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AMENDED CLINICAL TRIAL PROTOCOL 08

Protocol title:	**A Phase IIb, Randomised, Double-blind, Placebo-controlled, Parallel Group, Multicentre Dose Ranging Study of a Subcutaneous Anti-OX40L Monoclonal Antibody (KY1005) in Moderate-to-Severe Atopic Dermatitis**
Protocol number:	**KY1005-CT05/DRI17366**
Amendment number:	**08**
Compound number (INN/Trademark):	**KY1005/SAR445229 (Amlitelimab/Not applicable)**
Brief title:	**Study Testing Response Effect of KY1005 Against Moderate-to-Severe Atopic Dermatitis** **The STREAM-AD Study**
Study Phase:	**2b**
Sponsor name:	**Kymab Ltd, a Sanofi Company**
Legal registered address:	**The Bennet Building (B930)** **Babraham Research Campus** **Cambridge, CB22 3AT** **United Kingdom** **Tel: +44(0)1223 833301**
Monitoring team's representative name and contact information:	

Regulatory agency identifier number(s):

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WHO:	U1111-1271-1438
EUDAMED:	Not applicable
Other	Not applicable

Date: 1-Mar-2022 Total number of pages: 147

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 08	All	1 March 2022, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 07	Germany only	10 February 2022, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 06	Hungary only	03 February 2022, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 05	All	18 January 2022, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 04	All	14 December 2021, version 1 (electronic 1.0)
Clinical Study Protocol Version 3.0	Japan only	03 November 2021
Clinical Study Protocol Version 2.0	All	14 September 2021
Clinical Study Protocol Version 1.1	All	08 July 2021
Clinical Study Protocol Version 1.0 (original)	All	16 June 2021

Note: The name and numbering of the protocol is based on a new numbering system followed by the Sponsor.

Amended Clinical Trial Protocol 08 (1 March 2022)

This amended clinical trial protocol 08 is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The reasons for this amendment to Protocol KY1005-CT05 are to fulfil requirements from the German authorities Paul-Ehrlich-Institut and Ethics Committee of the State of Berlin (Ethik-Kommission des Landes Berlin) with global impact, requirements from Czech Health Authorities (STÁTNÍ ÚSTAV PRO KONTROLU LÉČIV), requirements from Hungarian Emberi Erőforrások Minisztériuma, (Ministry of Human Capacities). Also the inclusion of an interim analysis, modification in the biopsy requirements, and overall clarifications.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis, Section 3.1, Section 6.6.2	[redacted]	[redacted]
Protocol Synopsis, Section 4.2	Adding clarification in inclusion criterion 10 that the signed informed consent form must actually be present at the time of inclusion.	To clarify that the signed informed consent form should be present when patient is included into this study.
Protocol Synopsis, Section 4.2	Inclusion criterion 11 "For patients at sites selected for skin biopsy collection: (until up to approximately one third [30%] of patients have enrolled to the skin biopsy sub-study), able and willing to provide skin biopsies at required timepoints." has been changed to "For patients who decide to join the biopsy sub-study at sites selected for skin biopsy collection, be able and willing to provide skin biopsies at [redacted]	To keep consistency with the optional skin biopsy sub-study.
Protocol Synopsis, Section 4.3	Adding clarifications on excluded systemic therapy for AD and targeted biologic and small molecule treatments in exclusion criterion 1.	To further clarify criterion on excluded systemic therapy for AD and targeted biologic and small molecule treatments.
Protocol Synopsis, Section 4.3	Exclusion criterion 4 "completion of required administrations of COVID-19 vaccine within 14 days prior to Baseline or within 7 days immediately prior to or following IMP administration" has been changed to "completion of required administrations of COVID-19 vaccine within 14 days prior to Baseline or within 14 days immediately prior to or following IMP administration."	To clarify that patients who complete COVID-19 vaccine within 14 days immediately prior to or following IMP administration should be excluded.
Protocol Synopsis, Section 4.3, Section 17.15.5	Exclusion criterion 6 "Basal and squamous cell skin cancer in the last 3 years prior to Baseline. Any other malignancies in the last 5 years prior to Baseline (excluding in situ cervical carcinoma that has been excised and cured)" has been changed to "Any malignancies or history of malignancies prior to Baseline (except for non-melanoma skin cancer that has been excised and cured for more than 3 years prior to Baseline; in situ cervical carcinoma that has been excised and cured)."	To clarify the requirement on malignancies of enrolled patients. To fulfil requirement from the Czech Health Authorities (STÁTNÍ ÚSTAV PRO KONTROLU LÉČIV).

Section # and Name	Description of Change	Brief Rationale
	Country-specific clarification has been added regarding the exclusion criterion 6 "Any malignancies or history of malignancies prior to Baseline (except for non-melanoma skin cancer that has been excised and cured for more than 3 years prior to Baseline; in situ cervical carcinoma that has been excised and cured). Where a patient meets the above criteria but is still under the care of an oncologist, the investigator should confirm with oncologist that enrolment into this Phase 2b study is suitable."	
Protocol Synopsis, Section 4.3	Exclusion criterion 10 "Elective surgery planned to be scheduled for any time in the period up to 12 weeks following the last dose of IMP" has been changed to "Elective surgery planned to be scheduled for any time in the period from Screening up to 12 weeks following the last dose of IMP that in the investigator's opinion would impact the conduct of the trial".	To clarify requirements on planned elective surgery of enrolled patients.
Protocol Synopsis, Section 4.3	Exclusion criterion 11 "Anticipated initiation of prohibited medications up to 12 weeks following the last dose of IMP" has been changed to "Anticipated initiation of prohibited medications from Screening up to 12 weeks following the last dose of IMP.	To clarify that those patients have anticipated initiation of prohibited medications from Screening up to 12 weeks following the last dose of IMP should be excluded.
Protocol Synopsis, Section 4.3	Adding clarification regarding history of or known or suspected hypersensitivity to KY1005/placebo and other mAbs in exclusion criterion 18.	To clarify that patients with history of or known or suspected hypersensitivity to KY1005/placebo and other mAbs should be excluded.
Protocol Synopsis, Section 4.3	Changing "prisoner" in exclusion criterion 19 to "persons who have been placed in an institution on the basis of an official or court order" for clarification.	To clarify the definition of patients under coercion.
Protocol Synopsis, Section 3.3, Section 10.4.8	Wording regarding interim analysis has been added.	To obtain early information for planning the phase 3 program, the interim analysis is added to support the timely analysis of data from patients who have completed the Day 113 (Week 16) assessments. No study conduct will be modified based on interim analysis results.
Protocol Synopsis, Section 10.4.2	Information on how the type I error rate will be controlled has been added.	To elaborate specific approach used to control the overall type I error rate for multiple comparisons requested by German Ethics Committee of the State of Berlin (Ethik-Kommission des Landes Berlin).
Section 1.1	Adding information that KY1005 also refers to SAR445229 or amlitelimab.	To elaborate terminology of KY1005, especially the International Nonproprietary Name (INN) of amlitelimab.

Section # and Name	Description of Change	Brief Rationale
Section 3.5	Adding specific reasons which may be used by the sponsor to make a decision to terminate the study: approval or the favorable opinion is revoked; in the event of a negative change in the benefit/risk ratio when the necessary adjustment to the maximum sum insured is not possible.	To elaborate specific reasons which may be used by the sponsor to terminate the study requested by German Ethics Committee of the State of Berlin (Ethik-Kommission des Landes Berlin).
Section 3.7	Specific description regarding IDMC access to unblinded data has been added: IDMC members can have access to unblinded data sooner than the mentioned timepoint if that is necessary to perform data monitoring activities, and for safety purposes.	To elaborate that IDMC members can access to unblinded data sooner than timepoint (Day 169 [Week 24]) if for data monitoring activities and safety purposes.
Section 4.5	Adding specific requirements on breastfeed of female patients: female patients must not breastfeed until 5 months after Day 337 (Week 48) or the early termination visit (if prior to Day 337).	To clarify the requirements on breastfeed of female patients.
Section 5.2.6, Section 8.1.3	The definition of overdose has been updated.	To align the overdose definition within the program.
Section 5.2.7	[redacted]	[redacted]
Section 5.3.3	A consideration of the impact of KY1005 on other vaccines besides COVID-19 vaccination in AD patients has been added: The impact of KY1005 on overall vaccination response, new and recall response, for both COVID19 and other vaccines, has not been tested to date in AD patients. "The vaccine should not be administered within 7 days immediately prior to, or following, IMP administration." has been changed to "The vaccine should not be administered within 14 days immediately prior to, or following, IMP administration."	To clarify the impact of amlitelimab on overall vaccinations in AD patients and to clarify that when the study is ongoing the COVID 19 vaccine should not be administered within 14 days immediately prior to or following, IMP administration.
Section 5.3.4	"No rescue is permitted in the first 14 days following randomisation. Any administration of topical or systemic therapies during this period will result in permanent discontinuation from the study." has been changed to "No AD rescue therapy is permitted in the first 14 days following randomisation. Any AD rescue therapy administration either topical or systemic during this period will result in permanent discontinuation from the IMP. Bland emollients are not considered rescue therapy for AD, and	To clarify rescue therapy for AD, especially to claim that bland emollients are not considered rescue therapy.

Section # and Name	Description of Change	Brief Rationale
	should be maintained during this period as per protocol."	
Section 6.1 (Table 6-1), Section 6.6.2	[redacted]	[redacted]
Section 6.2.3.1	Clarification regarding how to interpret and handle QuantiFERON®-TB Gold blood test results has been added.	To clarify QuantiFERON®-TB Gold blood test results interpretation.
Section 6.7 (Table 6-6)	Blood volume per safety sample and total blood volume has been adjusted.	To adjust safety blood volume.
Section 7	The sample storing time has been changed to 25 years.	To keep consistency with Sanofi requirements on sample retention time.
Section 17.15.3	Adding clarification that patients in Hungary will need to have received the COVID-19 vaccines and booster(s) approved in Hungary in accordance with the official recommendations.	To fulfil requirements from Hungarian Emberi Erőforrások Minisztériuma, (Ministry of Human Capacities).
Throughout the document	Other minor editorial changes (eg, grammatical, stylistic, and minor typographical corrections).	To increase the clarity or consistency of the protocol.

STUDY PERSONNEL

Sponsor:	Kymab Ltd, a Sanofi Company, The Bennet Building (B930) Babraham Research Campus Cambridge, CB22 3AT United Kingdom Tel: +44 (0) 1223 833301
Sponsor Authorised Protocol Approver:	Kymab Ltd, a Sanofi Company
Global Project Head:	[redacted]
Clinical Research Director:	[redacted]
Medical Monitor:	[redacted]
<u>Emergency Numbers</u> **Emergency Contact:**	[redacted]

This study will be conducted in compliance with:

- This protocol.
- International Conference on Harmonisation (ICH) E6(R2) Good Clinical Practice (GCP) guidelines.
- The applicable regulatory requirement(s).
- The general principles of the Declaration of Helsinki.

COMPLIANCE STATEMENT

The study will be conducted in compliance with the protocol, informed consent regulations, the general principles of the Declaration of Helsinki and the International Conference on Harmonisation (ICH) E6(R2) guidelines related to Good Clinical Practice (GCP). In addition, the study will adhere to all applicable local regulatory requirements.

The electronic data capture (EDC) systems and other applicable electronic systems used in the conduct of the study will comply with ICH E6(R2), Section 5.5.3 guidance on use of electronic trial data handling and/or remote electronic trial data systems, the Food and Drug Administration (FDA), 21 CFR Part 11, Electronic Records, Electronic Signatures, and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials.

All analyses will be performed in laboratories qualified in accordance with the procedures of the Sponsor or Sponsor's contracted Clinical Research Organisation (CRO).

All episodes of non-compliance will be documented and addressed. Significant non-compliance (with potential to impact on safety or the integrity of data) will be notified to the Sponsor promptly. Non-compliance with the protocol, SOPs, ICH GCP, and/or applicable regulatory requirement(s) will lead to prompt action by the Sponsor to secure compliance. If serious and/or persistent non-compliance is identified on the part of an Investigator/institution, Sponsor will terminate the Investigator's/institution's participation in the trial in accordance with ICH GCP.

The Sponsor will ensure oversight of any trial-related duties and functions carried out on its behalf, by contracted vendors, and where applicable ensure the Sponsor's contracted CRO(s) have appropriate systems and processes to provide oversight of duties subcontracted to another party by them.

PROTOCOL SYNOPSIS

Protocol identifier:	KY1005-CT05 (DRI17366)
Study title:	A Phase IIb, Randomised, Double-blind, Placebo-controlled, Parallel Group, Multicentre Dose Ranging Study of a Subcutaneous Anti-OX40L Monoclonal Antibody (KY1005) in Moderate to Severe Atopic Dermatitis Brief title: **S**tudy **T**esting **R**esponse **E**ffect of KY1005 **A**gainst **M**oderate to Severe **A**topic **D**ermatitis (STREAM-AD)
Protocol version:	8.0
Sponsor:	Kymab Ltd, a Sanofi Company
Development Phase:	2b
Study type:	Interventional
Indication:	Atopic dermatitis (AD)
Study sites:	Sites will be selected globally to participate in this study.
Study rationale and purpose:	The aim of this study is to characterise the efficacy (including dose/exposure response) and safety of KY1005 across a range of doses/exposures for a maximum duration of 52 weeks in adult patients with moderate-to-severe AD who have had an inadequate response to topical therapies or where topical therapies are not advised. In addition, the durability of response and pharmacokinetics (PK) following withdrawal from the Investigational Medicinal Product (IMP) from Day 169 (Week 24) will be characterised. KY1005 is a human anti-OX40 ligand (OX40L) immunoglobulin G (IgG) 4 monoclonal antibody (mAb) that, via blockade of the OX40/OX40L pathway, is expected to suppress T helper (Th) cell Th2-driven inflammation, as well as potentially modulating Th1, Th17 and Th22 responses. Atopic dermatitis is a chronic/relapsing inflammatory skin disease, characterised by intense pruritus and recurrent eczematous lesions, driven by epidermal barrier dysfunction and cluster of differentiation (CD) 4+ driven inflammation which is dominated by Th2 cytokines.
Primary objective:	To characterise the efficacy (including dose/exposure-response) across a range of KY1005 exposures compared to Placebo on the signs of AD using the Eczema Area and Severity Index (EASI) in those patients with a documented history, within 6 months prior to Baseline, of either inadequate response to topical treatments or inadvisability of topical treatments. Dose response of 4 different dose regimens of KY1005 in patients with AD versus Placebo will be evaluated. The primary efficacy endpoint will be the percentage change in EASI from Baseline to Day 113 (Week 16).
Secondary objectives:	The key secondary efficacy objectives will be to characterise the efficacy (including dose/exposure-response) across a range of KY1005 exposures compared to Placebo on additional physician assessments of AD activity/severity: EASI at Day 169 (Week 24), EASI-75, Investigator Global Assessment [IGA], and Numerical Rating Scale [NRS] for pruritus. Other secondary objectives include: To characterise: • Safety and tolerability of KY1005. • The PK profile of KY1005 across a range of KY1005 doses/exposures. • The response across a range of KY1005 exposures on additional physician assessments of AD activity/severity EASI, EASI 50, EASI 75, EASI 90, EASI 100, IGA, SCORing of Atopic Dermatitis (SCORAD) Index and affected body surface area (BSA).

	• The response across a range of KY1005 exposures on patient reported AD activity/severity (Patient Oriented [PO] Eczema Measure [POEM], Dermatology Quality of Life Index [DLQI], Atopic Dermatitis Control Tool [ADCT], Hospital Anxiety and Depression Scale [HADS], NRS for pruritus). • The pharmacodynamic (PD) response to KY1005 including but not limited to: ○ The immunogenicity of KY1005, including the anti-KY1005 antibody response. • The maintenance of clinical response in patients randomised to withdrawal of IMP who achieve ≥ EASI 75 or who attain IGA 0/1 response following 24 weeks of treatment.
Exploratory objectives:	• [redacted] ○ [redacted] • [redacted] • [redacted] • [redacted] • [redacted]
Study design:	This is a Phase IIb, randomised, double-blind, placebo-controlled, parallel group, multicentre dose ranging study to characterise the efficacy and safety of subcutaneous (SC) administered KY1005 in adult patients with moderate-to-severe AD who have a documented history, within 6 months prior to Baseline, of either inadequate response to topical treatments or inadvisability of topical treatments. The study will include a Screening period of up to 28 days. During the Screening period, [redacted] Patients who continue to meet the eligibility criteria at Baseline will be randomised 1:1:1:1:1 to receive a SC dose of KY1005, or matching Placebo. At Baseline those patients not receiving a KY1005 loading dose will receive both KY1005 and Placebo to maintain the study blind. Four different SC KY1005 dosing regimens will be tested versus Placebo. From Baseline up to Day 169 (Week 24), IMP will be administered at the following doses and intervals; 500 mg loading dose (given as [redacted] SC administration) followed 28 days later and thereafter with 250 mg every 4 weeks (Q4W) or the following regimens from Baseline: 250 mg Q4W, or 125 mg Q4W or 62.5 mg Q4W or Placebo Q4W. In accordance with the study blind at Baseline, a [redacted] Placebo SC dose will be administered along with the [redacted] KY1005 SC administration. All patients will therefore receive [redacted] SC doses at Baseline. As part of the study design, patients initially enrolled at Baseline into the Placebo, 62.5 mg, 125 mg and 250 mg KY1005 treatment arms who do not achieve ≥ EASI 75 or IGA 0/1 at Day 169 (Week 24) will have the opportunity to receive KY1005 from Day 169 (Week 24) by enrolling in a long-term extension (LTE) study (LTS17367, LTE). The LTE is a separate study to KY1005-CT05 (DRI17366) and will therefore have a separate protocol and undergo submission for regulatory approval separately to the parent study. This

	LTE enables all enrolled patients to have an opportunity to receive treatment at doses expected to elicit a meaningful clinical response (based on observations from the Phase 2a KY1005-CT02 study). Patients who achieve ≥ EASI 75 or who attain IGA 0/1 at Day 169 (Week 24) will be randomised 3:1 to either enter a maintenance withdrawal phase or continue on their pre-Week 24 dose/interval. The purpose being to characterise the durability of response in conjunction with PK following treatment discontinuation in those withdrawn from therapy and to assess the clinical response and long-term safety in those continuing to receive Q4W treatment at their pre-Week 24 dose. Those patients who are re-randomised at Day 169 (Week 24) and who subsequently lose clinical response, defined during that study period as the first instance of < EASI 50 and where rescue therapy is no longer permitted as per Section 5.3.4 on or after the Day 197 (Week 28) study visit, will be offered the opportunity to receive retreatment with KY1005 in the LTE study. Results from this randomised withdrawal maintenance phase will inform the subsequent later stage development of KY1005 in the treatment of AD. At Day 365 (Week 52), patients who complete the second study period without loss of clinical response will have an additional 112 days' safety follow-up to Day 477 (Week 68) and will then be discharged from the study. The last dose will be administered no later than Day 337 (Week 48). If during safety follow-up or after the end of study this cohort of patients experience worsening of their AD, and in the investigator's opinion re-treatment with KY1005 is considered appropriate, they may be considered for enrolment in the LTE (subject to meeting inclusion/exclusion criteria). [redacted]
Number of subjects:	A total of 350 patients (approximately 70 patients per treatment arm) will be randomised.
Study population:	Adult patients with moderate-to-severe AD who have a documented history, within 6 months prior to Baseline, of either inadequate response to topical treatments or inadvisability of topical treatments (eg, not well tolerated).
Key inclusion criteria:	Patients must fulfil all the following inclusion criteria for entry into the study: 1. Adults (18 to <75 years of age) with AD, as defined by the American Academy of Dermatology Consensus Criteria, for 1 year or longer at Baseline (Day 1; prior to first administration of IMP). For United Kingdom, see Section 17.15.2 (Appendix 15). 2. EASI of 12 or higher at the Screening Visit and 16 or higher at Baseline. 3. IGA of 3 or 4 at Baseline. 4. AD involvement of 10% or more of BSA at Baseline. 5. Baseline worst/maximum pruritus NRS of ≥4. The Baseline weekly average of daily worst/maximum pruritus NRS will be calculated from the 7 consecutive days immediately preceding the Baseline visit. A minimum of 4 daily scores out of the 7 will be required.

