebrikizumab + topical treatment.

Patients with AD are known to be at an increased risk for clinically important co-morbidities such as skin infections, herpes infections, conjunctivitis, depression and sleep disorders. The risk for skin infections and conjunctivitis was reflected in the overall incidence of adverse events.

The overall safety profile of lebrikizumab is overall acceptable and considered manageable. The data suggest that most AEs occur within the first few months of drug treatment and that the AE pattern does not change over time, although some commonly occurring events such as conjunctivitis and conjunctivitis allergic expectedly had higher incidences with longer follow-up. The immunogenicity and allergic potential of lebrikizumab is low.

Safety data are appropriately reported in the product information.

Further data on long term safety of lebrikizumab in AD will be provided post-approval (category 3 PASS, see RMP).

3.7.2. Balance of benefits and risks

The efficacy of lebrikizumab for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years of age and older with a body weight of at least 40 kg who are candidates for systemic therapy has been demonstrated. The risks associated with lebrikizumab in the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years of age and older with a body weight of at least 40 kg who are candidates for systemic therapy have been adequately characterised in the clinical programme. The applicant initially applied for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years of age and older who are candidates for systemic therapy. Considering that all subjects had a weight of ⩾40 kg, the final indication was agreed to include bodyweight. Overall, based on the data presented the beneficial effects of lebrikizumab outweigh the unfavourable effects.

3.7.3. Additional considerations on the benefit-risk balance

Patient representatives provided their feedback and emphasised the impact of atopic eczema on quality of life and everyday activities regardless of age, gender, socioeconomic or other differences. They expressed their perspective on how the disease can affect people's lives, starting from the early years, when caregivers are heavily involved in the disease management, throughout the adolescence and adulthood. Specifically, they pointed out that in clinical trials, both men and women should be equally represented so that safety and efficacy can be established for each group. In their view, it is also imperative that a new medicine is assessed by individuals from all age, gender, and socioeconomic groups, in an equal manner. Further views on the disease and its management that still need further attention were also provided.

The contribution of patient representatives is highly appreciated.

3.8. Conclusions

The overall benefit/risk balance of Ebglyss is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ebglyss is favourable in the following indication(s):

"Ebglyss is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older with a body weight of at least 40 kg who are candidates for systemic therapy".

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that lebrikizumab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0286/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.