	6. Documented history, within 6 months prior to Baseline, of either inadequate response to topical treatments or inadvisability of topical treatments: a) Acceptable documentation includes contemporaneous chart notes that record TCS (topical corticosteroids) and topical medication prescription and treatment outcome, or Investigator documentation based on communication with the patient's treating physician. b) Failure to achieve and maintain remission or low disease activity (eg, IGA 0, clear skin to 2, mild disease) despite treatment with TCS of medium to high potency (± topical calcineurin inhibitor as appropriate), applied daily for at least 28 days or for the maximum duration recommended by the product prescribing information (eg, 14 days for super-potent TCS), whichever was shorter. NOTE: Patients who failed systemic therapies intended to treat AD within 6 months preceding screening, such as cyclosporine, methotrexate, azathioprine, and mycophenolate will be also considered as surrogate for having inadequate response to topical therapy. Washout of prior systemic medications must be completed as per the protocol requirements. c) Important side effects or safety risks defined as those that outweigh the potential treatment benefits including (but not limited to) hypersensitivity reactions, significant skin atrophy, treatment intolerance and adverse systemic effects, as assessed by the investigator or treating physician. 7. Must have applied a stable dose of topical bland emollient (simple moisturiser, no additives [eg, urea]) at least twice daily for a minimum of 7 consecutive days before Baseline. 8. Able to complete patient questionnaires, including collection of NRS (pruritus) on each of the 7 days prior to Baseline. For patients who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomisation date, randomisation should be postponed until this requirement is met, but without exceeding the 28-day maximum duration for screening. 9. Able and willing to comply with requested study visits/telephone visits and procedures. 10. Able and willing to provide written informed consent. This document must also actually be presented at the time of inclusion. 11. For patients who decide to join the biopsy sub-study at sites selected for skin biopsy collection, be able and willing to provide skin biopsies at [redacted]
Key exclusion criteria:	Patients fulfilling any of the following criteria will be excluded from the study: 1. Treatment with any of the following prior to first IMP administration (Baseline): o Systemic corticosteroids, and systemic calcineurin inhibitors (tacrolimus and cyclosporin) [redacted] o Leukotriene inhibitors [redacted] o Systemic therapy for AD, including but not limited to methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 (PDE4)-inhibitors, IFN-γ and mycophenolate mofetil [redacted] (except for the drugs mentioned on other criteria with specific washout periods); o Targeted biologic and small molecule treatments [redacted] o Previous treatment with systemic janus kinase (JAK) inhibitors [redacted] o Topical corticosteroids, tacrolimus or pimecrolimus, or topical PDE4 [redacted]

	○ Prescription or non-prescription moisturisers with additives (eg, urea, filaggrin) [redacted] ○ Phototherapy or allergen immunotherapy [redacted] ○ Regular use (>2 visits/week) of a tanning booth/parlour [redacted]; ○ Any prior use of anti OX40 or anti OX40L mAb, including KY1005. ○ Investigational therapy for the treatment of AD or other conditions within 5 half-lives or the limit of PD effects or 12 weeks where the $t_{1/2}$ is unknown. 2. Known history of, or suspected, significant current immunosuppression, including history of invasive opportunistic or helminth infections despite infection resolution or otherwise recurrent infections of abnormal frequency or prolonged duration. 3. Weight <40 kg or >150 kg at Baseline. [redacted] 4. Treatment with a live (attenuated) immunisation within 12 weeks prior to Baseline; completion of required administrations of COVID-19 vaccine within 14 days prior to Baseline or within 14 days immediately prior to or following IMP administration. [redacted] 5. Men and women (of reproductive potential) unwilling to use birth control and women who are pregnant or breastfeeding. 6. Any malignancies or history of malignancies prior to Baseline (except for non-melanoma skin cancer that has been excised and cured for more than 3 years prior to Baseline; in situ cervical carcinoma that has been excised and cured). [redacted] 7. Positive for human immunodeficiency virus, hepatitis B surface antigen, hepatitis B core antibody or hepatitis C antibody at the Screening Visit. [redacted] 8. History (within last 2 years prior to Baseline) of prescription drug or substance abuse, including alcohol, considered significant by the Investigator. 9. Current or any past history of tuberculosis or non-tuberculous mycobacterial infections (including a positive QuantiFERON®-Tuberculosis Gold blood test at the Screening Visit). 10. Elective surgery planned to be scheduled for any time in the period from Screening up to 12 weeks following the last dose of IMP that in the investigator's opinion would impact the conduct of the trial. 11. Anticipated initiation of prohibited medications from Screening up to 12 weeks following the last dose of IMP. 12. Severe concomitant illness that would in the Investigator's opinion inhibit the patient's participation in the study, including for example, but not limited to, hypertension, renal disease, neurological conditions, heart failure and pulmonary disease. 13. Skin comorbidity that would adversely affect the ability to undertake AD assessments. 14. Any medical or psychiatric condition which, in the opinion of the investigator may present an unreasonable risk to the study patient as a result of his/her participation in this clinical study, may make patient's participation unreliable, or may interfere with study assessments. 15. Any active or chronic infection requiring systemic treatment within 2 weeks prior to Baseline (1 week in the event of superficial skin infections). 16. Laboratory values at the Screening Visit: • [redacted]

	• [redacted] [redacted] • In the Investigator's opinion, any additional clinically significant laboratory results from the clinical chemistry, haematology or urinalysis tests at the Screening visit. 17. In the Investigator's opinion, any significant abnormality on 12-lead electrocardiogram (ECG) at the Screening Visit. 18. History of or known or suspected hypersensitivity to KY1005 or the matching placebo formulation, or excipients used in the presentation of KY1005 or placebo, or in preparation for administration. History of or known or suspected severe hypersensitivity reactions to other mAbs and/or their excipients. 19. Patients for whom coercion by either the Investigator or the Sponsor (eg, employee, student or persons who have been placed in an institution on the basis of an official or court order) cannot be discounted. (No patients will be included who are related to, or in a relationship with, or employed by the Investigator, the Sponsor or any organisations contracted on behalf of the Sponsor in the design, setting up or running of the study). 20. Concurrent participation in any other clinical study, including noninterventional studies.
Investigational medicinal products:	At Baseline, those patients not receiving a KY1005 loading dose will receive both KY1005 and placebo to maintain the study blind. Thereafter, patients will receive either SC KY1005 or matching Placebo.
Route of administration:	Subcutaneous administration to the abdomen (or outer thigh if skin involvement entirely precludes the abdominal region. However, the anatomical region of administration must remain consistent throughout study participation and documented in the electronic case report form).
Treatment regime(s):	All patients will receive IMP every 4 weeks from Day 1 to Day 337 (Week 48). Randomisation will occur on Day 1, and re-randomisation on Day 169 (Week 24) for patients who achieve ≥ EASI 75 or who attain IGA 0/1. IMP will be administered in a [redacted] volume to the abdomen by SC injection. *From Baseline (Day 1) to Day 169 (Week 24)* Patients will receive either: a) 500 mg loading at Baseline [redacted] followed 28 days later with 250 mg KY1005 Q4W as a single [redacted] administration to Day 169 (Week 24). b) 250 mg KY1005 Q4W. c) 125 mg KY1005 Q4W. d) 62.5 mg KY1005 Q4W. e) 0.0 mg Placebo Q4W. To maintain the blind for all those groups that do not have a 500 mg loading dose, a [redacted] Placebo administration will be given at Baseline along with the [redacted] administration of the allocated KY1005 dose or Placebo. *From Day 169 (Week 24) to Day 365 (Week 52):* Patients who achieve ≥ EASI 75 or attain IGA 0/1 at Day 169 (Week 24) only • Patients who achieve ≥ EASI 75 or attain IGA 0/1 at Day 169 (Week 24) will be randomised 3:1 to withdrawal or to remain on their pre-Week 24 dose/interval. Those randomised to withdrawal will receive Placebo Q4W.
Main efficacy/PD assessments:	The following efficacy/PD assessments will be performed in this study: • EASI, IGA, SCORAD Index, affected BSA, POEM, DLQI, ADCT, HADS, NRS for pruritus. • Anti-KY1005 anti-drug antibodies (ADAs).

Safety assessments:	The safety and tolerability of KY1005 will be assessed by the measurement/recording of: • Adverse events and serious adverse events. • Adverse events of special interest (AESI). • Vital signs. • Laboratory safety tests (haematology, clinical chemistry, and urinalysis). • 12-lead ECGs. • Physical examination, including injection site reactions. • Concomitant medications.
Pharmacokinetic and anti-drug antibody variables:	Serum PK and ADA samples on [redacted], plus additional assessment of PK and ADA from [redacted] (plus safety follow-up where it occurs beyond study [redacted]). Pharmacokinetic and ADA samples will be collected from all patients including those receiving Placebo.
Primary endpoints	• Percentage change in EASI from Baseline to Day 113 (Week 16).
Secondary endpoints:	<u>Safety endpoints:</u> • Incidence of treatment emergent adverse events including AESIs. <u>Pharmacokinetic endpoints:</u> • Serum KY1005 concentration assessed throughout the study for each patient (receiving KY1005). <u>Key secondary efficacy endpoints:</u> • Percentage change from Baseline in EASI at Day 169 (Week 24). • Percentage of patients with at least a 75% reduction from Baseline in EASI (EASI 75) at Days 113 (Week 16) and 169 (Week 24). • Percentage of patients with a response of IGA 0 or 1 and a reduction from Baseline of ≥2 points at Days 113 (Week 16) and 169 (Week 24). • Proportion of patients with improvement (reduction) of weekly average of pruritus NRS ≥4 with a Baseline pruritis NRS of ≥4 from Baseline to Days 113 (Week 16) and 169 (Week 24). <u>Other secondary efficacy endpoints:</u> • Absolute change from Baseline in EASI at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24). • Percentage change from Baseline in EASI at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12) and 141 (Week 20). • Percentage of patients with at least a 50% reduction from Baseline in EASI (EASI 50) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24). • Percentage of patients with at least a 75% reduction from Baseline in EASI (EASI 75) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12) and 141 (Week 20). • Percentage of patients with at least a 90% reduction from Baseline in EASI (EASI 90) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24). • Percentage of patients with a 100% reduction from Baseline in EASI (EASI 100) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24). • Change in IGA from Baseline to Day 113 (Week 16) and over time. • Percentage of patients with a response of IGA 0 or 1 and a reduction from Baseline of ≥2 points at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12) and 141 (Week 20).

	• Absolute and percentage change in SCORAD Index from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in affected BSA from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in POEM from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in DLQI from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in ADCT from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in HADS from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in weekly average of pruritus NRS from Baseline to Day 169 (Week 24) and over time. • Proportion of patients with improvement (reduction) of weekly average of pruritus NRS ≥3 with a Baseline pruritis NRS of ≥3 from Baseline to Days 113 (Week 16) and 169 (Week 24). <u>PD endpoints:</u> • Anti-KY1005 antibody titre and number of patients with positive response.
Main exploratory endpoints:	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted]
Statistical analysis:	**Sample Size:** A sample size of 350 patients (70 patients / treatment arm) in the target population, (adults with moderate-to-severe AD who have a documented history, within 6 months prior to Baseline, of either inadequate response to topical treatments or inadvisability of topical treatments), randomised 1:1:1:1:1 to 4 KY1005 groups or Placebo group is estimated to provide at least 84% power to detect a pairwise difference in means between each KY1005 and Placebo with respect to the percentage change in EASI from Baseline to Day 113 (Week 16), based on a 2-sided 2-sample equal-variance t-test. [redacted] **Analysis Sets:** ***Efficacy Analysis Set:*** The full analysis set (FAS) includes all randomised patients. Efficacy analysis will be based on treatment allocated at randomisation and stratified by disease severity (moderate/severe) and region. **Methods:** Statistical analysis of all endpoints will be defined in detail in the Statistical Analysis Plan. For continuous variables, descriptive statistics will include: the number of patients, mean, median, standard deviation, minimum, and maximum. For categorical or ordinal data, frequencies and percentages will be displayed for each category.

	Efficacy Analyses: An overall test for the treatment effect of KY1005 will be conducted. For each treatment regimen and all efficacy variables, the analysis will be comparisons of each of the KY1005 treatment groups with the Placebo group. For the primary endpoint, the overall type I error rate will be controlled using a hierarchical testing procedure across the four dose regimens against placebo. For each secondary endpoint analyzed, the same multiplicity adjustment approach will be applied as for the primary endpoint. No multiplicity adjustment will be made across the endpoints. For the continuous endpoints: An analysis of covariance (ANCOVA) model will be used. This model includes treatment, randomisation strata (region, disease severity) as fixed effects, and baseline value as a covariate. [redacted] A mixed-effect model with repeated measures will be used as a sensitivity analysis for primary and continuous key secondary endpoints. This model includes the factors (fixed effects) for treatment, randomisation strata (region, disease severity), visit, treatment-by-visit interaction, and relevant baseline value. For the categorical endpoints: Cochran-Mantel-Haenszel test stratified by randomisation strata (region, disease severity) will be used at each analysis timepoint. [redacted] Data will be presented graphically, where applicable, and with summary statistics by visit and by treatment regimen. ***Safety Analyses:*** Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, latest version) and will be summarised in incidence tables by System Organ Class and Preferred Term, and by treatment regimen. Adverse events will be further summarised by maximum severity and relationship to study medication. Concomitant medications will be coded using the World Health Organization Drug Dictionary and will be summarised in incidence tables by Drug Class and Preferred name, and by treatment regimen. Other routine safety assessments such as vital signs, 12-lead ECG and safety laboratory tests will be summarised by treatment regimen using statistics for continuous or categorical data, as appropriate. ***Pharmacokinetic Analyses:*** For each KY1005 treatment regimen, PK endpoints for each patient will be determined once final dose regimens confirmed. Charts to demonstrate both the individual concentration-time profiles and the mean (with standard errors, untransformed and with logarithmic transformation of concentrations) profiles will be generated by KY1005 regimen. Summary statistics by treatment group will be provided. ***Pharmacodynamic Analyses:*** Data will be presented graphically, where applicable, and with summary statistics by visit and by treatment regimen.

	Interim analysis: An interim analysis will be planned when approximately [redacted] participants in each arm complete the Day 113 (Week 16) assessments. The interim analysis will evaluate the percentage change in EASI from baseline to Day 113 (Week 16) and proportions of participants with EASI 75 at Day 113 (Week 16), as well as the other available data as needed.
Planned study dates: **Start of clinical phase:** **End of treatment phase:**	 November 2021 March 2024
Duration of the study:	The duration of the study will be up to 28 days for screening and then up to approximately Day 477 (last dose no later than Day 337 plus 140 days safety follow-up) for all patients unless enrolled into the LTE protocol at either Day 169 depending on responder status or no later than Day 365 due to loss of clinical response.
Key words:	KY1005, Monoclonal Antibody, Atopic Dermatitis, Atopic Eczema, OX40L, Phase IIb.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AD	Atopic dermatitis
ADA	Anti-drug antibody
ADCT	Atopic Dermatitis Control Test
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the serum concentration curve
BMI	Body mass index
BSA	Body surface area
cEv	Intercurrent event
C1q	Complement component 1q
CCL	Chemokine [C-C motif] ligand
CD	Cluster of differentiation
C_{max}	Maximum observed serum/plasma drug or metabolite concentration
C_{min}	Trough concentrations
CFR	Code of Federal Regulations
CI	Confidence interval
CMC	Chemistry and Manufacturing Controls
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CPK	Creatine phosphokinase
CRO	Contract Research Organisation
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DC	Dendritic cells
DLQI	Dermatology Quality of Life Index
DMP	Data management plan
DNA	Deoxyribonucleic acid
DTH	Delayed type hypersensitivity
EASI	Eczema Area and Severity Index
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study

Abbreviation	Definition
EP	Endpoint
ePRO	Electronic patient-reported outcome
eTMF	Electronic Trial Master File
FAS	Full analysis set
FBC	Full blood count
FDA	Food and Drug Administration
FIH	First-in-human
Foxp3	Forkhead box P3
FSH	Follicle-stimulating hormone
GATA3	GATA Binding Protein 3
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HADS	Hospital Anxiety and Depression Scale
Hb	Haemoglobin
HbsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HCT	Haematocrit
HD	High dose
HIV	Human immunodeficiency virus
IB	Investigator Brochure
IC90	90% inhibitory concentration
IcEv	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IF	Immunofluorescence
IFN	Interferon
Ig	Immunoglobulin
IGA	Investigator Global Assessment
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive response technology
ISF	Investigator Site File

Abbreviation	Definition
IV	Intravenous(ly)
JAK	Janus kinase
JAKi	Janus kinase inhibitor
K16	Keratin 16
KLH	Keyhole limpet haemocyanin
LD	Low dose
LDH	Lactate dehydrogenase
LoE	Lack of efficacy
LS	Least squares
LTE	Long-term extension
mAb	Monoclonal antibody
MCH	Mean cell haemoglobin
MCHC	Mean cell haemoglobin concentration
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect model with repeated measures
NA	Not applicable
NOAEL	No observed adverse effect level
NRS	Numerical Rating Scale
OX40L	OX40 ligand
PBO	Placebo
PD	Pharmacodynamic(s)
PDE4	Phosphodiesterase type 4
PEI	Paul-Ehrlich-Institut
PI	Principal Investigator
PIS	Patient information sheet
PK	Pharmacokinetic
PO	Patient Oriented
POEM	Patient Oriented Eczema Measure
PRO	Patient reported outcome
PT	Preferred term
Q4W	Every 4 weeks
QoL	Quality of life
RBCC	Red blood cell count
RNA	Ribonucleic acid
SAE(s)	Serious adverse event(s)
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	Subcutaneous(ly)

Abbreviation	Definition
SCORAD	SCORing of Atopic Dermatitis
SEM	Standard error of the mean
SD	Standard deviation
SDV	Source data verification
SDTM	Study Data Tabulation Model
SOC	System organ class
SOP	Standard operating procedure
SUSAR(s)	Suspected unexpected serious adverse reaction(s)
$t_{1/2}$	Half-life
TARC	Thymus- and activation-regulation chemokine
TB	Tuberculosis
TCS	Topical corticosteroids
TDAR	T-dependent antibody response
TEAE(s)	Treatment emergent adverse event(s)
Th	T helper
t_{max}	Time to maximum observed concentration
TReg	Regulatory T cell(s)
TSLP	Thymic stromal lymphopoietin
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
UV	Ultraviolet
VAS	Visual analogue scale
WBCC	White blood cell count
WOCBP	Women of childbearing potential
WHO	World Health Organisation

Definition of Terms

Investigator	The Principal Investigator, person responsible for the conduct of the study at each site or their appropriately qualified delegate
Baseline	Last observation before first administration of IMP (Day 1)

1 BACKGROUND INFORMATION

1.1 Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a common, chronic inflammatory skin disorder, which has a significant impact on the health and quality of life (QoL) of individuals with the disease especially social functioning and psychological well-being. Treatment of AD in general depends on the extent and severity/activity of the disease, and when topical therapies are insufficient to treat signs and symptoms, systemic therapy or phototherapy are added. Although several systemic treatments are available, many patients do not derive optimal benefit due to either incomplete treatment responses or to adverse reactions. KY1005 (also refers to SAR445229 or amlitelimab), a human anti-OX40 ligand (OX40L) monoclonal antibody (mAb), has therefore been developed to address the significant unmet medical need for treatment options in this patient population.

1.2 Introduction to Atopic Dermatitis and its Biology/Mechanism of Action

Atopic dermatitis is a chronic/relapsing inflammatory skin disease, characterised by intense pruritus and recurrent eczematous lesions, driven by epidermal barrier dysfunction and cluster of differentiation (CD) 4+ driven cutaneous inflammation [Weidinger Nat Rev 2018, Langan The Lancet 2020]. Lesional skin shows an altered expression of genes related to keratinocyte activity and differentiation as well as T cell infiltration and activity, of genes encoding T helper (Th) cell Th2 associated (interleukin [IL]-4, IL-10, IL-13) and Th22-associated (IL-22) proteins. In more chronic disease stages, Th1-mediated and Th17-mediated responses appear to be upregulated as well.

1.3 Overview of Disease and Current Trends in Treatment

Atopic dermatitis is the most common inflammatory skin disorder in the developed world. Data from the World Health Organisation (WHO) Global Burden of Diseases initiative indicate that at least 230 million individuals worldwide have AD (lifetime prevalence >15%), with AD being the leading cause of the non-fatal disease burden conferred by skin conditions on a global level [Weidinger Nat Rev 2018]. At the patient level, AD has a diverse and marked negative impact on QoL and places a tremendous financial burden on society and patients [Drucker J Invest Dermatol 2017]. Atopic dermatitis can manifest at any point in life, but the incidence peaks in infancy with an estimated 80% of cases showing an onset before 6 years of age [Kay J Am Acad Dermatol 1994; Perkin Pediatr Allergy Immunol 2004]. After initiation, the course may be continuous for long periods, but may also show a relapsing remitting nature [Garmhausen Allergy 2013]. Conventional clinical teaching is that AD clears in more than 50% of affected children, but recent data indicate that the proportion of patients with persistent or adult-onset disease or with relapses after longer asymptomatic intervals is much higher, and that AD is a lifelong disease with a highly variable phenotypic expression [Abuabara Allergy 2018; Silverberg J Allergy Clin Immunol 2013].

Atopic dermatitis management aims to improve symptoms and establish long-term disease control using a multi-stepped approach. The main principles are continuous epidermal barrier repair with emollients and anti-inflammatory therapy with topical corticosteroids or calcineurin inhibitors. When topical therapies are insufficient to treat signs and symptoms, systemic

therapy or phototherapy are indicated. The duration of use of many systemic immunomodulatory agents are limited due to (cumulative) toxicity. Newer biologic agents such as dupilumab which target the IL-4 receptor (IL-4R) have been shown to significantly improve both clinical and patient reported outcomes, but the long-term durability of response and the ability to be disease modifying will only become apparent with broader and long-term use. There remains a significant unmet need in AD with a real need to develop disease modifying therapies that can address the underlying immunopathogenic process and improve the outcomes for patients with this common but often disabling skin disease [Weidinger Nat Rev 2018].

1.4 Investigational Medicinal Product(s)

The Investigational Medicinal Products (IMPs) are KY1005 and matching Placebo.

1.4.1 Overview of KY1005

KY1005 (also known as KY1005-2D10) is a biotechnology derived human anti-OX40L mAb (subclass G4) generated by a Chinese Hamster Ovary (CHO) cell line that binds OX40L to block the interaction with its receptor, OX40 (CD134). The Fc regions were modified to the immunoglobulin (Ig) G4PE variant to reduce Fc receptor binding and stabilise the antibody hinge region. The resulting molecule is therefore expected to have null effector function (known not to deplete target cells) and would not undergo fragment antigen-binding arm exchange as has been reported for natural IgG4.

Blockade of the OX40/OX40L co-stimulation pathway represents a scientifically plausible approach to modulating the persistent inflammation caused by autoreactive memory T-cell populations and may provide a means of inducing immune tolerance to autoantigens (eg, in autoimmune disease) or alloantigens (eg, following transplants).

OX40L is inducibly expressed on professional antigen-presenting cells, such as B-cells, dendritic cells (DCs) and macrophages upon activation [Webb Clin Rev Allergy Immunol 2016]. Other cells such as endothelial cells, smooth muscle cells, mast cells and natural killer cells can also be induced to express OX40L [Croft Annu Rev Immuno 2010]. OX40L interacts ‘monogamously’ with OX40, which is expressed on activated T-cells [Brunner J Allergy Clin Immuno 2017], CD4 and CD8 T-cells), inducing differentiation towards Th2, Th1, Th17 and Th22. The OX40/OX40L axis has also been shown to enhance the proliferation and activation of memory T cells and abrogate forkhead box P3 (Foxp3) positive regulatory T cells (Treg) function [Kitamura Int J Cancer 2009]. OX40-OX40L interaction is also necessary for the differentiation of activated B-cells into highly Ig-producing cells.

The interaction between OX40 and OX40L occurs during the T-cell-DC interaction, between hours and days after antigen recognition. After disengaging from DCs, the OX40-expressing T-cell may then interact with other OX40L-expressing cells, which in turn provide essential signals for the generation of memory T-cells with a drive to Th2 polarisation and the prolongation of the inflammatory responses. OX40 signals render T-cells resistant to Treg cell-mediated suppression and furthermore, OX40 signalling in Treg cells directly inhibits their suppressive function.

In AD, OX40L has been observed to be upregulated on DCs by several different factors including exogenous allergens, thymic stromal lymphopoietin (TSLP) and other cytokines from Langerhans cells and keratinocytes. It is these activated DCs that appear to require OX40/OX40L interaction to drive the observed Th2 activation [Ilves J Eur Acad Dermatol

Venereol 2013]. OX40 blockade has been shown to reduce the Th2 response in AD, and suppression of Th1 and Th17/Th22 inflammatory biomarkers has also been observed supporting the notion that the OX40/OX40L pathway has a central role in both acute and chronic phases of AD [Guttman-Yassky J Invest Dermatol 2018].

KY1005 has been administered to healthy volunteers and to patients with moderate-to-severe AD. The findings from both studies are summarised below in Section 1.4.1.2 and more detailed information can be found in the KY1005 Investigator's Brochure (IB).

Further to the data generated with KY1005an anti-OX40 IgG1 mAb, GBR 830/ISB830, has been tested in patients with moderate-to-severe AD in a Phase 2a study (NCT02683928) [Guttman-Yassky J Invest Dermatol 2018; Gutman-Yassky J Allergy Clin Immunol 2019]. Data from this study also support inhibition of the OX40/OX40L pathway as a target for the treatment of AD. Clinical improvement elicited by GBR 830 was associated with statistically significant reductions from Baseline ($p < 0.01$) in AD biomarkers, including Th2 chemokines (chemokine [C-C motif] ligand [CCL] 17 and 11, TSLP receptor), Th1/interferon (IFN) markers (IFN-γ, chemokine [C-X-C motif] ligand [CXCL] 10) and Th17/Th22-associated products (IL-23p19, S100A9/S100A12), indicating an effect on both the acute and chronic stages of AD.

These data support the hypothesis that blocking the OX40/OX40L pathway may not only deliver symptomatic relief but also have potential to be disease modifying. There was no immediate evidence of treatment limiting adverse events (AEs), although it should be noted that only small numbers of patients were treated.

1.4.1.1 Non-clinical Data

In Vitro Characterisation

KY1005 has high affinity for human OX40L and blocks its interaction with OX40 in biochemical assays in vitro. OX40L evoked cytokine release was inhibited in a concentration dependent manner by KY1005 in primary human T-cell preparations and in an allogeneic mixed lymphocyte reaction stimulated by native human OX40L expressed on primary DCs. Demonstration of poor or no binding to human Fcγ receptors indicates that KY1005 is unlikely to cause Fcγ receptor-mediated OX40L-superclustering and consequent activation of target downstream pathway(s).

In Vivo Characterisation

Treatment of cynomolgus monkeys with KY1005 resulted in inhibition of the T-dependent antibody response (TDAR). KY1005 reduced the IgG antibody response to primary and secondary keyhole limpet haemocyanin (KLH) challenge to a similar extent at all dose levels tested (5 to 100 mg/kg).

Pharmacokinetics and Non-clinical Safety

[redacted]

[redacted]

1.4.1.2 Clinical Data

KY1005 has been administered to healthy volunteers (Studies KY1005-CT01 and KY1005-CT04) and to patients with moderate-to-severe AD (Study KY1005-CT02). These studies are summarised below; further information can be found in the KY1005 IB.

Study KY1005-CT01

Study KY1005-CT01 was the First-in-Human (FIH) study of KY1005 that explored the safety and tolerability of single and repeat doses of KY1005 in healthy volunteers.

This study was conducted at a single investigative site, in line with a typical FIH dose escalation design. The study was composed of 8 ascending dose cohorts. All cohorts comprised 8 healthy volunteers allocated at random to either active (6 subjects) or matching Placebo (2 subjects).

[redacted]

Study KY1005-CT02

The recently completed Phase 2a (KY1005-CT02), randomised, double-blind, placebo controlled, parallel group, multicentre study was designed to explore the efficacy and safety of monotherapy KY1005 in adult patients with moderate-to-severe AD who have a documented history, within 6 months prior to Baseline, of either inadequate response to topical treatments or inadvisability of topical treatments.

During the screening period, treatments for AD including topical corticosteroids were washed out for at least 14 days prior to Baseline (except bland moisturisers). Patients were randomised in a 1:1:1 ratio to receive either an IV lower dose (200 mg loading/100 mg maintenance) or higher dose (500 mg loading/250 mg maintenance) of KY1005, or matching Placebo. Patients received KY1005 or Placebo every 4 weeks (Q4W) from Baseline to Day 85 (Week 12) when the last dose was received.

The primary analysis occurred once all patients had completed Day 113 (Week 16) (or earlier/withdrawal). All patients were expected to be followed to Day 253 (Week 36) for

safety. The co-primary endpoints were percentage change in the EASI score from Baseline to Day 113 (Week 16) and the incidence of treatment-emergent adverse events (TEAEs).

To explore the durability of effect for up to Day 253 (Week 36) from Baseline, patients who responded (IGA 0/1) at the Day 113 (Week 16) assessment were invited to continue with assessments up to the time that they relapse or commence drugs that have a significant impact on AD.

All patients were followed from Day 113 (Week 16) to Day 253 (Week 36) as part of safety follow-up.

Efficacy Outcomes

Meaningful efficacy differences in the key endpoints (EASI and SCORAD) between those receiving KY1005 and Placebo from Day 15 (Week 2) and maintained to the primary endpoint (Day 113 [Week 16]). Supporting efficacy, an improvement in pruritis was also observed. No meaningful difference between the KY1005 treatment arms was noted (Table 1-1).

Table 1-1: Efficacy Data for the Primary and Key Secondary Endpoints from Baseline to Day 113(Week 16)

		KY1005 LD (n=27)	**KY1005 HD (n=27)**	**Placebo (n=24)**
Primary Endpoint:				
% change in EASI MMRM (FAS)	Least Square Means [95% CI]	-80.12 [-95.55, -64.68]	-69.97 [-85.04, -54.90]	-49.37 [-66.02, -32.72]
	P =	0.009	0.072	
Key Secondary Endpoints:				
% change in SCORAD MMRM (FAS)	Least Square Means [95% CI]	-60.30 [-72.57, -48.04]	-58.96 [-71.04, -46.87]	-36.79 [-49.94, -23.65]
	P =	0.011	0.016	
IGA 0/1 with ≥2 point improvement CMH (FAS)	N (%) [95% CI]	12 (44.4%) [25.70, 63.19]	10 (37.0%) [18.82, 55.25]	2 (8.3%) [0.00, 19.39]
	P =	<0.001	<0.001	
EASI 75 Descriptive statistics (FAS)	N (%) [95% CI]	16 (59.3%) [40.73, 77.79]	14 (51.9%) [33.01, 70.70]	6 (25.0%) [7.68, 42.32]
EASI 90 Descriptive statistics (FAS)	N (%) [95% CI]	9 (33.3%) [15.55, 51.11]	8 (29.6%) [12.41, 46.85]	3 (12.5%) [0.00, 25.73]
		KY1005 LD (n=19)	**KY1005 HD (n=24)**	**Placebo (n=21)**
NRS improvement of ≥4-point improvement based on patients with a baseline NRS of at least 4 Descriptive statistics	N (%) [95% CI]	11 (57.9%) [35.69, 80.10]	15 (62.5%) [43.13, 81.87]	8 (38.1%) [17.33, 58.87]

CI=confidence interval; EASI=Eczema Area and Severity Index: FAS=full analysis set: MMRM=Mixed-effect model with repeated measures; NRS=numerical rating scale; SCORAD=SCORing of Atopic Dermatitis.

In those patients achieving a IGA of 0/1 at Day 113 (Week 16), additional efficacy assessments through the safety follow-up demonstrated a maintenance of response in the majority of patients of up to 5.5 months (End of Study [EOS]) following the last dose of KY1005 (see Table 1-2).

Table 1-2 Efficacy Data for in Those Subjects Defined as a Responder at Day 113 (Week 16) (IGA 0/1) from Baseline to Day 169 (Week 24) and Day 253(Week 36)

		KY1005 LD (n=12)	KY1005 HD (n=10)	Placebo (n=2)
Primary Endpoint:				
% change in EASI Least Square Means [95% CI] Descriptive statistics (FAS)	Day 169 (Week 24)	-94.34 [-98.81, -89.87]	-95.71 [-101.78, -89.64]	-85.15 [-210.31, 40.01]
	Day 253 (Week 36)	-83.85 [-97.44, -70.27]	-94.10 [-101.77, -86.43]	-87.65 [-134.03, -41.27]
Key Secondary Endpoints:				
% change in SCORAD Least Square Means [95% CI] Descriptive statistics (FAS)	Day 169 (Week 24)	-79.43 [-90.10, -68.75]	-87.72 [-96.31, -79.13]	-58.05 [-298.83, 182.73]
	Day 253 (Week 36)	-68.29 [-88.58, -48.00]	-83.00 [-96.68, -69.32]	-57.75 [-166.39, 50.89]
IGA 0/1 with ≥2-point improvement N (%) [95% CI] Descriptive statistics (FAS)	Day 169 (Week 24)	10 (83.3%) [62.25, 100.00]	9 (90.0%) [71.41, 100.00]	1 (50.0%) [0.00, 100.00]
	Day 253 (Week 36)	8 (66.7%) [39.99, 93.34]	7 (70.0%) [41.60, 98.40]	1 (50.0%) [0.00, 100.00]
EASI 75 N (%) [95% CI] Descriptive statistics (FAS)	Day 169 (Week 24)	12 (100.0%) [100.00, 100.00]	9 (90.0%) [71.41, 100.00]	2 (100.0%) [100.00, 100.00]
	Day 253 (Week 36)	8 (66.7%) [39.99, 93.34]	7 (70.0%) [41.6, 98.4]	2 (100%) [100.00, 100.00]
EASI 90 N (%) [95% CI] Descriptive statistics (FAS)	Day 169 (Week 24)	11 (91.7%) [76.03, 100.00]	9 (90.0%) [71.41, 100.00]	1 (50.0%) [0.00, 100.00]
	Day 253 (Week 36)	6 (50.0%) [21.71, 78.29]	7 (70.0%) [41.60, 98.40]	1 (50.0%) [0.00, 100.00]
		KY1005 LD (n=11)	**KY1005 HD (n=10)**	**Placebo (n=1)**
NRS improvement of ≥4-point improvement based on patients with a Baseline NRS of at least 4 N (%) [95% CI] Descriptive statistics	Day 169 (Week 24)	8 (72.7%) [46.41, 99.05]	6 (60.0%) [29.64, 90.36]	0 (0.0%) [0.00, 0.00]
	Day 253 (Week 36)	9 (81.8%) [59.03, 100.00]	5 (50.0%) [19.01, 80.99]	0 (0.0%) [0.00, 0.00]

Source: Tables 14.2.2-1 E, 14.2.2-3 E, 14.2.2-4 E, 14.2.2-6 E, 14.2.2-7 E, 14.2.2-23 E
LD: low dose KY1005 arm (200 mg/100 mg)
HD: high dose KY1005 arm (500 mg/250 mg)
CI=confidence interval; EASI=Eczema Area and Severity Index: FAS=full analysis set: NRS=numerical rating scale.

Safety Outcomes

[redacted]

Study KY1005-CT04

KY1005-CT04 (NCT04449939) was a Phase 1, open label study to assessing the PK of KY1005 after single dose administration by the SC and IV routes in male healthy volunteers. The purpose of this study was to assess the PK of KY1005 after SC administration and to compare the safety and tolerability of KY1005 when given via SC injection and IV infusion, to support SC administration. Intravenous KY1005 was included as a reference treatment. Twenty-four healthy volunteers were enrolled as 3 treatment groups of 8 healthy male subjects.

The primary endpoint was the characterisation of the PK of SC and IV administered KY1005 after a single dose. Key secondary endpoints included safety and tolerability.

[redacted]

1.5 Rationale

1.5.1 Study Rationale and Purpose

The aim of this current study is to further characterise the efficacy (including dose/exposure-response) and safety of KY1005 across a range of doses/exposures for a maximum duration of 52 weeks in adult patients with moderate-to-severe AD who have had an inadequate response to topical therapies or where topical therapies are not advised. This 24-week Placebo-controlled dose ranging period will be followed, in those patients who achieve an ≥ EASI 75 and/or IGA 0/1, with a randomised withdrawal period to Day 365

(Week 52) to characterise the durability of response ahead of the anticipated Phase III programme.

KY1005 is a subclass G4 mAb that targets human OX40L to block interaction with its receptor OX40 and is predicted to suppress the inflammatory responses associated with AD. The ability of KY1005 to improve the signs and symptoms of this disease has been reported in an initial Phase 2a study (Study KY1005-CT02) in this patient population. Based on observations from the completed healthy volunteer studies (KY1005-CT01 and KY1005-CT04), and the KY1005-CT02 study in AD, KY1005 has, to date, been shown to be well tolerated.

Whilst KY1005 has previously been evaluated as an IV formulation the current study will evaluate SC KY1005. A SC formulation would potentially provide more flexible options for patients, enabling treatment in a patient's home as well as in the clinic. In a toxicology study in cynomolgus monkeys using the same SC formulation intended for administration to humans, no KY1005-specific risks associated with any local toxicity at the injection sites were identified. In the healthy volunteer SC KY1005-CT04 safety and tolerability study no treatment limiting AEs were noted and the safety and tolerability profile was unremarkable. Based on these data, in combination with the available information for the IV formulation, the SC KY1005 is anticipated to be well tolerated.

1.5.2 Rationale for Dose Selection

A total of 4 dosing groups plus Placebo will be tested in this study. The chosen doses and dosing regimens will allow for thorough assessment of the dose and exposure response relationship. This type of approach has been adopted in previous Phase 2b studies in AD [Thaçi D et al, 2016, Guttman-Yassky E 2020]. Given the challenges of needle burden on compliance in AD the ability to provide less frequent dosing has been an influencing factor on the choice of doses and intervals proposed.

[redacted] The 250 mg SC Q4W with a 500 mg loading dose, 250 mg SC Q4W, 125 mg SC Q4W and 62.5 mg SC Q4W KY1005 doses will be administered to patients to assess the dose/exposure response across an appropriate exposure range. [redacted]

[redacted]

Initial treatment period: Dose and interval justification to Day 169 (Week 24)

The dose and dosing regimen that is expected to be able to maintain similar exposures to those observed in CT02 trial, as well as concentrations in tissues above the targeted range [redacted], during the 24-week double-blind period is a dose of 250 mg administered Q4W. A broad range of doses will be tested in this dose response study to cover the dose range which will capture the dose response and inform the benefit/risk assessment across these dose levels.

The dose and dosing regimen for the period from Baseline to Day 169 (Week 24) for dosing Group 1 is 250 mg administered Q4W, 28 days following a loading dose of 500 mg at Baseline ([redacted]). Using this approach, this dose and dose regimen is expected to achieve an earlier steady-state, and a C_{max}, from the first dosing, close to that observed in the CT02 trial.

The dose and dosing regimen for the period from Baseline to Day 169 (Week 24) for dosing Group 2 is 250 mg SC administered Q4W [redacted] with a second injection of [redacted] placebo dose at Baseline (Day 1) to protect the blind. Using this approach this dose and dosing regimen is expected to maintain concentrations in blood (C_{min}) [redacted]

The dose and dosing regimen for the period from Baseline to Day 169 (Week 24) for dosing Group 3 is 125 mg administered Q4W [redacted] with a second injection of [redacted] Placebo dose at Baseline (Day 1) to protect the blind. This is expected to provide exposures slightly lower than the ones observed in CT02 at the low dose. This dose and dosing regimen is expected to maintain concentrations in blood [redacted]

The dose and dosing regimen for the period from Baseline to Day 169 (Week 24) for the last KY1005 dosing Group 4 is 62.5 mg administered Q4W [redacted] with a second injection of [redacted] placebo dose at Baseline (Day 1) to protect the blind. The objective of this dose and dosing regimen is to characterize a dose response that was not evaluated during the

Phase 2a where only 2 dose levels were tested. The addition of this dose level will allow for expanded characterization of the dose response. [redacted]

The 24-week Placebo-control period has been selected as based on the Phase 2a study the maximum clinical response was not observed at the Day 113 (Week 16) primary endpoint after 12 weeks of treatment ie, a plateau in clinical response was not achieved. It is expected with further treatment improved benefits will be observed. The use of a 24-week Placebo controlled period has been employed in the AD study setting before [Silverberg et al. 2019]. The primary endpoint of percentage change in EASI will be at Day 113 (Week 16). This timepoint is typical for Phase 2b studies in AD. Topical rescue therapy will be permitted from Day 15 (Week 2) of the study for intolerable symptoms of AD (Section 5.3.4). Recipients of topical therapies will be handled as outlined in Section 5.3.

Safety considerations

The highest dose-regimen chosen for the Phase 2b study (a loading dose of 500 mg SC followed by Q4W administration of 250 mg SC) is the same as the highest dose administered via the IV route in the Ph 2a study (KY1005-CT02). [redacted] Even higher doses were administered to healthy volunteers in the FIH study (KY1005-CT01), where the top (loading) dose was 12 mg/kg, which in an 85 kg individual would equate to a single flat dose of 1,020 mg. In this study, one AE of note occurred at the top dose of systemic allergic reaction. However, this dose level was far higher than that being tested in patients in the Phase 2b study. No otherwise clinically significant AEs, SAEs or deaths occurred at any dose level in KY1005-CT01.

The total patient exposure (years) for KY1005-CT02 is 15.4 patient years for KY1005 low dose, and 16.5 patient years for KY1005 high dose. However, no safety or tolerability concerns have been identified across the clinical development programme to date, and the overall adverse event profile of KY1005 is unremarkable.

[redacted]

Post Week 24 period: Randomised withdrawal design to inform Phase III extended dosing interval

As part of this study, the intention is to build on the sustained clinical response observed in the Phase 2a study with an assessment of the durability of response during a 28-week withdrawal period in those patients who achieve ≥ EASI 75 or who attain IGA 0/1 at Day 169 (Week 24).

[redacted]

Loss of clinical response

Loss of clinical response is defined as the first instance of <EASI 50 during the second study period and where rescue therapy is no longer permitted as per Section 5.3.4.

If loss of clinical response occurs on or after the Day 197 (Week 28) visit, Investigators will be able to choose to either discontinue the patient from KY1005-CT05 (DRI17366) or to progress to the LTE study (LTS17367, LTE). [redacted]

1.5.3 Study Design Rationale

This Phase IIb study is a randomised, double-blind, placebo-controlled study of 365 days duration (plus screening and safety follow-up) that will be conducted to assess the efficacy and safety of monotherapy SC KY1005 in approximately 350 adult patients with moderate-to-severe AD. Sites will be selected globally to participate in this study. A parallel group design will be employed due to the testing of up to 4 different dose regimens versus Placebo. This is considered appropriate for a study of this type (EMEA/CHMP/SWP/28367/07 [Rev. 1] and ICH E4).

The study design, including the washout period and the use of Placebo, is in keeping with other trials in moderate-to-severe AD. The study is designed to assess monotherapy KY1005 in patients with limited treatment options. All patients therefore must have either had an inadequate response to topical therapies or be individuals for whom such topical treatment is inadvisable. It is recognised, based on prior studies in AD with a similar design [Thaçi The Lancet 2016], that the dropout rate can be relatively high (~20%) and this has been factored into the anticipated numbers of patients that will be recruited.

Although the study represents the initial clinical evaluation of SC KY1005, the enrolment of up to 350 patients in a Phase IIb study is considered to be acceptable due to the available clinical data for IV KY1005 in which no KY1005-specific risks have been identified. Furthermore, the non-clinical and clinical data for SC KY1005 have identified no KY1005-specific risks or local toxicity at the injection sites at clinically relevant doses.

The primary objective of this study will be to compare the dose response of 4 different dose regimens of KY1005 in patients with AD versus Placebo to Day 113 (Week 16). As part of the study design, patients initially enrolled at Baseline into the Placebo, 62.5 mg,125 mg and 250 mg KY1005 treatment arms who do **not** achieve ≥ EASI 75 or IGA 0/1 at Day 169 (Week 24) will have the opportunity to be to receive KY1005 from Day 169 (Week 24) by enrolling in an LTE study. This will enable all enrolled patients to have an opportunity to receive treatment at doses expected to elicit a meaningful clinical response (based on what was observed in the Phase 2a KY1005-CT02 study).

Patients who achieve ≥ EASI 75 or who attain IGA 0/1 at Day 169 (Week 24) be randomised 3:1 to either enter a maintenance withdrawal phase or continue their pre-Week 24 dose/interval. The purpose being to characterise the durability of response in conjunction with PK following treatment discontinuation in those withdrawn from therapy and to assess the clinical response in those continuing to receive Q4W treatment at their pre-Week 24 dose. Those patients who are randomised to the second study period who subsequently lose clinical response will be offered the opportunity to receive retreatment with KY1005 in the LTE study. Results from this randomised withdrawal maintenance phase will inform the subsequent later stage development of KY1005 in the treatment of AD.

The maximum length of the study is 365 days plus safety follow-up. Those patients who achieve ≥ EASI 75 or who attain IGA 0/1 at Day 169 (Week 24) and complete the second study period without loss of clinical response at Day 365 (Week 52) will have an additional 112-day safety follow-up after Day 365 (Week 52) (total of 140 days safety follow-up from receipt of last dose of IMP on Day 337 [Week 48]). If during safety follow-up or after the end of study this cohort of patients experience worsening of their AD, and in the investigator's opinion re-treatment with KY1005 is considered appropriate, they may be considered for enrolment in the LTE (subject to meeting inclusion/exclusion criteria).

1.5.4 Study Setting

The Sponsor plans to conduct the study at selected global sites.

All study procedures will be conducted by trained Investigators and medical staff with appropriate levels of training, including Good Clinical Practice (GCP) and experience of clinical trials. Investigators must understand specific characteristics of the IMP and of its target and mode of action. This information can be found within this protocol and within the IB.

Unless Appendix 14 (Section 17.14) is activated, IMP administration must take place in appropriate clinical facilities, under controlled conditions with the possibility of close

supervision of study patients during and after dosing, as required by the protocol. Units must have immediate access to equipment and appropriately qualified staff for resuscitating and stabilising individuals in an acute emergency (such as cardiac emergencies, anaphylaxis, cytokine release syndrome, convulsions, hypotension), and ready availability of intensive care unit and other hospital facilities.

1.6 Summary of Known and Potential Risks and Benefits

Clinical and non-clinical studies confirm that KY1005 exerts the intended pharmacological effect in relevant immune systems, and can provide meaningful clinical improvement in the signs and symptoms of AD. The benefits of KY1005 in moderate-to-severe AD have been demonstrated in the KY1005-CT02 Phase 2a study where both KY1005 treatment groups provided clinically meaningful improvements in the signs and symptoms of disease.

KY1005-specific risks, including none associated with SC administration, have not been identified to date from the non-clinical or clinical programme. Potential risks include malignancy and impaired response to infection (discussed [redacted] tested to date. One patient in the prior healthy volunteer study (KY1005-CT01) experienced a reaction of the mouth and throat during systemic administration on first exposure to KY1005. No similar events were noted in the KY1005-CT02 Phase 2a study in AD patients nor the KY1005-CT04 SC healthy volunteer study. Systemic or localised allergic reactions that require immediate treatment are therefore defined as an adverse event of special interest (AESI; see Section 8.1.3) so that specific information can be collected prospectively.

[redacted]

Overall, to date blockade of OX40/OX40L in humans is precedented without acute severe adverse consequences. These findings suggest that OX40L-mediated clearance is not relevant at pharmacological doses and that such binding, in disease states in which OX40L is

upregulated, does not lead to common adverse reactions. Mitigation of the theoretical risks is possible through selection of appropriate study populations and monitoring in clinical trials. The overall benefit risk is therefore in favour of continued development of KY1005 in immune mediated disease such as AD.

Further details can be found in the IB.

1.6.1 Benefit/Risk of KY1005 Regarding Potential Infections with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2)

There is no change in the overall benefit/risk of treating patients with KY1005 regarding the Coronavirus Disease 2019 (COVID-19) pandemic. In case of the implementation of restrictions due to COVID-19, the advice provided in Section 17.14 (Appendix 14) should be followed.

1.7 Route of Administration, Dosage, Dosage Regimen and Treatment Period(s)

KY1005 will be administered by SC injection. Each dose will be administered as described in the Pharmacy manual (Section 5.2). Following completion of the SC injection, patients will be monitored for at least 60 minutes.

Patients will receive treatment with KY1005 or matching Placebo every 28 days throughout the study. Those patients randomised to withdrawal post-Week 24 will be administered Placebo every Q4W when KY1005 is not received. This is to maintain the blinding of the study.

The dosing schedule is presented in Table 1-3.

Table 1-3 DosingSchedule

	Baseline**	**Day 29 (Week 4) to Day 169 (Week 24)****	**Randomised Withdrawal Period From Day 169 (Week 24) to Day 365 (Week 52)**
Treatment regime	**Dose IMP (SC)**	**Dose IMP (SC)**	**Dose IMP (SC)**
Group 1	500 mg [redacted]	[redacted] 250mg Q4W	Withdrawal: Placebo [redacted] 0 mg Q4W
			Pre-Week 24: [redacted] 250 mg Q4W
Group 2	[redacted] and [redacted] PBO (0 mg)*	[redacted] 250 mg Q4W	Withdrawal: Placebo [redacted] 0 mg Q4W
			Pre-Week 24: [redacted] 250 mg Q4W
Group 3	[redacted] 125 mg and [redacted] PBO (0 mg)*	[redacted] 125 mg Q4W	Withdrawal: Placebo [redacted] 0 mg Q4W
			Pre-Week 24: [redacted] 125 mg Q4W
Group 4	[redacted] 62.5 mg and [redacted] PBO (0 mg)*	[redacted] 62.5 mg Q4W	Withdrawal: Placebo [redacted] 0 mg Q4W
			Pre-Week 24: [redacted] 62.5 mg Q4W
Placebo	[redacted] PBO (0 mg)*	[redacted] 0 mg Q4W	Withdrawal: Placebo [redacted] 0 mg Q4W
			Pre-Week 24: [redacted] 0 mg Q4W

IMP=investigational medicinal product; PBO=placebo; Q4W= every 4 weeks; SC=subcutaneous.
* Placebo will be administered as a second [redacted] SC injection at Baseline to maintain the blind.
[redacted]

2 OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective and Endpoint

Objective	Endpoint
To characterise the efficacy (including dose/exposure-response) across a range of KY1005 exposures compared to Placebo on the signs of AD using the Eczema Area and Severity Index (EASI) in those patients who have who have a documented history, within 6 months prior to Baseline, of either inadequate response to topical treatments or inadvisability of topical treatments.	• Percentage change in EASI from Baseline to Day 113 (Week 16).

2.1.2 Secondary Objectives and Endpoints

Objectives	Endpoints
Safety and tolerability of KY1005.	• Incidence of treatment-emergent adverse events.
The pharmacokinetic profile across a range of KY1005 doses/exposures.	• Serum KY1005 concentration assessed throughout the study.
The response across a range of KY1005 exposures on additional physician assessment-s of atopic dermatitis (AD) activity/severity (EASI 50, EASI 75, EASI 90, EASI 100, Investigator Global Assessment [IGA], SCORing of Atopic Dermatitis [SCORAD] Index and affected body surface area [BSA]).	Key secondary endpoints: • Percentage change from Baseline in EASI at Day 169 (Week 24). • Percentage of patients with at least a 75% reduction from Baseline in EASI (EASI 75) at Days 113 (Week 16) and 169 (Week 24). • Percentage of patients with a response of IGA 0 or 1 and a reduction from Baseline of ≥2 points at Days 113 (Week 16) and 169 (Week 24). • Proportion of patients with improvement (reduction) of weekly average of pruritus NRS ≥4 with a Baseline pruritis NRS of ≥4 from Baseline to Days 113 (Week 16) and 169 (Week 24). Other secondary endpoints: • Absolute change from Baseline in EASI at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24). • Percentage change from Baseline in EASI at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12) and 141 (Week 20). • Percentage of patients with at least a 50% reduction from Baseline in EASI (EASI 50) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24). • Percentage of patients with at least a 75% reduction from Baseline in EASI (EASI 75) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), and 141 (Week 20).

Objectives	Endpoints
	• Percentage of patients with at least a 90% reduction from Baseline in EASI (EASI 90) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24). • Percentage of patients with at least a 100% reduction from Baseline in EASI (EASI 100) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24). • Change in IGA from Baseline to Day 169 (Week 24) and over time. • Percentage of patients with a response of IGA 0 or 1 and a reduction from Baseline of ≥2 points at Days 15 (Week 4), 29 (Week 4), 57 (Week 8), 85 (Week 12), and 141 (Week 20). • Absolute and Percentage in SCORAD Index from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in affected BSA from Baseline to Day 169 (Week 24) and over time.
The response across a range of KY1005 dose/exposures on patient reported AD activity/severity (Atopic dermatitis Control Tool [ADCT], Patient Oriented [PO] Eczema Measure [POEM], Dermatology Quality of Life Index [DLQI], Hospital Anxiety and Depression Scale [HADS], and Numerical Rating Scale [NRS] for pruritus).	• Absolute and Percentage change in POEM from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in DLQI from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in ADCT from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in HADS from Baseline to Day 169 (Week 24) and over time. • Absolute and Percentage change in weekly average of pruritus NRS from Baseline to Day 169 (Week 24) and over time. • Proportion of patients with improvement (reduction) of weekly average of pruritus NRS ≥3 with a Baseline pruritis NRS of ≥3 from Baseline to Days 113 (Week 16) and 169 (Week 24).
The pharmacodynamic response to KY1005 including but not limited to: The immunogenicity of KY1005, including the anti-KY1005 antibody response.	• The immunogenicity of KY1005, including the anti-KY1005 antibody response.
The explore the continued clinical response in those patients who achieve ≥ EASI 75 or who attain IGA 0/1 at Day 169 (Week 24)	• Continued assessment of the efficacy endpoints from Day 169 (Week 24) and over time. • Time to loss of EASI 75 in participants randomised to withdrawal post-Week 24. • Time to loss of IGA 0/1 in participants randomised to withdrawal post-Week 24. • Time to loss of EASI 50 in participants randomised to withdrawal post-Week 24. • Continued assessment of patient reported AD activity/severity endpoints from Day 169 (Week 24) and over time.

2.1.3 Exploratory Objectives and Endpoints

Objectives	Endpoints
[redacted]	

3 STUDY DESIGN

3.1 Overall Study Design and Plan

This is a Phase IIb, randomised, double-blind, placebo-controlled, parallel group, multicentre dose ranging study to characterise the efficacy and safety of SC administered KY1005 in adult patients with moderate-to-severe AD who have a documented history, within 6 months prior to Baseline, of an inadequate response to, or inadvisability of, topical treatments.

[redacted]

Up to 350 patients (approximately 70 patients per treatment arm) will be enrolled. Patients who continue to meet the eligibility criteria at Baseline will be randomised to 1 of 5 treatment groups (4 different KY1005 regimens or Placebo) in an equal (1:1:1:1:1) ratio.

From Baseline up to Day 169 (Week 24) IMP will be administered at the following dose and intervals:

- 500 mg loading at baseline ([redacted]) followed 4 weeks later with 250 mg Q4W as [redacted];

Or

- 250 mg [redacted] at Baseline followed 4 weeks later with 250 mg Q4W [redacted];

Or

- 125 mg ([redacted] at Baseline followed 4 weeks later with 125 mg Q4W as [redacted];

Or

- 62.5 mg ([redacted] at Baseline followed 4 weeks later with 62.5 mg Q4W as [redacted];

Or

- Placebo given as [redacted] at Baseline followed 4 weeks later with [redacted] Placebo (0 mg).

At Baseline, those patients not receiving a KY1005 loading dose will receive both KY1005 and Placebo to maintain the study blind.

The Day 113 (Week 16) primary analysis will occur once all patients have reached the Day 169 (Week 24) visit (or earlier in the event of termination).

To enable Placebo patients and those patients randomised to the KY1005 62.5 mg Q4W, 125 mg and 250mg Q4W treatment arms to receive KY1005 at a dose expected to elicit a meaningful clinical response (based on prior clinical evidence), patients who do **not** achieve ≥ EASI 75 or IGA 0/1 at Day 169 (Week 24) will be invited to enrol in the LTE study where they will receive KY1005.

In those patients who achieve ≥ EASI 75 or who attain IGA 0/1 at Day 169 (Week 24), a randomisation will occur pre-dose at Day 169 (Week 24) and patients will enter the second study period. This will occur irrespective of whichever dose group the patient was randomised to at Baseline including Placebo. Patients will be randomised in a 3:1 manner to be withdrawn from therapy or to continue their pre-Week 24 dose/interval. To maintain the blind, those patients randomised to the Withdrawal arm will receive Placebo Q4W. Those patients who are re-randomised at Day 169 (Week 24) who lose their clinical response will be offered the opportunity to be retreated with KY1005 in the LTE study. Loss of clinical response is defined as the first instance of <EASI 50 during the second study period and where rescue therapy is no longer permitted as per Section 5.3.4. If loss of clinical response from Day 197 (Week 28) occurs, Investigators will be able to choose to discontinue the patient from KY1005-CT05 (DRI17366) or to progress to the LTE study. [redacted] Where patients prematurely withdraw from the KY1005-CT05 (DRI17366) study and enter the LTE study, an early termination visit must be completed as per the Schedule of Assessments before enrolment in the LTE study.

At Day 365 (Week 52), patients who have completed the post-Week 24 period and have not experienced loss of clinical response will have an additional 112 days' safety follow-up up to Day 477 (Week 68) and then be discharged from the study. The last dose will be given no later than Day 337 (Week 48) and as such safety follow-up will be 140 days following last dose of IMP. If during safety follow-up or after the end of study this cohort of patient's experience worsening of their AD, and in the investigator's opinion re-treatment with KY1005 is considered appropriate, they may be considered for enrolment in the LTE (subject to meeting inclusion/exclusion criteria).

[redacted]

[redacted]

The overall study design is presented in Figure 3-1.

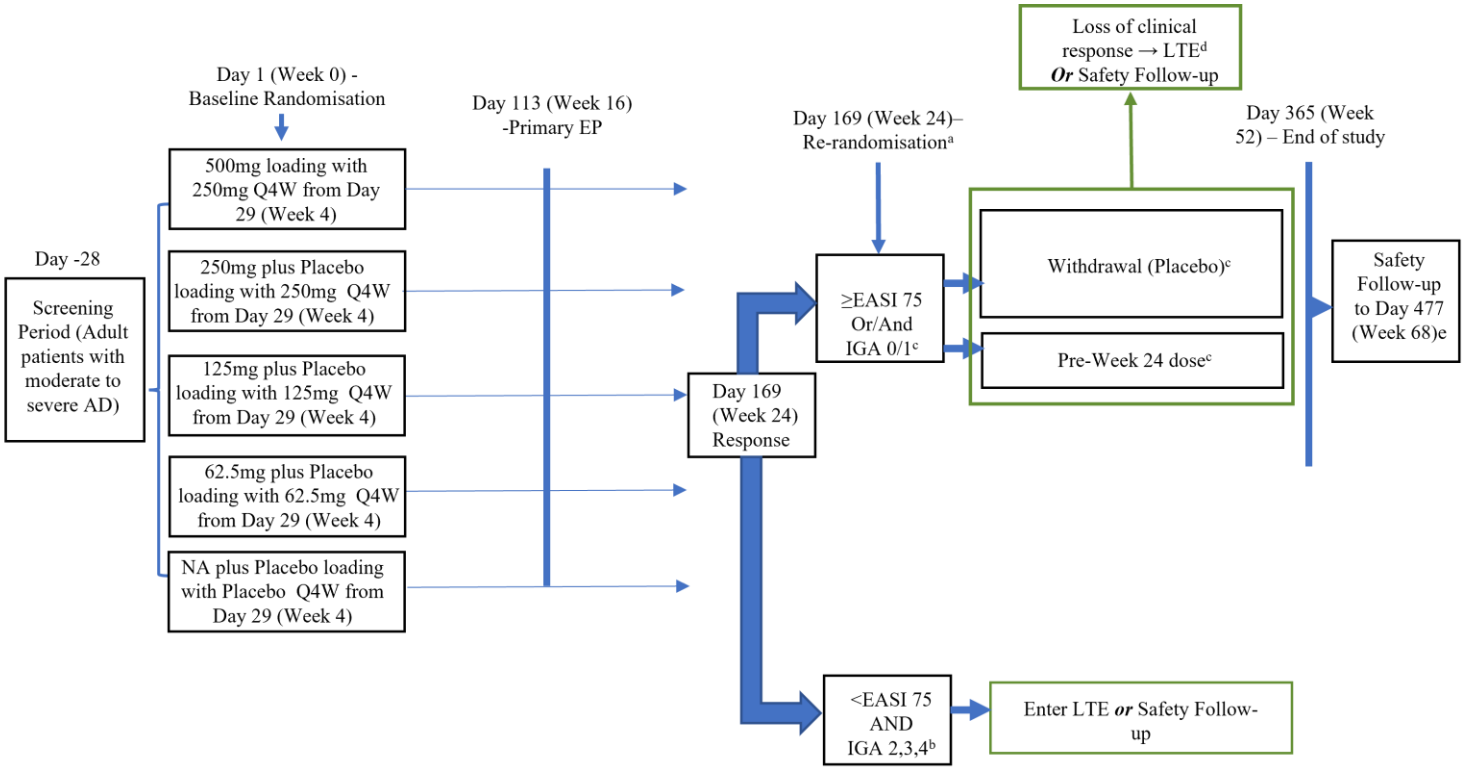
3.2 Study Duration

The duration of the study will be up to 28 days for screening and then up to approximately Day 477 (Week 68) (to Day 365 [Week 52] plus 112 days safety follow-up, [redacted] for all patients unless enrolled into the LTE study at Day 169 (Week 24) or due to loss of clinical response at or after Day 197 (Week 28). The last dose will be given no later than Day 337 (Week 48).

3.2.1 Study flow

The overall study design is presented in Figure 3-1.

Figure 3-1: Overall StudyDesign



AD=atopic dermatitis; IMP=investigational medicinal product; EP=endpoint; EASI=eczema area and severity index; IGA= investigator global assessment; LTE=long-term extension; Q4W=every 4 weeks; NA=not applicable.

a On Day 169 (Week 24), patients are re-randomised prior to IMP administration on the basis of their Day 169 (Week 24) response.

b Patients initially enrolled at Baseline into the Placebo, 62.5 mg, 125 mg and 250 mg KY1005 treatment arms who do not achieve ≥ EASI 75 or IGA0/1 at Day 169 (Week 24) will have the opportunity to receive KY1005 Q4W from Day 169 (Week 24) by enrolling in a long-term extension (LTE) study (LTS17367 LTE). Participation in the LTE is subject to meeting the inclusion/exclusion criteria. Any patient who in the Investigator's opinion should not be enrolled into the LTE, or where the patient declines further participation will have an additional 112 days safety follow-up from Day 141 (Week 20) and then be discharged from the study.

c Patients who achieve ≥ EASI 75 or who attain IGA0/1 at Day 169 (Week 24), irrespective of their Baseline group will be randomised 3:1 to either enter a maintenance withdrawal phase or continue on their pre-Week 24 dose/interval.

d If loss of response from Day 197 (Week 28) occurs between visits and retreatment with KY1005 is considered appropriate, patients will be permitted to move to the LTE (subject to meeting the inclusion/exclusion criteria for the LTE). Loss of clinical response is defined as < EASI 50 during the second study period and where rescue therapy is no longer permitted as per Section 5.3.4. Patients who in the Investigator's opinion should not be enrolled into the LTE, or where the patient declines further participation, will enter safety follow-up.

e Patients who are responders at Day 169 (Week 24) and complete the second study period to Day 365 (Week 52) without loss of clinical response will enter safety follow-up. If during safety follow-up or after end of study the patients experience worsening of their AD, and in the investigator's opinion re-treatment with KY1005 is considered appropriate, they may be considered for enrolment in the LTE (subject to meeting inclusion/exclusion criteria).

3.3 Timing of Interim Analysis and Design Adaptations

An interim analysis will be planned when approximately [redacted] participants in each arm complete the Day 113 (Week 16) assessments. The purpose of the interim analysis would be to obtain early information for planning the phase 3 program. No study conduct will be modified based on interim analysis results.

The interim analysis will evaluate the percentage change in EASI from baseline to Day 113 (Week 16) and proportions of participants with EASI 75 at Day 113 (Week 16), as well as the other available data as needed. Details will be documented in the statistical analysis plan (SAP).

3.4 Definition of End of Study

The EOS is defined as the last patient undergoing the last visit of the study. This will either be:

- Day 169 (Week 24) (or earlier termination) for those patients who do **not** achieve ≥ EASI 75 or IGA 0/1 at Day 169 (Week 24), and are subsequently enrolled in the LTE;

Or

- Day 281 (Week 40) (or earlier termination) for those patients who do **not** achieve ≥ EASI 75 or IGA 0/1 at Day 169 (Week 24), and are **not** enrolled in the LTE and have additional safety follow-up to a total of 140 days after the last dose of IMP;

Or

- Day 365 (Week 52) (or earlier termination) for those patients who achieve ≥ EASI 75 or who attain IGA 0/1 at Day 169 (Week 24) and continue on either their pre-Week 24 dose/interval or enter the withdrawal arm, experience loss of clinical response at or after Day 197 (Week 28) and are enrolled in the LTE. Those patients **not** enrolled in the LTE will have additional safety follow-up to a total of 140 days after the last dose of IMP;

Or

- Day 477 (Week 68) (or earlier termination) for those patients who reach Day 365 (Week 52), are still considered to be responding to study treatment, and are **not** enrolled in the LTE and have additional safety follow-up to a total of 140 days after the last dose of IMP.

3.5 Early Study Termination

The study can be terminated at any time for any reason by the Sponsor (including approval or the favourable opinion is revoked, in the event of a negative change in the benefit/risk ratio when the necessary adjustment to the maximum sum insured is not possible; failure to enrol; futility; safety decision etc). If the trial is suspended or terminated early, the Investigator will promptly inform the trial patients and should assure appropriate therapy and follow-up.

No further IMP will be given to a patient if any study permanent discontinuation rules are met (see Section 9.1), including recommendation of the Independent Data Monitoring Committee (IDMC; Section 3.8). If a patient withdraws from the study treatment early but consent is retained, study assessments may be continued until a) Day 169 (Week 24) for patients who withdraw from study treatment during the first study period and therefore are **not** eligible for

LTE, or b) until Day 365 (Week 52) or the end of the safety follow-up period in patients who withdraw from study treatment after Day 169 (Week 24).

Unless patients continue in the LTE at Day 169 (Week 24) or due to loss of clinical response at or after Day 197 (Week 28), a safety follow-up for 140 days after the last dose of IMP will be required.

In addition, the Investigator may withhold further IMP from a patient if they report moderate-or-severe (regardless of seriousness) adverse reactions which are attributed to the IMP. There will be no obligation to unblind treatment allocation in making this decision.

The Sponsor may discontinue the entire study at any time based on information received during the running of the study that demonstrates an unexpected risk or absence of benefit to patients. This may for example follow the request of the IDMC or where additional information emerges either during the study or from other sources (eg, literature or Health Authorities).

If the study is discontinued, where patients withdraw early or where IMP has been discontinued by the Investigator, patients will be required to be followed-up for a minimum of 140 days for safety evaluation.

Further details of IMP discontinuation are provided in Section 9.1.

3.6 Randomisation

The Investigator must follow the study randomisation procedures when assigning patients to treatment within the study.

The patient randomisation list will be generated by PPD using Statistical Analysis System (SAS®).

All patients who have completed all Screening assessments and are confirmed as eligible by the Investigator will be randomised to treatment at Baseline. In cases where screen failure occurs due to a laboratory abnormality and is due to reasons expected to change at re-screening and based upon the Investigator's clinical judgment, the patient may be re-screened one time for this study following notification to the Sponsor. Randomisation may be performed up to 24 hours prior to the first administration of KY1005 if all inclusion/exclusion criteria have been satisfied. Each of the 5 treatment regimens (see Table 5-1) will comprise approximately 70 patients (based on 30% drop out rate to Day 169 [Week 24], it is assumed that 49 patients will complete the study) who will be allocated to treatment with KY1005 or Placebo in an equal (1:1:1:1:1) ratio.

Patients will be centrally randomised. Once confirmed as eligible for the study, patients will be allocated a randomisation number using an IRT system, corresponding to the next available randomised treatment, in a consecutive order starting with the lowest number.

The randomisation will be stratified by disease severity (moderate/severe) and region.

Further randomisation will occur at Day 169 (Week 24) in those patients who achieve ≥ EASI 75 or who attain IGA 0/1. Patients will be randomised in a 3:1 ratio to either enter a withdrawal cohort (receiving Placebo Q4W) or to remain on their pre-Week 24 dose/interval. This Day 169 (Week 24) randomisation will be stratified by IGA response (IGA 0/1 or IGA 2, 3, 4).

3.7 Blinding

The study is double-blind. All patients, the Investigators and their study teams, the Sponsor (with exception of Sponsor Chemistry and Manufacturing Controls [CMC] Clinical Supplies Manager), Clinical Contract Research Organisation (CRO) (with the exception of the unblinded statistician(s), PPD Drug Supply Manager and IRT team), clinical laboratories (except those responsible for drug concentration analysis) and the IDMC will be blinded to treatment regimen until Day 169 (Week 24) has been completed for all patients and the database has been locked for analysis for the Day 169 (Week 24) data. IDMC members can have access to unblinded data sooner than the mentioned timepoint if that is necessary to perform data monitoring activities, and for safety purposes. Thereafter, the study data up to Day 169 (Week 24) will be unblinded to everyone except the study site and patients.

Re-randomisation from Day 169 (Week 24) will not be unblinded to the team (except for those team members listed above).

Study sites and patients will not be unblinded at any stage until after the final Data Base Lock.

If deemed necessary by the IDMC, PPD will select an unblinded statistician among its statisticians.

The work of PPD unblinded staff in support of the IDMC will be performed on an unblinded portal with access to unblinded personnel only.

PPD will generate the trial treatment randomisation codes and provide these to the IRT for inclusion in the IRT system. Randomisation codes will be controlled in the IRT system and procedures for breaking the codes in an emergency will be made available to relevant members of study site staff, the PPD Medical Monitor and the Sponsor Study Responsible medical Officer.

At the assay institutions charged for ADA and PK measurements, samples will be analysed prior to database lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the Operation's Team and results will not be communicated to the sites during the study.

Following written confirmation of database lock, assignment of patients to the analysis populations and finalisation of the study SAP, the study will be unblinded. The date, time, signature and printed name of the persons responsible for database lock, for the assignment of patients to the analysis populations and for treatment code-break (unblinding) will be recorded in order to verify that unblinding occurred in the correct sequence.

For procedures to unblind an individual patient treatment in an emergency, see Section 8.2.1.

Following database lock, the randomisation codes will be made available to all members of Sponsor and CRO staff as required. Randomisation codes will be made available to site staff once all patients have completed the study and the database has been locked.

3.8 Independent Data Monitoring Committee

An IDMC with members independent from the Sponsor and the investigators is implemented to make appropriate recommendations on the conduct of the clinical trial to ensure the protection and the safety of the enrolled patients on the study. The IDMC reviews and analyses, on a regular basis, safety and, if requested, efficacy data throughout the study. Blinded data will primarily form the basis for the IDMCs review. Unblinded data will be available alongside blinded data at the request of the IDMC. Formal data review meetings will be conducted approximately every 2 months to evaluate safety and efficacy data (frequency may need to be reviewed depending on recruitment) and are projected to begin once 10% of participants have received the first dose of IMP or 3 months after first patient dosed, whichever occurs first.

A detailed IDMC charter will be written to outline the working procedures and duties of the IDMC in detail. The data to be considered by the IDMC, the process for quality control of reports and data, and the documentation of decisions will be described in detail in the mutually agreed charter prior to the study start. The primary responsibility of the IDMC will be to protect the safety of the study patients and will make recommendations to the Sponsor regarding the ongoing conduct of the study. The IDMC may make recommendations to stop the study, continue the study with changes or continue without changes. For example, the IDMC may make a recommendation to terminate a specific dose level, so that if a dose level is not tolerated then no further patients receive a dose that is not safe.

4 STUDY POPULATION

Adult patients with moderate-to-severe AD who have a documented history, within 6 months prior to Baseline, of either inadequate response or inadvisability of topical treatments.

4.1 Number of Patients

Up to 350 patients (approximately 70 patients per treatment arm at Baseline) will be randomised.

4.2 Inclusion Criteria

Patients must fulfil all the following inclusion criteria for entry into the study:

1. Adults (18 to <75 years of age) with AD as defined by the American Academy of Dermatology Consensus Criteria [Eichenfield et al., 2014] for 1 year or longer at Baseline (Day 1; prior to first administration of IMP). For United Kingdom, see Section 17.15.2 (Appendix 15).
2. EASI of 12 or higher at the Screening Visit and 16 or higher at Baseline.
3. IGA of 3 or 4 at Baseline.
4. AD involvement of 10% or more of body surface area (BSA) at Baseline.
5. Baseline worst/maximum pruritus NRS of ≥4. The baseline weekly average of daily worst/maximum pruritus NRS will be calculated from the 7 consecutive days immediately preceding the Baseline visit. A minimum of 4 daily scores out of the 7 will be required.
6. Documented history, within 6 months prior to Baseline, of either inadequate response or inadvisability of topical treatments.

a) Acceptable documentation includes contemporaneous chart notes that record TCS/TCI prescription and treatment outcome, or Investigator documentation based on communication with the patient's treating physician.
b) Failure to achieve and maintain remission or low disease activity (eg, IGA 0, clear skin to 2, mild disease) despite treatment with TCS of medium to high potency (± topical calcineurin inhibitor as appropriate), applied daily for at least 28 days or for the maximum duration recommended by the product prescribing information (eg, 14 days for super-potent TCS), whichever was shorter.
NOTE: Patients who failed systemic therapies intended to treat AD within 6 months preceding screening, such as cyclosporine, methotrexate, azathioprine, and mycophenolate will be also considered as surrogate for having inadequate response to topical therapy. Washout of prior systemic medications must be completed as per the protocol requirements.
c) Important side effects or safety risks defined as those that outweigh the potential treatment benefits including (but not limited to) hypersensitivity reactions, significant skin atrophy, treatment intolerance and adverse systemic effects, as assessed by the investigator or treating physician.

7. Must have applied a stable dose of topical bland emollient (simple moisturiser, no additives [eg, urea]) at least twice daily for a minimum of 7 consecutive days before Baseline.
8. Able to complete patient questionnaires, including collection of NRS (pruritus) on each of the 7 days prior to Baseline. For patients who do not have at least 4 daily scores reported during the 7 days immediately preceding the planned randomisation date, randomisation should be postponed until this requirement is met, but without exceeding the 28-day maximum duration for screening.
9. Able and willing to comply with requested study visits/telephone visits and procedures.
10. Able and willing to provide written informed consent. This document must also actually be presented at the time of inclusion.
11. For patients who decide to join the biopsy sub-study at sites selected for skin biopsy collection, be able and willing to provide skin biopsies at required timepoints.

4.3 Exclusion Criteria

Patients fulfilling any of the following exclusion criteria will be excluded from the study:

1. Treatment with any of the following prior to first IMP administration (Baseline):
   - Systemic corticosteroids, and systemic calcineurin inhibitors (tacrolimus and cyclosporin) [redacted];
   - Leukotriene inhibitors [redacted];
   - Use of mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, dapsone, intravenous immunoglobulin, Kineret (anakinra), Enbrel (etanercept), or any other immunosuppressant not mentioned in this exclusion criterion [redacted]
   - Use of infliximab, adalimumab, golimumab, abatacept, tocilizumab, certolizumab, secukinumab, IFN-γ, and any other biologic or targeted-synthetic disease modifier drug

not mentioned in this exclusion criterion or in the exclusion criterion above, as well as plasmapheresis [redacted]

- Previous treatment with systemic janus kinase (JAK) inhibitors [redacted]
- Use of anti-CD20 drugs such as rituximab, ofatumumab, other long-acting biologics [redacted]
- Topical corticosteroids, tacrolimus or pimecrolimus, or topical phosphodiesterase-4 (PDE4) inhibitor [redacted]
- Prescription or non-prescription moisturisers with additives (eg, urea, filaggrin) within [redacted]
- Phototherapy or allergen immunotherapy [redacted]
- Regular use (>2 visits/week) of a tanning booth/parlour [redacted]
- Dupilumab (aIL-4Rα) [redacted]
- Any prior use of any anti-OX40, anti-OX40L mAb including KY1005;
- Investigational therapy for the treatment of AD or other conditions within 5 half-lives or the limit of PD effects or 12 weeks where the $t_{1/2}$ is not known.

2. Known history of or suspected significant current immunosuppression, including history of invasive opportunistic infections despite infection resolution or otherwise recurrent infections of abnormal frequency or prolonged duration.
3. Weight <40 kg or >150 kg at Baseline. [redacted]
4. Treatment with a live (attenuated) immunisation within 12 weeks prior to Baseline; completion of required administrations of COVID-19 vaccine within 14 days prior to Baseline or within 14 days immediately prior to or following IMP administration. [redacted]
5. Men and women (of reproductive potential) unwilling to use birth control and women who are pregnant or breastfeeding (see Section 4.4 and Section 4.5).
6. Any malignancies or history of malignancies prior to Baseline (except for non-melanoma skin cancer that has been excised and cured for more than 3 years prior to Baseline; in situ cervical carcinoma that has been excised and cured). [redacted]
7. Positive for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) or hepatitis C antibody at the Screening Visit. [redacted]
8. History (within last 2 years prior to Baseline) of prescription drug or substance abuse, including alcohol, considered significant by the Investigator.
9. Current or any past history of tuberculosis or non-tuberculous mycobacterial infections (including a positive QuantiFERON®-Tuberculosis (TB) Gold blood test at the Screening Visit).

10. Elective surgery planned to be scheduled for any time in the period from Screening up to 12 weeks following the last dose of IMP that in the investigator's opinion would impact the conduct of the trial.
11. Anticipated initiation of prohibited medications from Screening up to 12 weeks following the last dose of IMP.
12. Severe concomitant illness that would in the Investigator's opinion inhibit the patient's participation in the study, including for example, but not limited to, hypertension, renal disease, neurological conditions, heart failure and pulmonary disease.
13. Skin co-morbidity that would adversely affect the ability to undertake AD assessments.
14. Any medical or psychiatric condition which, in the opinion of the Investigator may present an unreasonable risk to the study patient as a result of his/her participation in this clinical study, may make patient's participation unreliable, or may interfere with study assessments.
15. Any active or chronic infection requiring systemic treatment within 2 weeks prior to Baseline (1 week in the event of superficial skin infections).
16. Laboratory values at the Screening Visit:
    - [redacted]
    - [redacted]
    - In the Investigator's opinion, any additional clinically significant laboratory results from the clinical chemistry, haematology or urinalysis tests at the Screening Visit.
17. In the Investigator's opinion, any significant abnormality on 12-lead electrocardiogram (ECG) at the Screening Visit.
18. History of or known or suspected hypersensitivity to KY1005 or the matching placebo formulation, or excipients used in the presentation of KY1005 or placebo, or in preparation for administration. History of or known or suspected severe hypersensitivity reactions to other mAbs and/or their excipients.
19. Patients for whom coercion by either the Investigator or the Sponsor (eg, employee, student or persons who have been placed in an institution on the basis of an official or court order) cannot be discounted. (No patients will be included who are related to, or in a relationship with, or employed by the Investigator, the Sponsor or any organisations contracted on behalf of the Sponsor in the design, setting up or running of the study).
20. Concurrent participation in any other clinical study, including non-interventional studies.

4.4 Reproductive Status

Women of childbearing potential (WOCBP) are permitted to participate in the study provided adequate birth control measures are taken during the whole length of the study, including the post-dose safety follow-up period (see Section 4.5). A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range should be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.

Permanent sterilization methods include:

- Documented hysterectomy;
- Documented bilateral salpingectomy;
- Documented bilateral oophorectomy;
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of IMP, additional evaluation should be considered. The Investigator must consult the Medical Monitor if there is doubt whether a patient is of childbearing potential.

See Section 4.5 for adequate birth control (contraception and sterilisation) for WOCBP.

Males participating in the study with partners of childbearing potential must ensure adequate birth control measures are taken from Baseline and for a period after they last receive IMP (see Section 4.5).

The Investigator must consult the Medical Monitor if there is doubt whether a patient qualifies as undertaking adequate birth control.

4.5 Contraceptive Precautions

- WOCBP and males with partners of childbearing potential (see Section 4.4) must ensure adequate birth control precautions are undertaken from Baseline until 5 months after Day 337 (Week 48) or the early termination visit (if prior to Day 337) unless entering the LTE. WOCBP should agree to use a contraceptive method that is highly effective (with a failure rate of <1% per year), as described in Section 17.10 (Appendix 10) Contraception and Barrier Guidance.
- Adequate contraception includes the combined oral contraceptive pill (if judged by the Investigator to be taken regularly), intra-uterine devices and contraceptive implants. Periodic abstinence, single barrier methods of contraception and progesterone-only pills not associated with inhibition of ovulation, even in those aged over 40 years are examples of inadequate contraception. See Section 17.10 (Appendix 10) for further detail.
- For both WOCBP and males with a partner of childbearing potential adequate sterilisation includes vasectomy and abdominal (including laparoscopic) and hysteroscopic female sterilisation.

- Male patients should be advised of the benefit for a female partner to use a highly effective method of contraception (as described in Section 17.10 (Appendix 10) Contraceptive and Barrier Guidance) as a condom may break or leak when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.
- Male patients with a pregnant partner must undertake some barrier protection, such as a condom until 5 months after Day 337 (Week 48) or the early termination visit (if prior to Day 337).
- Female patients must not breastfeed until 5 months after Day 337 (Week 48) or the early termination visit (if prior to Day 337).
- Patients must not donate or cryopreserve sperm/ova until 5 months after Day 337 (Week 48) or the early termination visit (if prior to Day 337). If male patients with a pregnant partner enter the LTE study, then barrier protection should be used as per the study protocol.

The Investigator must consult the Medical Monitor if there is doubt whether a patient qualifies as undertaking adequate birth control.

4.6 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomised. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

In cases where original screen failure was as a result of a laboratory abnormality due to reasons expected to change at re-screening and based upon the Investigator's clinical judgment, the patient may be re-screened one time for this study after notification of the Sponsor. A different patient identification number will be issued. There is no requirement for a waiting period between the screen-failure and the re-screening. Patients that are re-screened will be required to sign a new consent form.

4.7 Strategies for Recruitment and Retention

Recruitment for this study will be competitive.

Patients may be selected from the participating sites patient databases (if applicable) in accordance with the study eligibility criteria (see Section 4.2 and Section 4.3). Patients may be contacted by telephone, e-mail or in writing if applicable. Advertisements may be used to aid patient recruitment; however, prior to implementation, all advertising and marketing material available to patients must be submitted to the Independent Ethics Committee (IEC)/Independent Review Board (IRB) for approval (see Section 12.1). After provision of the Informed Consent Form (ICF), patients will be screened at the respective site.

5 TREATMENT OF PATIENTS

5.1 Presentation of Investigational Medicinal Product(s)

The IMPs are KY1005 (SAR445229), hereby known as KY1005, or matching Placebo.

5.1.1 KY1005

[redacted]

5.1.2 Matching Placebo

[redacted]

5.1.3 Non-investigational Medicinal Products/Auxiliary Medicinal Products/ Ancillary Treatments

There will be no Non-investigational Medicinal Products, Auxiliary Medicinal Products or Ancillary Treatments used in this study.

5.2 Study Treatment Administration

All dosages prescribed and dispensed to patients and all dose changes during the study must be recorded in the patient's hospital files and on the electronic case report form (eCRF).

5.2.1 Treatment Regimen

Patients may receive study treatment every 4 weeks from Day 1 to Day 337 (Week 48) according to the scheme in Figure 3-1.

All study treatment regimens are presented in Table 5-1. Randomisation will occur pre-injection on Day 1, with re-randomisation pre-injection on Day 169 (Week 24) should the patient achieved an ≥ EASI 75 or attain IGA 0/1 (see Section 3.6).

From Baseline up to Day 169 (Week 24) IMP will be administered at the following dose and intervals:

- 500 mg loading at Baseline ([redacted]) followed 4 weeks later with 250 mg Q4W as [redacted] injection;

  Or

- 250 mg ([redacted]) plus [redacted] Placebo at Baseline followed 4 weeks later with 250 mg Q4W [redacted]

Or

- 125 mg (as [redacted] injection) plus [redacted] Placebo at Baseline followed 4 weeks later with 125 mg Q4W as [redacted]

Or

- 62.5 mg ([redacted]) plus [redacted] Placebo at Baseline followed 4 weeks later with 62.5 mg Q4W as [redacted]

Or

- Placebo given [redacted] at Baseline followed 4 weeks later with [redacted] placebo (0 mg).

At Baseline, those patients not receiving a KY1005 loading dose will receive both KY1005 and Placebo to maintain the study blind.

- From Day 169 (Week 24) to Day 365 (Week 52) in patients who achieve ≥ EASI 75 or who attain IGA 0/1 at Day 169 (Week 24) will be randomised 3:1 to either Withdrawal or will continue to receive their pre-Week 24 dosing.
- Patients randomised to Withdrawal will receive Placebo Q4W. Those patients not randomised to Withdrawal will continue to receive their pre-Week 24 dose/interval.
- Re-randomisation from Day 169 (Week 24) will not be uncoded to the team, study sites or patients until after the final Data Base Lock. Those patients who do **not** achieve ≥ EASI 75 or IGA 0/1 at Day 169 (Week 24) will have the possibility to enrol into the LTE where they will receive KY1005.

Table 5-1 TreatmentRegimes

Arm	Day 1		Day 29 (Week 4) to Day 169 (Week 24)			Day 169 (Week 24) to Day 365 (Week 52) in patients who achieve ≥ EASI 75 or who attain IGA 0/1at Day 169 (Week 24)		
	IMP	**Dose (mg)**	**IMP**	**Dose (mg)**	**Frequency**	**IMP**	**Dose (mg)**	**Frequency**
1	KY1005	500 mg ([redacted])	KY1005	250 mg	Q4W	KY1005	250 mg	Q4W *or*
						PBO	0	Q4W
2	KY1005	250 mg plus PBO loading	KY1005	250 mg	Q4W	KY1005	250 mg	Q4W *or*
						PBO	0	Q4W
3	KY1005	125 mg plus PBO loading	KY1005	125 mg	Q4W	KY1005	125 mg	Q4W *or*
						PBO	0	Q4W
4	KY1005	62.5 mg plus PBO loading	KY1005	62.5 mg	Q4W	KY1005	62.5 mg	Q4W*or*
						PB0	0	Q4W
5	Placebo	NA plus PBO loading	Placebo	NA	Q4W	PBO	0	Q4W *or*
						PBO	0	Q4W

IMP=investigational medicinal product; PBO= Placebo; NA=not applicable; Q4W=every 4 weeks.

All doses of KY1005 and Placebo will be administered [redacted]. At Baseline [redacted], one injection at each side of the region to be injected, to maintain the integrity of the blind.

5.2.2 Administration of IMP

[redacted] KY1005 or matching Placebo will be administered as a SC injection to the abdomen. If IMP administration to the abdomen is not possible due to the extent of skin involvement, the outer thigh may be selected. However, the same anatomical region must be used for IMP administration **throughout** study participation and documented in the eCRF. IMP should not be administered at the site of a recent injection or in areas which in the Investigator's opinion are not suitable eg, tender, bruised, red or hard. Details of administration will be documented in the study specific Pharmacy Manual.

5.2.3 Precautions for Administration

Only fully trained and qualified study site personnel should administer SC injections. The injection must be administered at a constant pressure.

5.2.4 Monitoring During Administration

After treatment administration, check for local skin reactions will be performed. Patients will be monitored with assessments of vital signs at the timepoints outlined in the Schedule of Assessments (Section 6.1, Table 6-1, Table 6-2, Table 6-3, Table 6-4).

5.2.5 Treatment Duration

All patients treated with KY1005 or matching Placebo will be randomised and begin study treatment on Day 1. Patients will initially receive SC injections of IMP Q4W to Day 169 (Week 24). The Day 113 (Week 16) primary analysis will occur once all patients have reached the Day 169 (Week 24) visit (or earlier in the event of termination).

Those patients in the 500 mg loading with 250 mg Q4W treatment arm will [redacted] commence 250 mg Q4W on Day 29 (Week 4). [redacted]

As outlined previously, those patients who achieve ≥ EASI 75 or who attain IGA 0/1 at Day 169 (Week 24) will be re-randomised pre-injection at Day 169 (Week 24) to either the Withdrawal arm (and receive Placebo Q4W) or remain on their pre-Week 24 dose for the second study period.

The duration of treatment will therefore be up to Day 365 (Week 52), with last dose administered on Day 337 for those patients who achieve ≥ EASI 75 or who attain IGA 0/1 at Day 169 (Week 24), irrespective of whether response is maintained to Day 365 (Week 52) and they enter safety follow-up or they experience loss of clinical response at or after Day 197 (Week 28) and enter the LTE.

Those patients who do **not** achieve ≥ EASI 75 or IGA 0/1 at Day 169 (Week 24) will have the possibility to enter the LTE at Day 169.

5.2.6 Guidance for Overdose

Overdose is defined [redacted] In the unlikely event that an overdose of KY1005 is administered, the patient will be observed and treated symptomatically. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

[redacted] If severe adverse reactions occur after an overdose of KY1005, then plasmapheresis (or infusion of albumin) to reduce the drug exposure may be considered.

All instances of symptomatic overdose, both serious and non-serious, will be reported to the Sponsor (or designee) as AESIs within 24 hours of learning of the event (see Section 8.1.3).

5.2.7 Dose Modification

[redacted]

5.3 Concomitant Medication and Dietary Supplements

Any treatment (including nutritional supplements) or procedure administered from the time of consent to the EOS Visit is considered concomitant and will be recorded in the eCRF. This includes permitted medications ongoing at the time of consent. Concomitant medications and procedures are allowed, except for those listed in Section 5.3.2.

Prior medications will not be recorded in the eCRF, except for prior use of systemic corticosteroids, systemic calcineurin inhibitors, and systemic treatment for AD or other indications with an immunosuppressive/immunomodulating substance including (but not limited to) dupilumab, JAKi and aIL13 mABs, with reason for discontinuation recorded where available.

5.3.1 Permitted Concomitant Therapy

Other than the prohibited medications listed in Section 5.3.2, treatment with concomitant medication is permitted during the study. This includes treatment with oral contraceptives, nasal, otological, and inhaled corticosteroids for any duration, and oral or topical antibiotics for up to 2 weeks for AD-associated superficial skin infections.

5.3.2 Prohibited Concomitant Therapy (and Procedures)

Treatment with the following concomitant medications is prohibited during the study:

- Dupilumab.
- Topical or systemic tacrolimus and pimecrolimus (exceptions might apply, see Section 4.3 and Section 5.3.4, Section 5.3.5).

- Topical or systemic corticosteroids (exceptions might apply, see Section 4.3 and Section 5.3.4).
- Leukotriene inhibitors.
- Allergen immunotherapy.
- Systemic treatment with an immunosuppressive/immunomodulating substance (including, but not limited to aIL13 mABs, JAKi, aOX40 mAbs, cyclosporine, mycophenolate-mofetil, IFN-γ, azathioprine, methotrexate, or biologics).
- Treatment with a live (attenuated) immunisation (Note: immunisation with inactivated seasonal influenza vaccine and inactivated adenovirus COVID-19 vaccines is permitted (see Section 5.3.3). COVID-19 vaccines should not be administered within 14 days prior to Baseline or within 14 days immediately prior to, or following, IMP administration.

The following concomitant procedures are prohibited during study participation:

- Elective surgical procedures.
- Ultraviolet (UV) procedures (phototherapy [narrowband UVB, UVB, UVA1 orpsoralen UVA]).
- Tanning in a booth/parlour.
- More than 2 bleach baths per week.

5.3.3 COVID-19 Vaccination and Other Vaccines

To allow for an optimal immune response as well as protection against COVID-19, it is strongly recommended that patients complete their COVID-19 vaccination schedule (per local requirements) a minimum of 14 days prior to receiving the first dose of IMP. [redacted]

The safety profile and effectiveness of COVID-19 vaccines on people with compromised immune systems or therapies (such as KY1005) that modify or that suppress their immune response is not yet established.

While vaccination with an approved COVID-19 vaccine (including booster dose) is widely recommended (AAD COVID-19 Vaccine Administration Guidance, 2021; EADV Task Force Covid Vaccination Advice, 2021), a patient's decision to have a COVID-19 vaccination during the study should only be made after discussing with his/her physician and the Investigator to assess the benefits/risks of receiving a COVID-19 vaccination during this study. In this instance, if the vaccine is authorised, available, and recommended by the local regulatory health authority, it may be administered during the study and should be administered according to the label or local health authority recommendations. The vaccine should not be administered within 14 days immediately prior to, or following, IMP administration. Details of the COVID-19 vaccine should be recorded in the eCRF.

The impact of KY1005 on overall vaccination response, new and recall response, for both COVID19 and other vaccines, has not been tested to date in AD.

5.3.4 Rescue Therapy

No AD rescue therapy is permitted in the first 14 days following randomisation. Any AD rescue therapy administration either topical or systemic during this period will result in permanent discontinuation from the IMP. Bland emollients are not considered rescue therapy for AD, and should be maintained during this period as per protocol.

If medically unavoidable after Day 14 (ie, to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the Investigator. For the purpose of efficacy analysis, patients who receive rescue topical treatment during this study treatment period will be considered treatment failures but can continue study treatment if the rescue treatment consists of topical medications only.

If topical corticosteroids (TCS) are needed, it is recommended that the investigator start with the least potent TCS for the face (eg, hydrocortisone 2.5% cream/ointment) and moderately potent TCS for the body (eg, triamcinolone acetonide 0.1% cream/ointment), applied up to twice daily. Where the use of moderate potency topical corticosteroids (TCS) are not considered clinically appropriate, low potency TCS or topical calcineurin inhibitors can be used, however, these should be reserved for problem areas only. Topical PDE4 inhibitors are also permitted.

Participants should use topical rescue therapy only for as long as necessary to control problem areas on a maximum of 2 occasions during study participation, and for a maximum of 2 consecutive weeks on each occasion.

If a patient receives rescue treatment with high potency TCS, systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc) or receives more than 2 episodes of topical rescue treatment, study treatment will be immediately discontinued.

Investigators should conduct efficacy and safety assessments immediately before administering any rescue treatment. An unscheduled visit may be required.

All patients should complete the schedule of study visits and assessments whether or not they complete study treatment and whether or not they receive rescue treatment for AD. If a patient has IMP permanently discontinued due to the taking of systemic therapy rescue but consent is retained, study assessments may be continued until Day 169 (Week 24) for patients who discontinue IMP in the first study period, or until Day 365 (Week 52) or the end of the safety follow-up period (whichever is longer) in patients who discontinue IMP after Day 169 (Week 24).

5.3.5 Background Therapy

Patients are required to apply a stable dose of a topical bland emollient (simple moisturiser) at least twice daily for a minimum of 7 consecutive days before the Baseline Visit (see Section 4.2) and to continue with the same emollient at the same dose twice daily throughout their participation in the study.

To permit an adequate assessment of skin dryness, moisturisers should not be applied on area(s) of non-lesional skin, designated as such for assessment purposes, for at least 8 hours before each clinic visit.

Patients are permitted to use any simple bland prescription, over-the-counter or general purchase moisturiser providing it contains **NO** additives, such as corticosteroids or urea (even at low concentrations). The type/brand of emollient will be recorded in the eCRF. Prescription and non-prescription moisturisers with additives (eg, urea, filaggrin, niacinamide, ceramides, bisabolol) are not permitted within 2 weeks prior to first IMP administration (Baseline; see Section 4.3) or during the study.

5.4 Lifestyle Restrictions

Patients must maintain a relatively constant level of exercise during study participation through to Day 365 (Week 52) and refrain from unusually strenuous physical activities to avoid a potentially confounding effect on safety assessments caused by exercise-related changes in serum enzymes of clinical importance (eg, creatine phosphokinase [CPK], lactate dehydrogenase, aspartate aminotransferase [AST], alanine aminotransferase [ALT]). In addition, patients should avoid excessive alcohol intake and the use of drugs of abuse during the study.

5.5 Patient Numbering and Treatment Assignment

Patients will be identified with unique patient numbers assigned by an IRT system at the time of screening. This unique patient number will identify the patient in all study databases (eg, eCRF, central laboratory, etc) and will be linked to the patient's name in an identification list retained in the Investigator Site File (ISF). Patient numbers assigned by IRT will be retained regardless of whether the patient subsequently fulfils the eligibility criteria. If a patient withdraws from the study the patient number will not be re-used.

Patient eligibility will be established before IMP is allocated to individual patients by the IRT system.

5.6 Supply, Packaging, Labelling and Storage

[redacted]

The KY1005 and Placebo will be provided by the Sponsor to the investigational sites in a blinded condition as kits in tamper-sealed cartons. IMP kits will be packaged and labelled according to the randomisation list. Each vial and each finished kit will be labelled in accordance with EudraLex, Volume 4 GMP Guidelines, Annex 13, IND and other local regulatory requirements. Labels will be translated in local language as required. Replacement supplies will be available at each site, in case of damage to the originally assigned kit. The replacement kits will also be assigned to the patient via the IRT system.

Procedures for breaking the codes in an emergency will be provided via the IRT system, to relevant members of study site staff and the PPD Medical Monitor. This will be activated prior to or concurrent with receipt of the IMPs and will be described in the study specific Pharmacy Manual.

After release procedures have been completed in accordance with Sponsor or designee Standard Operating Procedures (SOPs), and as needed thereafter, IMPs will be shipped with temperature monitoring equipment to the responsible person at the investigational site in temperature-controlled shippers. The responsible person will check the amount and condition of the IMP received and will acknowledge receipt in IRT.

If the temperature monitoring device shows that shipment conditions have fallen outside the specified range, the site will take measures to prevent the IMPs being dispensed and contact the Sponsor as directed in the study specific Pharmacy Manual to discuss the potential implications and any action(s) that may be necessary.

[redacted]

The responsible person at the investigational site will prepare blinded individual patient IMP doses using IMP kits assigned by the IRT system and in accordance with the instructions provided in the study specific Pharmacy or IRT Manuals.

[redacted]

Records of the actual storage conditions during the period of the study must be maintained (eg, records of the date and time and initials of person checking, and the daily (weekday) temperatures of the area used for storage of study drug) and provided to the Sponsor for retention in the electronic Trial Master File (eTMF).

5.7 Procedures for Monitoring Patient Compliance

The Investigator is responsible for the administration of the IMP. The Study Monitor will assess compliance throughout the study by reviewing drug reconciliation/accountability records on a periodic basis as outlined in the monitoring plan and guidelines.

Sites should also discuss study procedure compliance with the patients, as required.

5.8 Study Drug Accountability Records

The Investigator is responsible for accountability of all used and unused IMP supplies at the site. IMP must only be used for the purpose of the study in accordance with the protocol.

IMP accountability will be recorded by the Investigator and filed in the ISF. The IMP accountability details should be kept current and should contain the dates and quantities of drug received at site, kit number, patient number, date, time, and quantity of drug dispensed to each patient, and the name/initials of the authorised dispenser. Any issues with the IMP administration (eg, spillage, blockage etc) must be recorded as per the study specific Pharmacy Manual.

All IMP accountability documents must be made available for inspection by the Study Monitor, Sponsor or Sponsor's representatives and regulatory agency inspectors.

At the end of the study all documents related to IMP lifecycle must be filed in the ISF and eTMF.

Final IMP reconciliation must also be performed by the IMP distributers of stocks remaining at or returned to by the sites to all distribution centres. The Sponsor or Sponsor's representatives must be granted access on reasonable request to all distribution centres to check drug storage, dispensing procedures and accountability records.

5.9 Study Drug Destruction

All IMP supplies including unused, partially used, or empty containers, will be retained at site prior to completion of accountability. At the EOS, or as directed in writing by the Sponsor, and after final IMP reconciliation completed by study monitor, the Sponsor will give written approval for destruction of IMP locally or return to a central location for destruction.

Local or institutional regulations may require immediate destruction of used study drug for safety reasons. In these cases, it may be acceptable for the study site staff to destroy dispensed study drug prior to a monitoring inspection, if source document verification is performed on the remaining inventory and reconciled against the documentation of quality supplied, dispensed, returned, and destroyed. Written authorisation must be obtained from the Sponsor prior to destruction.

Proof of delivery, certificates of destruction and/or study drug return documentation will be filed in the eTMF.

6 STUDY PROCEDURES

6.1 Study Schedule of Assessments

The schedule of procedures and assessments during the study is summarised and presented in Table 6-1, Table 6-2 and Table 6-3 for all patients, plus Table 6-4 for patients who are not enrolled into the LTE and have additional safety follow-up. Where possible, the patient reported outcome (PRO) assessments completed at the study site are to be completed by patients prior to the completion of other study assessments and the administration of study drug.

In general, and wherever possible, patients will be assessed at the approved study clinics/facilities. Section 17.14 (Appendix 14) details contingency procedures that are suggested for a regional or national emergency declared by a governmental agency that prevents access to the study site, to ensure the safety of the patients, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance.

Table 6-1: Schedule of Assessments Screening to Day 113(Week 16)

Visit	1		2[b]	3	4	5	6[a]	7[a]	8[a]	9[a]	ET[#]
Visit days	**-29 to -8**	**-7 to 1**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	-
Visit weeks	**-4 to -1**	**- 1**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	-
Visit window (days)	**0**	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	-
	Screening		**Baseline**	**Treatment**							
Description	**Clinic**		**Clinic**	**Clinic**	**Clinic**	**Telephone[m]**	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic**
Informed consent	X										
Demographics	X										
Medical history	X										
Concomitant medications - including emollients	X		X[a]	X	X	X	X	X	X	X	X
AEs (including SAEs)	<==========									==========>	X
Inclusion/exclusion criteria	X		X								
Physical examination	X		X		X		X	X	X	X	X
Body weight and height (height at Screening only)	X		X							X	X
Vital signs[c]	X		X				X	X	X	X	X
12-lead ECG	X		X					X		X	X
EASI	X		X		X		X	X	X	X	X
BSA	X		X		X		X	X	X	X	X
IGA	X		X		X		X	X	X	X	X

Visit	1		2[b]	3	4	5	6[a]	7[a]	8[a]	9[a]	ET[#]
Visit days	-29 to -8	-7 to 1	1	8	15	22	29	57	85	113	-
Visit weeks	-4 to -1	- 1	0	1	2	3	4	8	12	16	-
Visit window (days)	0	0	0	±3	±3	±3	±3	±3	±3	±3	-
	Screening		Baseline	Treatment							
Description	Clinic		Clinic	Clinic	Clinic	Telephone[m]	Clinic	Clinic	Clinic	Clinic	Clinic
SCORAD Index[l]	X		X				X	X	X	X	X
DLQI[l]			X		X			X		X	X
ADCT[l]			X							X	X
HADS[l]			X					X		X	X
Blood samples for virology (HIV, Hepatitis B and C) and TB (QuantiFERON®-TB Gold blood test)[n]	X										
Safety tests (FBC, non-fasting biochemistry, electrolytes, urinalysis), FSH for post-menopausal women at Screening	X[k]		X				X	X	X	X	X
Pregnancy test – females only (serum at Screening, urine thereafter)[e]	X		X				X	X	X	X	X
Blood samples for serum concentrations of KY1005 (PK)[a]			X[a]	X	X		X	X	X	X	X
Blood samples for serum concentrations of ADAs[d]	[redacted]										
[redacted]											

Visit	**1**		**2[b]**	**3**	**4**	**5**	**6[a]**	**7[a]**	**8[a]**	**9[a]**	**ET[#]**
Visit days	**-29 to -8**	**-7 to 1**	**1**	**8**	**15**	**22**	**29**	**57**	**85**	**113**	**-**
Visit weeks	**-4 to -1**	**- 1**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**-**
Visit window (days)	**0**	**0**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**-**
	Screening		**Baseline**	**Treatment**							
Description	**Clinic**		**Clinic**	**Clinic**	**Clinic**	**Telephone[m]**	**Clinic**	**Clinic**	**Clinic**	**Clinic**	**Clinic**
POEM[l]			X				X	X	X	X	X
NRS (pruritus) – internet-enabled device[g]		X[h]	X	→	→	→	→	→	→	→	→
Contact IRT	X		X	X	X	X	X	X	X	X	X
Randomisation[i]			X								
IMP administration and check of local skin reaction[j, o]			**X**				X	X	X	X	

[redacted]

ADA=anti-drug antibody; ADCT=atopic dermatitis control tool; AEs=adverse events; BSA=body surface area; DLQI=Dermatology Quality of Life Index; EASI=Eczema Area and Severity Index; ECG=electrocardiogram; FBC=full blood count; FSH=follicle-stimulating hormone; HADS= Hospital Anxiety and Depression Scale; HIV=human immunodeficiency virus; IgE=immunoglobulin E; IMP=Investigational Medicinal Product; NRS=Numerical Rating Scale; POEM=Patient Oriented Eczema Measure; PK=pharmacokinetics; PRO=patient reported outcome; SAE=serious adverse event; SCORAD=SCORing of Atopic Dermatitis; TB=tuberculosis; IGA= Investigator Global Assessment.

\# Early Termination could be done by the Investigator (see Section 3.4, Section 3.5 and Section 9).

a On IMP administration days, all assessments, including taking blood samples, will be performed pre-injection unless stated otherwise.

b Baseline assessments may be performed up to 24 hours prior to the first IMP injection (Day 1).

c On IMP administration days up to and including Day 113 (Week 16) vital signs will be measured pre-injection and at 15-, 30- and 60-minutes post-injection. The tolerance on vital signs measurements after dosing is ±5 minutes.

d [redacted]

e If urine pregnancy test is positive, a serum control must be done before IMP administration

f [redacted]

g NRS (pruritus) will be recorded daily, ideally in the morning, based on the previous 24 hours, with worst (maximum) itch intensity recorded.

h Patients will be asked to assess their worst itching due to atopic dermatitis over the last 7 days prior to Baseline on an NRS anchored by the terms “no itch” (0) and “worst itch imaginable” (10).

i May be performed up to 24 hours prior to first injection as long as all inclusion/exclusion criteria are satisfied.

j [redacted]

k Screening laboratory assessments may be repeated a maximum of once where initial results are in the Investigator’s opinion, clinically significant

l Where possible, the PRO assessments completed at the study site are to be completed by patients prior to the completion of other study assessments and the administration of IMP.

m A telephone visit is defined as a videoconference, video call or telephone call.

n [redacted]

o [redacted]

Table 6-2: Schedule of Assessments - Day 120 (Week 17) to Day 169 (Week 24)

Visit	**10**	**11**[a]	**12**	**13**	**14**	**15**[a]	**ET**[#]
Visit days	**120**	**141**	**148**	**155**	**162**	**169**	-
Visit weeks	**17**	**20**	**21**	**22**	**23**	**24**[k]	-
Visit window (days)	**±1**	**±3**	**±1**	**±1**	**±1**	**±3**	-
	Treatment						-
Description	**Clinic**	**Clinic**	**Telephone**[h]	**Telephone**[h]	**Telephone**[h]	**Clinic**	**Clinic**
Concomitant medications – including emollients	X	X	X	X	X	X	X
AEs (including SAEs)	<==========					==========>	X
Physical examination							X
Vital signs[b]		X				X	X
12-lead ECG						X	X
EASI		X				X	X
BSA		X				X	X
IGA		X				X	X
SCORAD Index[g]		X				X	X
DLQI[g]		X				X	X
ADCT[g]						X	X
HADS[g]		X				X	X
Safety tests (FBC, non-fasting biochemistry, electrolytes, urinalysis)		X				X	X

Visit	**10**	**11**[a]	**12**	**13**	**14**	**15**[a]	**ET**[#]
Visit days	**120**	**141**	**148**	**155**	**162**	**169**	-
Visit weeks	**17**	**20**	**21**	**22**	**23**	**24**[k]	-
Visit window (days)	**±1**	**±3**	**±1**	**±1**	**±1**	**±3**	-
	Treatment						-
Description	**Clinic**	**Clinic**	**Telephone**[h]	**Telephone**[h]	**Telephone**[h]	**Clinic**	**Clinic**
Pregnancy test - females only (urine)[i]		X				X	X
Blood samples for serum concentrations of KY1005 (PK)[a]	X	X				X	X
Blood samples for serum concentrations of ADAs[c]	[redacted]						
[redacted]							
POEM[g]		X				X	X
NRS (pruritus) – internet-enabled device[d]	→	→	→	→	→	→	→
Contact IRT	X	X	X	X	X	X	X
Re-randomisation						X[e]	
IMP administration and check of local skin reaction[f, g, j]		**X**				X	

ADA=anti-drug antibody; ADCT=atopic dermatitis control tool; AEs=adverse events; BSA=body surface area; DLQI=Dermatology Quality of Life Index; EASI=Eczema Area and Severity Index; ECG=electrocardiogram; FBC=full blood count; IgE=immunoglobulin E; IMP=Investigational Medicinal Product; NRS=Numerical Rating Scale; POEM=Patient Oriented Eczema Measure; PK=pharmacokinetics; PRO=patient reported outcome; SAE=serious adverse event; SCORAD=SCORing of Atopic Dermatitis; IGA= Investigator Global Assessment; HADS= Hospital Anxiety and Depression Scale.

Early Termination Visit could be done by the Investigator (see Section 3.4, Section 3.5 and Section 9).

a On IMP administration days, all assessments, including taking blood samples, will be performed pre-injection unless stated otherwise.

b On IMP administration days vital signs will be measured pre-injection and 30 minutes post injection. The tolerance on vital signs after dosing is ±5 minutes.

c [redacted]

d NRS (pruritus) will be recorded daily, ideally in the morning, based on the previous 24 hours with worst (maximum) itch intensity recorded.

e Where IMP administration occurs on a re-randomisation day the IMP injection is to be administered after re-randomisation (with the new regimen where applicable).

f [redacted]

g Where possible, the PRO assessments completed at the study site are to be completed by patients prior to the completion of other study assessments and the administration of IMP.

h A telephone visit is defined as a videoconference, video call or telephone call.

i If urine pregnancy test is positive, a serum control must be done before IMP administration

j [redacted]

k The ICF from the DRI/Phase2b/parent study will not be valid as LTE informed consent. In order for patients to roll over to the LTE study, a specific LTE ICF will need to be applied, agreed upon and signed at the LTE study, as the LTE is a separated protocol.

Table 6-3: Schedule of Assessments - Day 176 (Week 25) to Day 365(Week 52)

Visit	**16**	**17[a]**	**18**	**19[a]**	**20**	**21[a]**	**22[a]**	**23**	**24[a]**	**25**	**26[a]**	**27**	**28[a]**	**ET[#]**
Visit days	**176**	**197**	**204**	**225**	**232**	**253**	**281**	**288**	**309**	**316**	**337**	**344**	**365**	
Visit weeks	**25[i]**	**28[i]**	**29[i]**	**32[i]**	**33[i]**	**36[i]**	**40[i]**	**41[i]**	**44[i]**	**45[i]**	**48[i]**	**49[i]**	**52[i]**	
Visit window (days)	**±1**	**±3**	**±1**	**±3**	**±1**	**±3**	**±3**	**±1**	**±3**	**±3**	**±3**	**±1**	**±3**	
	Treatment													**-**
Description	**Clinic**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Clinic**
Concomitant medications - including emollients	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs (including SAEs)	<==========												==========>	X
Physical examination		X					X						X	X
Vital signs[b]		X		X		X	X		X		X		X	X
12-lead ECG				X			X				X		X	X
EASI		X		X		X	X		X		X		X	X
BSA		X		X		X	X		X		X		X	X
IGA		X		X		X	X		X		X		X	X
SCORAD Index[g]		X		X		X	X		X		X		X	X
DLQI[g]		X		X		X	X		X		X		X	X
ADCT[g]						X							X	X

Visit	**16**	**17[a]**	**18**	**19[a]**	**20**	**21[a]**	**22[a]**	**23**	**24[a]**	**25**	**26[a]**	**27**	**28[a]**	**ET[#]**
Visit days	**176**	**197**	**204**	**225**	**232**	**253**	**281**	**288**	**309**	**316**	**337**	**344**	**365**	
Visit weeks	**25[i]**	**28[i]**	**29[i]**	**32[i]**	**33[i]**	**36[i]**	**40[i]**	**41[i]**	**44[i]**	**45[i]**	**48[i]**	**49[i]**	**52[i]**	
Visit window (days)	**±1**	**±3**	**±1**	**±3**	**±1**	**±3**	**±3**	**±1**	**±3**	**±3**	**±3**	**±1**	**±3**	
	Treatment													**-**
Description	**Clinic**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Telephone[f]**	**Clinic**	**Clinic**
HADS[g]		X		X		X	X		X		X		X	X
Safety tests (FBC, non-fasting biochemistry, electrolytes, urinalysis)		X		X		X	X		X		X		X	X
Pregnancy test - females only (urine)[i]		X		X		X	X		X		X		X	X
Blood samples for serum concentrations of KY1005 (PK)[a]	X	X		X		X	X		X		X		X	X
Blood samples for serum concentrations of ADAs[c]	[redacted]													

Visit	**16**	**17**[a]	**18**	**19**[a]	**20**	**21**[a]	**22**[a]	**23**	**24**[a]	**25**	**26**[a]	**27**	**28**[a]	**ET**[#]
Visit days	**176**	**197**	**204**	**225**	**232**	**253**	**281**	**288**	**309**	**316**	**337**	**344**	**365**	
Visit weeks	**25**[i]	**28**[i]	**29**[i]	**32**[i]	**33**[i]	**36**[i]	**40**[i]	**41**[i]	**44**[i]	**45**[i]	**48**[i]	**49**[i]	**52**[i]	
Visit window (days)	**±1**	**±3**	**±1**	**±3**	**±1**	**±3**	**±3**	**±1**	**±3**	**±3**	**±3**	**±1**	**±3**	
	Treatment													**-**
Description	**Clinic**	**Clinic**	**Telephone**[f]	**Clinic**	**Telephone**[f]	**Clinic**	**Clinic**	**Telephone**[f]	**Clinic**	**Telephone**[f]	**Clinic**	**Telephone**[f]	**Clinic**	**Clinic**
POEM[g]				X		X	X		X		X		X	X
NRS (pruritus) - internet-enabled device[d]	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP administration and check of local skin reaction[e]		**X**		**X**		**X**	**X**		**X**		**X**			

ADAs=anti-drug antibodies; ADCT=atopic dermatitis control tool; AEs=adverse events; BSA=body surface area; DLQI=Dermatology Quality of Life Index; EASI=Eczema Area and Severity Index; ECG=electrocardiogram; FBC=full blood count; IgE=immunoglobulin E; IMP=Investigational Medicinal Product; NRS=Numerical Rating Scale; POEM=Patient Oriented Eczema Measure; PK=pharmacokinetics; PRO=patient reported outcome; SAE=serious adverse event; SCORAD=SCORing of Atopic Dermatitis; IGA= Investigator Global Assessment; HADS= Hospital Anxiety and Depression Scale.

\# Early Termination could be done by the Sponsor or the Investigator (see Section 3.4, Section 3.5 and Section 9).

a On IMP administration days in this time period, all assessments, including taking blood samples, will be performed pre-injection unless stated otherwise.

b On IMP administration days in this time period, vital signs will be measured pre-injection and 30 minutes post- injection. The tolerance on vital signs after dosing is ±5minutes.

c [redacted]

d NRS (pruritus) will be recorded daily, ideally in the morning, based on the previous 24 hours with worst (maximum) itch intensity recorded.

e [redacted]

f A telephone visit is defined as a videoconference, video call or telephone call.

g Where possible, the PRO assessments completed at the study site are to be completed by patients prior to the completion of other study assessments and the administration of IMP.

i If urine pregnancy test is positive, a serum control must be done before IMP administration.

j The ICF from the DRI/Phase2b/parent study will not be valid as LTE informed consent. In order for patients to roll over to the LTE a specific LTE ICF will need to be applied, agreed upon and signed at the LTE study, as the LTE is a separated protocol.

Table 6-4: Schedule of Assessments - SafetyFollow-up

Visit	**29[a]**	**30[a]**	**31[a]**	**32[a]**	**ET[#]**
Visit days	**393**	**421**	**449**	**477**	
Visit weeks	**56[d]**	**60[d]**	**64[d]**	**68[d]**	
Visit window (days)	±7	±7	±7	±7	
Description	**Clinic**	**Telephone[b]**	**Clinic**	**Clinic**	**Clinic**
Concomitant medications - including emollients	X	X	X	X	X
AEs (including SAEs)	←----------	----------	----------	----------→	X
Physical examination			X	X	X
Vital signs	X		X	X	X
12-lead ECG	X		X	X	X
Safety tests (FBC, non-fasting biochemistry, electrolytes, urinalysis)	X		X	X	X
Pregnancy test – females only (urine)[c]	X		X	X	X
Blood samples for serum concentrations of ADAs	[redacted]				

ADA=anti-drug antibody; AEs=adverse events; ECG=electrocardiogram; FBC=full blood count; SAE=serious adverse event.

\# Early Termination could be done by the Sponsor or the Investigator (see Section 3.4, Section 3.5 and Section 9).

a For patients who are not enrolled into the LTE (LTS17367) and require additional safety follow-up.

b A telephone visit is defined as a videoconference, video call or telephone call.

c If urine pregnancy test is positive, a serum control must be done before IMP administration.

d The ICF from the DRI/Phase2b/parent study will not be valid as LTE informed consent. In order for patients to roll over to the LTE a specific LTE ICF will need to be applied, agreed upon and signed at the LTE study, as the LTE is a separated protocol.

6.2 Screening Procedures

6.2.1 Written Informed Consent

Written informed consent for the study will be obtained from each patient before any protocol-specific assessments or procedures are carried out.

At the Screening Visit (or at a prior interview), the Investigator will explain the aims, methods, anticipated benefits and potential risks of participating in the study and should inform the patient that participation is voluntary and that they can withdraw from the study at any time. Each patient will be given a study-specific Patient Information Sheet (PIS), as part of the informed consent process, to read and will be given adequate time to ask questions. In accordance with ICH GCP and 21 CFR 50, informed consent shall be documented using an ICF approved by the IECs/ IRBs. The ICF will be signed and personally dated by the patient (or patient's legal representative) and by the person who conducted the informed consent discussion.

In exceptional circumstances, such as a regional or national emergency declared by a governmental agency, consent may be collected through a remote solution if allowed through country and site regulations and following approval by the IEC/IRB. Implementation must have prior approval from the Sponsor (or its designee).

In case of ICF amendment while the patients are still included in the study, they must be re-consented to the most current version of the ICF(s). Where patients are no longer in the study, teams in charge of the amendment must define if those patients must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).

In addition to the ICF for the study, the patient will be asked if they would like to participate in the pharmacogenomic sampling section of the study. Consent for this will be in addition to the main consent. Lack of informed consent to participate in the pharmacogenomic sampling section of the study does not preclude patients from participating in the clinical study.

At selected sites, patients will be asked to participate in a biopsy sub-study. Consent for this will be in addition to the main study consent. Biopsies will not be conducted in patients if there is a contraindication to the procedure in the Investigator's opinion. Lack of consent to participate in the biopsy sub-study does not preclude patients from participating in the main clinical study.

In addition, the patient will be asked if the samples collected from them can be stored and used for possible future analyses. Lack of informed consent for future analysis of samples does not preclude patients from participating in the clinical study.

Informed consent will be documented in the patient's medical records, as required by 21 CFR Part 312.62. The patient should be given a copy of the PIS and their signed and dated ICF, and the original ICF should be filed in the ISF.

6.2.2 Demographic Information

Demographic information will be collected at the Screening Visit as follows:

- Age.
- Year of birth.

- Gender (sex).
- Race.
- Ethnicity.

6.2.3 Medical History

The Investigator will be responsible for review of the medical history (including AD history) of patients to ensure that they meet the criteria for eligibility for the study. This will include a review of the study inclusion and exclusion criteria, including review for drugs of abuse (see Section 6.4.6), which will be repeated at the Baseline Visit.

6.2.3.1 QuantiFERON®-TB Gold Blood Test

A whole blood sample will be collected from each patient at the Screening Visit for the QuantiFERON®-TB Gold blood test (see Section 6.7).

Detailed instructions for blood sample collection, preparation and shipping will be provided in a laboratory manual to be finalised before the samples are collected. Samples will be shipped to and analysed by PPD Central Labs.

Positive QuantiFERON®-TB Gold blood test is an exclusion criterion. If an indeterminate result is found at the first evaluable test, a retest should be performed as soon as possible. If the second evaluable test is negative, patient is not excluded. If the second evaluable test is either indeterminate or positive, patient is excluded. In the event of test cancelation, a retest should be performed as soon as possible, and the cancelation will not account as an evaluable test result for the procedure mentioned in this paragraph.

6.2.4 Concomitant Medications

Concomitant medications will be recorded at Screening and throughout the study at the timepoints outlined in the Schedule of Assessments (see Table 6-1, Table 6-2, Table 6-3 and Table 6-4).

Data should be collected for all medicines (including emollients and natural/herbal/prescription/over-the-counter/contraceptive etc). The following information should be recorded on the eCRF: drug/therapy name (product name), route, dose and units, frequency, indication, reference to AE if applicable, start date, end date or ongoing at the EOS.

6.3 Efficacy Assessments

The efficacy of KY1005 in the treatment of AD will be assessed using change in EASI, IGA, SCORAD Index and affected BSA. Investigator performed assessments should be carried out by the same assessor on each occasion for an individual patient. These assessments will be completed on an internet-enabled device. Patient reported outcomes will be assessed using the POEM, DLQI, HADS, ADCT and the NRS for pruritus. Patients will be required to use an internet-enabled device (eg, computer, mobile phone or tablet device) to complete an electronic diary to record the PROs in local languages where validated. Patients should bring their eDiary to visits and review with coordinators. Patients will be encouraged to continue completing diary information until their last visit.

Where possible, the PRO assessments completed at the study site are to be completed by patients prior to the completion of other study assessments and the administration of study drug.

All assessments will be performed at the timepoints outlined in the Schedule of Assessments (see Table 6-1, Table 6-2 and Table 6-3).

Sites should discuss study procedure compliance with the patients, as required.

6.3.1 Eczema Area Severity Index

The EASI is an Investigator-assessed validated tool used to measure the extent (area) and severity of AD [Hanifin 2001 Exp Dermatol]. A copy of the EASI is included in Section 17.2 (Appendix 2). This assessment will be completed using an internet-enabled device.

The Investigator will assess the severity of 4 disease characteristics (erythema [E], induration/papulation [I], excoriation (X) and lichenification [L]) in 4 body regions on a scale of zero (absent) to 3 (severe). In addition, the extent of involvement of 4 body regions (head/neck, trunk, upper extremities and lower extremities) will be assessed. The possible highest score for extent of involvement in each region is 100%. For each region, the percentage of BSA will be converted to an area score of zero (none in that region) to 6 (>90% to 100% of the entire region affected).

For each major region of the body (head, upper extremities, trunk and lower extremities), EASI score = (E + I + X + L) × Area Score. The total EASI score is the weighted total of the region EASI using the weights 10% (head), 20% (upper extremities), 30% (trunk) and 40% (lower extremities). The minimum possible EASI score is 0 and the maximum possible EASI score is 72, where a higher score indicates increased extent and severity of AD.

6.3.2 Investigator Global Assessment

The IGA is an Investigator--lead assessment scale used to determine severity of AD and clinical response to treatment. It is based on a 5-point scale, ranging from 0 (clear) to 4 (severe). A copy of the IGA is also included in Section 17.3 (Appendix 3).

This assessment will be completed using an internet-enabled device.

6.3.3 SCORing of Atopic Dermatitis Index

The SCORAD Index is a validated clinical tool that was developed to standardise the evaluation of the extent and severity of AD [SCORAD Dermatol Basel Switz 1993]. A copy of the SCORAD Index is included in Section 17.4 (Appendix 4). This assessment will be completed using an internet-enabled device.

To determine the extent of AD, the affected area (A) as a percentage of the whole body is determined, with a maximum score of 100% (head and neck [9%], upper limbs [9% each], lower limbs [18% each], anterior trunk [18%], back [18%], genitals [1%]). The severity (B) of 6 specific symptoms of AD (redness, swelling, oozing/crusting, scratch marks, skin thickening [lichenification], dryness [area where there is no inflammation]) is assessed on a 4-point scale, with a maximum score of 18: none (0), mild (1), moderate (2) or severe (3). Subjective symptoms (ie, itch and sleeplessness; C) are recorded as scored by the patient or relative on a visual analogue scale (VAS), where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20.

The SCORAD score for each patient is calculated as: A/5 + 7B/2 + C.

6.3.4 Body Surface Area Involvement of Atopic Dermatitis

Body surface area (BSA) affected by AD will be assessed for each section of the body (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined.

6.3.5 Patient Oriented Eczema Measure

The POEM is a tool used for monitoring atopic eczema severity. It focuses on the illness as experienced by the patient. This will be completed using an internet-enabled device. A copy of the POEM form is included in Section 17.5 (Appendix 5). The questionnaire consists of 7 questions pertaining to the symptoms of AD and their frequency. Scores are based on a scale of zero (no days) to 4 (every day in the last week) for each question, with a maximum score of 28 possible for all questions. A POEM total score is correlated to eczema severity (0-2 [clear or almost clear], 3-7 [mild], 8-16 [moderate], 17-24 [severe], 25-28 [very severe]).

6.3.6 Dermatology Life Quality Index

The DLQI is a dermatology-specific QoL instrument and is a simple, validated questionnaire. A copy of the DLQI is included in Section 17.6 (Appendix 6). This will be completed using an internet-enabled device.

The instrument consists of 10 questions pertaining to the effect of AD on QoL. Scores are based on a scale of "0" (not at all/not relevant/question unanswered) to "3" (very much/prevented work or studying), with a maximum score of 30 possible for all questions. The total score is correlated to the detrimental effect of AD on QoL (0-1 [no effect at all on patient's life], 2-5 [small effect], 6-10 [moderate effect], 11-20 [very large effect] and 21-30 [extremely large effect]).

6.3.7 Atopic Dermatitis Control Tool

The ADCT is a validated 6-item instrument with a 7-day recall period to measure AD disease control (Section 17.7 [Appendix 7]). This will be completed using an internet enabled device. The following domains are assessed: overall severity of symptoms, frequency of intense episodes of itching, severity of bother of itching, frequency of sleep impact, severity of daily activities impact, severity of mood or emotions impact. Each item is scored from 0 (none) to 4 (extreme). A total score of 7 or more points (derived by adding item scores) was identified during validation as an optimum threshold to identify patients whose AD is "not in control".

6.3.8 Hospital Anxiety and Depression Scale

The HADS is a validated 14-item PRO measure used to assess states of anxiety and depression over the past week. A copy of the HADS is included in Section 17.8 (Appendix 8). This will be completed using an internet-enabled device.

6.3.9 Numerical Rating Scale for Pruritus

The NRS for pruritus is an assessment tool that will be used to assess the patient's worst itch as a result of their AD in the previous 24 hours. This will be recorded daily, ideally in the morning, using an internet-enabled device with patients asked, "On a scale of "0" (no itch) to "10" (worst imaginable itch), how was your worst itch in the past 24 hours?" according to Section 17.9 (Appendix 9). Patients will additionally be asked to record NRS for 7 consecutive days immediately prior to Baseline. Sites will be encouraged to contact patients who have missed 2 consecutive e-diary entries to encourage patient compliance.

6.4 Safety and Tolerability Assessments

The Investigator will review results of safety assessments on a regular basis and the Sponsor must be kept fully informed of any clinically significant findings either at screening or subsequently during study conduct. All assessments will be performed at the timepoints outlined in the Schedule of Assessments (see Table 6-1, Table 6-2, Table 6-3 and Table 6-4).

6.4.1 Physical Examination

The Investigator will perform physical examinations throughout the study, consisting of assessment of general appearance, ears, eyes, nose, throat, mouth, neck, thyroid, skin, cardiovascular, respiratory, abdomen, neurological, musculoskeletal, lymph nodes and extremities.

6.4.2 Body Weight and Height

Body weight will be measured in kilograms (kg) and height in metres (m), with patients in light clothing and without shoes. Body weight will be assessed at Screening and during study treatment; height will be measured at Screening only.

Body mass index (BMI) will be calculated as follows:

$$\text{BMI} = \text{Weight (kg)} / \text{Height (m)}^2$$

6.4.3 Adverse Events

Investigators must carefully monitor patients for the occurrence of AEs, including clinical laboratory, vital signs and ECG variables. Assessments must be made of the seriousness, severity and relationship to the administration of study treatment (causality). Serious adverse events and specific AESI will require expedited reporting to the Sponsor. For details on definitions and reporting procedures see Section 8.1.

Adverse event assessments must be made by the Investigator or delegated to an appropriately trained and experienced physician. The Investigator is required to record the assessments in the eCRF and patient's medical notes. Any AEs already recorded and designated as "continuing" should be reviewed at each subsequent assessment.

During and following a patient's participation in this study, the Investigator must ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory values, related to the trial.

Adverse events and SAEs will be collected from the time of the patient signing the ICF until completion of the last visit. If an event that starts after the safety follow-up period is due to a late onset toxicity to study treatment, then it should be reported as an AE or SAE as applicable.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Sponsor should be notified.

6.4.4 Standard Laboratory Safety Tests

All standard safety laboratory parameters assessed will be evaluated centrally.

The standard laboratory safety tests consisting of haematology (full blood count [FBC]), clinical chemistry (electrolytes and non-fasting biochemistry) and urinalysis assessments defined in Table 6-5 will be performed throughout the study.

All WOCBP will also have a serum pregnancy test at Screening. Urine pregnancy tests will be performed pre-injection on IMP administration days, and at the early termination visit, Days 393 (Week 56), 449 (Week 64), and 477 (Week 68) of the safety follow-up period. These will be performed locally. If a urine pregnancy test result is positive, it must be confirmed by a serum pregnancy test.

For post-menopausal women only, a blood sample will also be taken at Screening for FSH.

Screening laboratory assessments may be repeated a maximum of once where initial results are in the Investigator's opinion, clinically significant and only provided the initial result is considered a temporary anomaly and there is a documented explanation as to the likely cause of the result (Section 4.6).

All laboratory reports should be reviewed, signed, and dated by a designated physician within 24 hours of receipt. These will be checked and verified by the Study Monitor during monitoring visits.

Table 6-5: Standard Laboratory SafetyTests

Category	Parameter
Haematology	WBCC and differentials, RBCC, RDW, Hb, HCT, nucleated red blood cells, platelet count, MCH, MCHC, MCV, and MPV
Clinical chemistry	Albumin, sodium, potassium, chloride, bicarbonate, urea, creatinine, glucose, calcium, phosphate, ALT, AST, GGT, LDH, alkaline phosphatase, total protein, iron, total bilirubin and CPK
Urinalysis	pH, protein, glucose, ketones and blood

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; GGT=gamma-glutamyl transferase; Hb=haemoglobin; HCT=haematocrit; LDH=lactate dehydrogenase; MCH=mean cell haemoglobin; MCHC=mean cell haemoglobin concentration; MCV=mean cell volume; MPV=mean platelet volume; RBCC=red blood cell count; RDW=red cell distribution width; WBCC=white blood cell count.

Assay methodology and procedures will be described in a laboratory manual to be finalised before the samples are collected. Samples will be shipped to and analysed by PPD Central Laboratory.

6.4.5 Virology

Blood samples for HIV and hepatitis virology tests (HBsAg and HBcAb and hepatitis C antibody, will be taken at the Screening Visit. [redacted] Any patients who are positive will be excluded from the study.

Assay methodology and procedures will be described in a Laboratory Manual to be finalised before the samples are collected. Samples will be shipped to and analysed by PPD Central Laboratory.

6.4.6 Drugs of Abuse Testing

History (within last 2 years) of current prescription drug or substance abuse, including alcohol, considered significant by the Investigator is an exclusion criterion for this study (see Section 4.3). Drug abuse is a patterned use of a substance in which the patient uses amounts or methods that are harmful to themselves or others during the study period. If the medical history suggests such abuse, then the Investigator should consider whether the patient meets the exclusion criteria. Drugs of abuse screening, including breath test, may be performed at the Investigator's discretion.

6.4.7 Vital Signs

Vital signs will be assessed throughout the study. On IMP administration Days 1 (Week 0), 29 (Week 4), 57 (Week 8), 85 (Week 12), and 113 (Week 16), vital signs will be measured pre-injection and at 15-, 30-, and 60-minutes post-injection. On all other IMP administration days, vital signs will be measured pre-injection and 30 minutes post-injection.

Evaluations of systolic and diastolic blood pressure, heart rate, and tympanic temperature will be performed (other methods may be used but they must be consistently used throughout the study for each individual patient). Heart rate and blood pressure will be taken after 5 minutes in the supine position.

Any changes from Baseline in blood pressure and heart rate findings judged to be clinically significant by the Investigator will be recorded as AEs. In such cases, vital signs will be repeated at appropriate intervals until they return to Baseline or to a level deemed acceptable by the Investigator or until the abnormality can be explained by an appropriate diagnosis.

Vital signs may be repeated a maximum of once where initial results are outside of the limits defined in the inclusion/exclusion criteria and only provided the initial result is considered a temporary anomaly and there is a documented explanation as to the likely cause of the result.

6.4.8 12-lead ECG

Standard 12-lead ECGs will be performed throughout the study after the patient has been supine for at least 5 minutes. All ECGs should be recorded with the patient in the same physical position. The ECG should be obtained either prior to the time of blood collection, or at least 15 minutes afterwards.

The ECG traces are to be reviewed by a qualified physician at the study site (physician to sign, date and record interpretation on ECG trace). The Investigator will enter a signed and dated clinical interpretation of the ECG trace in the CRF. Any ECG traces on heat sensitive paper must be photocopied before archiving.

6.4.9 Local Skin Reactions

[redacted]

Light pressure will be applied at the injection site and any pain, itchiness, tenderness, erythema, and induration will be recorded in the eCRF. Pain, itchiness and tenderness will be assessed according to the following scale:

Definitions of pain and tenderness:

- None nothing.
- Mild easily tolerated.
- Moderate interferes with daily activities.
- Severe prevents normal everyday activities or sleep.

The largest diameter of erythema and induration will be measured using a ruler, or a template supplied by the Sponsor.

6.5 Pharmacokinetic and Anti-drug Antibodies Assessments

6.5.1 Pharmacokinetic Procedures

Blood samples will be withdrawn periodically for KY1005 assay. Pharmacokinetic and ADA samples will be collected from all patients including those receiving Placebo.

6.5.1.1 Pharmacokinetic Sampling Schedule

Serum concentrations of KY1005 will be assessed from blood samples taken during the study using validated enzyme-linked immunosorbent assay (ELISA) bioanalytical methods. Assay methodologies and procedures will be described in analytical plans to be finalised before the start of sample analysis.

Samples will be collected at the timepoints specified in the Schedule of Assessments (see Table 6-1, Table 6-2 and Table 6-3). On IMP administration days, samples for serum concentration of KY1005 will be withdrawn pre-dose.

Tolerances for deviation from the nominal time of sampling are provided in the schedule of assessments (visit window). These tolerances indicate the best time to allow interpretation of data. However, samples taken outside these tolerances will be evaluated so should be taken. The exact date and time of sampling will be recorded. Samples may also be drawn for serum concentration, with prior agreement with the Medical Monitor, at unscheduled times.

6.5.1.2 Pharmacokinetic Sample Preparation and Shipment

The details of blood volume, type of tube, sample handling, storage and dispatch are described in the Laboratory Manual.

6.5.1.3 Pharmacokinetic Parameter Derivation

The following PK values will be derived for each patient receiving KY1005 and all KY1005 regimens:

- C_{max} following the first, or any doses where sampling permits. Peak concentrations following any doses where sampling permits.

- t_{max} following the first, or any doses where sampling permits.
- C_{min} following the first, second, third, fourth and any doses where sampling permits.

6.5.2 Anti-drug Antibody Procedures

Blood samples will be withdrawn periodically for anti-KY1005 antibody assays.

6.5.2.1 Anti-drug Antibody Sampling Schedule

Serum titres of anti-KY1005 antibodies will be assessed in blood samples taken during the study using a validated bioanalytical method. Characterisation of positive ADA samples, eg, KY1005 neutralising capacity, may be performed if required.

Samples will be collected at the timepoints specified in the Schedule of Assessments (see Table 6-1, Table 6-2, Table 6-3 and Table 6-4) and will be withdrawn before injection of IMP. Tolerances for deviation from the nominal time of sampling are provided in the schedule of assessments (visit window). These tolerances indicate the best time to allow interpretation of data. However, samples taken outside these tolerances will be evaluated and should therefore be collected. The exact date and time of sampling will be recorded on the eCRF.

[redacted]

6.5.2.2 Anti-drug Antibody Sample Preparation and Shipment

The details of blood volume, type of tube, sample handling, storage and dispatch are described in the Laboratory Manual.

[redacted]

6.6 Assessment of Pharmacodynamics Markers

[redacted]

[redacted]

[redacted]

6.7 Total Blood Volume

[redacted]

[redacted]

7 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, drug response and toxicity, and can help identify new drug targets or biomarkers that predict patient response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

[redacted]

Data and samples will be used in compliance with the information provided to patients in the section of the ICF related to future research.

All study patient data and samples will be coded such that no patient direct identifiers will be linked to them. Coded data and samples may be transferred to a Sponsor site (or a sub-contractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data.

The samples will be stored for a maximum of 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the

Sponsor (or its CRO) in writing. In such case, samples will be destroyed, and related coded data will be anonymised unless otherwise required by applicable laws.

Study patient coded data will be stored for future research for up to 25 years after the end of the study. If data are still considered of important scientific value after this period, coded data already available will be anonymised unless otherwise required by applicable laws (the same will apply to the data of a study patient who has requested the destruction of his/her samples).

Patient's coded data sets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalisation of the future research project report).

8 SAFETY MONITORING AND REPORTING

8.1 Definition of an Adverse Event

The ICH E6(R2) Good Clinical Practice Guideline defines an AE as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

An AE can include an undesirable medical condition occurring at any time, even if no investigational medicinal product has been administered. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere on the eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening are not considered AEs and will not be captured as AEs. Lack of efficacy or failure of expected pharmaceutical action per se will not be reported as an AE or a SAE. Such instances will be captured under the efficacy assessments. However, the signs symptoms and clinical sequelae resulting from lack of efficacy will be reported as an AE/SAE if they fulfil the definition of an AE or SAE.

This definition includes events occurring from the time of the patient giving informed consent until the 140 days after the last dose of IMP.

8.1.1 Adverse Events Categorisation, Recording, and Follow-up

Investigators must carefully monitor patients for the occurrence of AEs, including clinical laboratory, vital signs and ECG variables. Assessments must be made of the seriousness, severity and relationship to the administration of study treatment (causality). These assessments must be made by the Investigator or delegated to an appropriately trained and experienced physician. The Investigator must promptly record all identified AEs in the eCRF and patient medical notes.

The Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms, wherever possible. The Investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

During and following a patient's participation in this study, the Investigator must ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory values, related to the trial.

8.1.1.1 Severity of Adverse Events

Adverse events will be classified by the Investigator according to the following criteria:

- Mild (Grade 1 Common Terminology Criteria for Adverse Events [CTCAE]): Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate (Grade 2 CTCAE): Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Severe (≥ Grade 3 CTCAE): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden. Life-threatening consequences; urgent intervention indicated; Death related to AE.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of severity to be performed. Adverse events characterised as intermittent require documentation of onset and duration of each episode.

8.1.1.2 Causality of Adverse Events

The relationship of an AE to IMP administration will be classified by the Investigator according to the following:

- Related: The temporal relationship of the AE to IMP administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.
- Not related: The temporal relationship of the AE to IMP administration makes a causal relationship unlikely or remote, and other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

As this is a double-blind study, the causality assessment should be made under the assumption that the patient is receiving active study treatment. If considering unblinding, this assessment should be made prior to unblinding to avoid bias.

8.1.1.3 Follow-up of Adverse Events

During the study, all AEs will be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient discontinued the study.

Any AEs already recorded and designated as "continuing" should be reviewed at each subsequent assessment for their final outcome.

For any AE which remains unresolved after completion of the trial, detailed evaluation and follow-up should be attempted until the AE has been resolved or a reasonable explanation for its persistence is found.

8.1.2 Serious Adverse Event Assessment and Reporting to Sponsor

The Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets criteria for classification as a SAE requiring immediate notification to the Sponsor (or designee).

A SAE is any AE that:

- Results in death.
- Is life-threatening (ie, in the opinion of the Investigator, the patient is at immediate risk of death from the AE).
- Results in inpatient hospitalisation or prolongation of existing hospitalisation (hospitalisation is defined as an inpatient admission, regardless of length of stay; hospital admissions for procedures planned before administration of IMP do not need to be reported).
- Hospitalisation or prolongation of hospitalisation in the absence of a precipitating AE is not in itself an SAE. Examples include:
    - Social admission (eg, patient has no place to sleep);
    - Protocol-specified admission during a clinical study (eg, for a procedure required by the study protocol);
    - Optional admission not associated with a precipitating AE (eg, for elective cosmetic surgery);
    - Surgery that was planned prior to study enrolment (appropriate documentation is required for these cases) and was not caused by worsening of a pre-existing condition.
- Results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions.
- Results in congenital anomaly/birth defect in the offspring of a patient who received the IMP.
- Constitutes an important medical event that may not result in death, be life-threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

The Investigator must report all SAEs, regardless of treatment group or suspected relationship to investigational medicinal product, to the Sponsor or designee **within 24 hours** of knowledge of the event.

The following information is the minimum that must be provided:

- Investigator/reporter's name and contact details.
- Patient identification number.
- Description of the SAE, including criteria for seriousness and initial causality assessment.

The additional information included in the SAE form must be provided to Sponsor or designee as soon as it is available. The Investigator should always provide an assessment of causality for each event reported. Upon receipt of the initial report, the Investigator's causality assessment will be requested if it was not provided with the initial report.

The procedures for completing and transmitting SAE reports are provided in Section 17.11 (Appendix 11).

8.1.3 Adverse Events of Special Interest

Adverse events of special interest, defined below, will be reported to Sponsor or designee within 24 hours of learning of the event:

- Systemic or localised allergic reactions that require immediate treatment*.
- Severe injection site reactions that last longer than 24 hours.
- Any severe or opportunistic viral, bacterial or fungal infection and/or any uncommon, unanticipated or persistent infection (viral, parasitic, bacterial, or fungal).
- Any malignancy.
- Increase in alanine transaminase (ALT) >3 × upper limit of normal (ULN); see the "Increase in ALT" flow chart in Section 17.12 (Appendix 12).

The special situations of:

- Symptomatic overdose (serious or non-serious) with IMP (any administration that is twice or more than the intended dose administered in less than 3 weeks [21 days]).
- Pregnancy - discussed separately in Section 8.3.

* In the event that a patient has a systemic allergic reaction that requires immediate treatment, blood samples should be withdrawn as soon as feasible (not to interfere with treatment of the reaction) for the analysis of ADA, serum tryptase, C1q, C1 inhibitor, C3 and C4, and repeated at 4 hours and 24 hours. Detailed instructions for sample collection, preparation and shipping will be provided in a Laboratory Manual.

8.1.4 Deaths

All AEs resulting in death during the study or follow-up period must be reported as SAEs irrespective of the causality, and the Investigator should supply the Sponsor and IRB/IEC if applicable, with as much detail of the events leading to death as possible immediately and any additional requested information (eg, autopsy reports and terminal medical reports).

The convention for recording death is as follows:

- AE term: lead/exact cause of death (eg, multiple organ failure, pneumonia, myocardial infarction).

- Outcome: fatal.
- Causality assessment.

The only exception is if the cause of death is unknown (ie, sudden or unexplained death), in which case the AE term may be "death" or "sudden death". As many details about the fatal cases should be provided as possible and available.

8.1.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.1.6 Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC, and Investigators.

Serious adverse events that are considered expected will be specified in the reference safety information (specify IB or label), as applicable.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.1.7 Reporting to Regulatory Authorities, IECs/IRBs and other Investigators

The Sponsor will ensure that processes are in place for submission of reports of SUSARs and special situations etc occurring during the study to the regulatory authorities, IECs/IRBs and other Investigators concerned by the investigational medicinal product, as applicable. Reporting will be performed by the Investigator or the Sponsor (or designee) in accordance with the applicable regulatory requirements.

Details of procedures and responsibilities will be documented in a Safety/SAE management plan for the study.

8.2 Emergency Procedures

Each patient will be given an emergency card at the enrolment/randomisation visit and asked to carry it with them at all times in case of an emergency. The card will include the following study information as a minimum: a patient identifier, investigational drug name and name and 24-hour telephone number of the Investigator (or medically qualified designee). Patients should be asked to destroy this card at the end of the study.

If the Investigator needs urgent advice regarding the management of an SAE or any other safety issue, an 'on call' contracted medical advisor is available 24 hours a day by telephone, as per the details below.

Emergency contact for medical monitor is specified in the STUDY PERSONNEL section.

8.2.1 Emergency Treatment Code-break

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's intervention assignment is warranted (eg, in case of available antidote). Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, he/she may, at his/her discretion, contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable. If the code is broken upon Investigator's request, the participant must withdraw from IMP administration and the patient should return for a final study assessment (see Section 9.2).

8.3 Pregnancy

8.3.1 Maternal Exposure

If a patient becomes pregnant during the study, IMP should be discontinued immediately.

Although pregnancy is not considered an AE it does require reporting expeditiously with follow-up to an outcome, for up to 6 months post-partum, for mother and infant. If any study patient is found to be pregnant while enrolled in the study, the Investigator must submit a pregnancy report form within 24 hours of becoming aware of confirmation of the pregnancy (see Section 17.10 - Appendix 10 for a flow chart of the process).

Any event of pregnancy that occurs during the study (including long-term follow-up) or up to 5 months following the last dose of IMP will be reported. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

A follow-up report will be provided once the outcome of the pregnancy is definitive and the partner has given consent using a form approved by the relevant IEC for her personal medical information to be discussed, if applicable. Follow-up of offspring for 6 months is desirable. In the event of any abnormality, the neonate will also be followed up if there is parental consent in place for such information to be discussed.

8.3.2 Paternal Exposure

Pregnancy of a patient's partner is not considered to be an AE. However, any conception occurring from the date of dosing until 5 months after last dosing will be reported within 24 hours on pregnancy report form and followed up for its outcome.

9 WITHDRAWAL OF PATIENTS FROM TREATMENT AND/OR THE STUDY

Patients are free to withdraw from participation in the study at any time, without prejudice to their further care. In some circumstances, patients may be discontinued from study treatment but continue certain study assessments.

The Investigator should discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment will be discontinued and/or patients may be withdrawn from the study under the following circumstances:

1. Withdrawal of consent.
2. Severe noncompliance with the protocol as judged by the Investigator and/or the Sponsor.
3. Patients incorrectly initiated on study treatment (eg, patient has been determined to have met one or more of the exclusion criteria for study participation at study entry and continuing study treatment might constitute a safety risk).
4. AEs that, in the opinion of the Investigator or the Medical Monitor, contraindicate further dosing.
5. Pregnancy.
6. Disease progression in the investigator's point of view.
7. Study terminated by the Sponsor. This includes any decision on study termination after IDMC recommendation. The IDMC reviews and evaluates accumulating blinded and unblinded if deemed necessary safety and efficacy data (including by treatment arm or patient) to ensure the safety of trial subjects (please refer to Section 3.8 of the protocol).
8. Lost to follow-up.

9.1 Discontinuation of the Patient from Investigational Medicinal Product

9.1.1 Reasons for Permanent Discontinuation of Investigational Medicinal Product

The IMP will be permanently discontinued for any of the following reasons:

1. Anaphylactic reaction or other severe systemic reaction to the IMP injection.
2. Diagnosis of a malignancy during the study.
3. Major surgery.
4. Severe intercurrent illness.
5. Evidence of confirmed pregnancy.

6. Any infection that is opportunistic, such as active TB, non-tuberculous mycobacterial infections and other infections whose nature or course may suggest an immunocompromised status.
7. Severe laboratory abnormalities:
   - Absolute neutrophil count $\leq 0.5 \times 10^9$/L;
   - Platelet count $\leq 50 \times 10^9$/L;
   - Serum ALT >3 ULN and Total Bilirubin >2 ULN;
   - Serum ALT >5 ULN if baseline ALT ≤2 ULN or ALT >8 ULN if baseline ALT >2 ULN.

   Note: If the laboratory abnormality is considered causally related to the IMP, the IMP will be permanently discontinued. In cases where a causal relationship to the IMP can be reasonably excluded (ie, an alternative cause is evident), the IMP will be discontinued but it may be resumed when the laboratory abnormality is sufficiently normalised.
8. If a subject experiences an adverse event assessed as ≥ Grade 3 CTCAE [severe; see Section 8.1.1.1] (or ≥ Grade 2 CTCAE [moderate; see Section 8.1.1.1] for the System Organ Classes of Cardiac disorders and Blood and Lymphatic disorders) per CTCAE v5.0, the subject should be discontinued from further dosing. Such subjects should not be discontinued from the study, but they should be monitored by their medical practitioner and study investigator until the adverse event (AE) resolves or stabilizes.

Other reasons that may lead to the permanent discontinuation of IMP include:

- Treatment with any prohibited systemic concomitant medication or procedure (see Section 5.3.2 and Section 5.3.4).
- Treatment with any topical concomitant rescue therapy in the first 14 days from Baseline (see Section 5.3.4).
- After Day 14, treatment with topical concomitant rescue therapy on more than 2 occasions during study participation. The maximum permitted duration of topical concomitant rescue therapy on either occasion is 2 consecutive weeks. If duration of treatment is exceeded on either occasion this will also lead to permanent discontinuation of IMP.

9.1.2 Reasons for Temporary Discontinuation of Investigational Medicinal Product

Dosing of IMP should be temporarily interrupted for the following reasons:

1. Clinically important laboratory abnormalities, such as:
   - Absolute neutrophil count $\leq 1.0 \times 10^9$/L but $>0.5 \times 10^9$/L;
   - Platelet count $\leq 100 \times 10^9$/L but $>50 \times 10^9$/L;
   - Creatine phosphokinase >10 × ULN.
2. Other intercurrent illness.
3. An infection requiring systemic treatment with antibiotic, antifungal, antiviral, antiparasitic or antiprotozoal agents, or requiring oral treatment with such agents for more than 2 weeks.

9.1.2.1 Re-challenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned adverse event was unlikely and if the selection criteria for the study are still met (refer to Section 4).

If there is to be a delay to any dosing of IMP outside of the permitted visit windows as per the Schedule of Assessments (Section 6.1), the Investigator must consult with, and receive written confirmation that dosing can be rescheduled from, the Medical Monitor.

9.1.2.1.1 Study intervention restart or rechallenge after liver stopping criteria met

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

9.1.3 Follow-up of Patients Off Treatment

If a patient discontinues study treatment prematurely, she/he will be encouraged to remain in the study to complete all remaining study visits and to participate in all assessments according to the Schedule of Assessments. Their study data collected during their continued involvement is important to the study efficacy analysis and study value.

If a patient permanently withdraws from study treatment early but consent is retained, study assessments may be continued until Day 169 (Week 24) for patients who withdraw from study treatment in the first study period (and who are therefore no longer eligible for consideration for the LTE at Day 169 (Week 24) or progression to the next study period), or until Day 365 (Week 52) in patients who withdraw from study treatment after Day 169 (Week 24) and who decide not to participate in or are **not** eligible for the LTE study. This may be followed by the safety follow-up according to the Schedule of Assessments (Section 6.1).

If a patient chooses not to attend remaining visits in the event of withdrawal from study treatment early before Day 169 (Week 24) or Day 365 (Week 52), they will instead enter the safety follow-up and complete their assessments as per the Schedule of Assessments (Section 6.1).

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up, and evaluations should resume according to the protocol.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule.

- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient or next of kin by, for example, repeat telephone calls, certified letter to the patient's last known mailing address, or local equivalent methods. These contact attempts should be documented in the patient's medical record.
- Efforts to reach the patient should continue until the end of the study. Should the patient be unreachable at the end of the study, the patient should be considered to be lost to follow-up.

9.1.4 Discontinuation of the Patient from Study

Patients are free to withdraw from the study at any time without prejudice to further treatment. Patients who withdraw consent for further participation in the study will not receive any further IMP or further study assessments.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AEs. If a patient withdraws consent, they will be specifically asked if they are withdrawing consent for: all further participation in the study including any further follow-up (eg, telephone calls), and/or withdrawal of consent for the use of any samples.

9.2 End of Treatment and End of Study Procedures

At the EOS Visit (defined in Section 3.4), patients will undergo the procedures specified in the Schedule of Assessments. Following withdrawal for any reason, patients will attend an early termination visit and will undergo the procedures specified in the applicable Schedule of Assessments (Table 6-1, Table 6-2, Table 6-3 and Table 6-4), if possible. All data available for the patient at the time of withdrawal and all reasons for withdrawal, must be recorded in the eCRF.

9.3 Study Discontinuation

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. The study may be stopped if, in the judgment of the Sponsor, patients are placed at undue risk because of clinically significant findings that:

- Meet individual stopping criteria or are otherwise considered significant.
- Are assessed as causally related to study treatment.
- Are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

Reasons for the early closure of a study site by the Sponsor may include, but are not limited to, the following:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study intervention development.

9.4 Patient Replacement Policy

Patients who have been dosed will not be replaced.

Patients who are ineligible for study enrolment for reasons that are temporary, or who are unable to receive the first dose of study drug within the allowed Screening window for administrative reasons may be rescreened once after agreement to do so has been obtained in writing from the Medical Monitor.

10 STATISTICAL CONSIDERATIONS

An SAP based on the primary and secondary endpoints will be written and finalised before the study closure, ie, before database closure and unblinding of the randomisation code. The SAP will provide full details of the analyses, the data displays and the algorithms to be used for data derivations.

For all assessments, Baseline is defined as last recorded measurement prior to first IMP administration unless otherwise stated.

All safety and statistical programming, including PK analysis, will be conducted with Statistical Analysis System (SAS)® version 9.4 or higher for Windows (SAS Institute Inc., Cary, North Carolina, United States of America [USA]).

10.1 Sample Size Determination

A sample size of 350 patients (70 patients / group) in the target population, (adult with moderate-to-severe AD who have a documented history, within 6 months prior to Baseline, of either inadequate response to topical treatments or inadvisability of topical treatments), randomised 1:1:1:1:1 to 4 KY1005 groups or matching Placebo group is estimated [redacted] to detect a pairwise difference in means between each KY1005 and Placebo with respect to the percentage change in EASI from Baseline to Day 113 (Week 16), based on a 2-sided 2-sample equal-variance t-test.

[redacted]

10.2 Estimands and Intercurrent Event

[redacted]

[redacted]

[redacted]

10.3 Analysis Sets

10.3.1 Full Analysis Set

The full analysis set (FAS) includes all randomised patients. Efficacy analysis will be based on treatment allocated at randomisation which will be stratified by disease severity (moderate/severe) and region.

10.3.2 Safety Set

The safety set (SAF) will consist of all patients who take at least one dose of study treatment, including Placebo. Safety analysis will be based on actual treatment received.

10.3.3 Pharmacokinetic Set

The PK set will consist of all randomised and treated patients in the SAF with a Baseline assessment and at least one post-Baseline PK sample (with adequate documentation of dosing and sampling dates and times).

10.3.4 Anti-drug Antibody Set

The ADA set will consist of all randomised and treated patients in the SAF with a Baseline ADA result (positive, negative or inconclusive) and at least one post-Baseline ADA result (positive, negative or inconclusive).

10.4 Statistical Analyses

Full details of the statistical analyses of the data will be documented in an agreed SAP, which will be finalised prior to locking the database. Analyses will be performed by treatment regimen.

For continuous variables, descriptive statistics will include: the number of patients, mean, median, SD, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

10.4.1 Demographic and Baseline Characteristics

Demographic variables (age, gender and ethnicity) and medical history (coded according to the Medical Dictionary for Regulatory Activities [MedDRA]) will be summarised by treatment regime for FAS and SAF. Body weight, height and BMI will also be summarised by treatment regimen.

10.4.2 Efficacy Analysis

An overall test for the treatment effect of KY1005 will be conducted. Pairwise comparisons of each KY1005 treatment group versus Placebo group will be performed. [redacted]

For the continuous endpoints

An analysis of covariance (ANCOVA) model will be used. This model includes treatment, randomisation strata (region, disease severity) as fixed effects, and baseline value as a covariate. [redacted]

A mixed-effect model with repeated measures (MMRM) will be used as a sensitivity analysis for primary and continuous key secondary endpoints. This model includes the factors (fixed effects) for treatment, randomisation strata (region, disease severity), visit, treatment-by-visit interaction, and relevant baseline value. Within the framework of MMRM, the treatment difference will be tested at the pre-specified primary timepoint, Day 113 (Week 16), as well as at the other timepoints by timepoint-specific contrasts from the MMRM model. [redacted]

For the categorical endpoints

Cochran-Mantel-Haenszel test stratified by randomisation strata (region, disease severity) will be used at the analysis timepoint. [redacted]

Other sensitivity analysis might be performed and details will be specified in the SAP.

Data will be presented graphically, where applicable, and with summary statistics by visit and by treatment regimen.

10.4.2.1 Primary Analysis

The primary efficacy endpoint is the percentage change in EASI from Baseline to Day 113 (Week 16). This will be assessed using an ANCOVA model.

The primary analysis will be conducted on the FAS after all patients have reached the Day 169 (Week 24) visit/early termination.

[redacted]

10.4.2.2 Secondary Analysis

The key secondary efficacy endpoints for the study are:

- Percentage change from Baseline in EASI at Day 169 (Week 24).
- Percentage of patients with at least a 75% reduction from Baseline in EASI (EASI 75) at Days 113 (Week 16) and 169 (Week 24).
- Percentage of patients with a response of IGA 0 or 1 and a reduction from Baseline of ≥2 points at Days 113 (Week 16) and 169 (Week 24).
- Proportion of patients with improvement (reduction) of weekly average of pruritus NRS ≥4 with a Baseline pruritis NRS of ≥4 from Baseline to Days 113 (Week 16) and 169 (Week 24).

Additional secondary efficacy endpoints for the study are:

- Absolute change from Baseline in EASI at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24).
- Percentage change from Baseline in EASI at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12) and 141 (Week 20).
- Percentage of patients with at least a 50% reduction from Baseline in EASI (EASI 50) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24).
- Percentage of patients with at least a 75% reduction from Baseline in EASI (EASI 75) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12)and 141 (Week 20).
- Percentage of patients with at least a 90% reduction from Baseline in EASI (EASI 90) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24).
- Percentage of patients with a 100% reduction from Baseline in EASI (EASI 100) at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12), 113 (Week 16), 141 (Week 20) and 169 (Week 24).
- Change in IGA from Baseline to Day 113 (Week 16) and over time.
- Percentage of patients with a response of IGA 0 or 1 and a reduction from Baseline of ≥2 points at Days 15 (Week 2), 29 (Week 4), 57 (Week 8), 85 (Week 12) and 141 (Week 20).
- Absolute and percentage change in SCORAD Index from Baseline to Day 169 (Week 24) and over time.
- Absolute and Percentage change in affected BSA from Baseline to Day 169 (Week 24) and over time.
- Absolute and Percentage change in POEM from Baseline to Day 169 (Week 24) and over time.
- Absolute and Percentage change in DLQI from Baseline to Day 169 (Week 24) and over time.

- Absolute and Percentage change in ADCT from Baseline to Day 169 (Week 24) and over time.
- Absolute and Percentage change in HADS from Baseline to Day 169 (Week 24) and over time.
- Absolute and Percentage change in weekly average of pruritus NRS from Baseline to Day 169 (Week 24) and over time.
- Proportion of patients with improvement (reduction) of weekly average of pruritus NRS ≥3 with a Baseline pruritis NRS of ≥3 from Baseline to Days 113 (Week 16) and 169 (Week 24).
- Time to loss of EASI 75 in patients randomised to withdrawal post-Week 24.
- Time to loss of IGA 0/1 in patients randomised to withdrawal post-Week 24.
- Time to loss of EASI 50 in patients randomised to withdrawal post-Week 24.

10.4.2.3 Exploratory Analysis

[redacted]

10.4.2.4 Safety Analysis

All safety data will be included in the patient data listings.

Summaries will be presented by treatment regime and by timepoint and will be summarised for the SAF.

10.4.2.4.1 Adverse Events

The primary safety endpoint is the incidence of TEAEs.

All AEs in the clinical trial database will be coded according to MedDRA, which will be used to summarise AEs by primary System Organ Class (SOC) and Preferred Term (PT). All AEs will be displayed in listings.

A TEAE is defined as an AE observed starting after the first administration of IMP up until 140 days after the last IMP administration. All TEAEs collected during the main study (to Day 169 [Week 24]) will be summarised. Additionally, all TEAEs collected during the second study period in those patients who achieve ≥ EASI 75 or who attain IGA 0/1 response following 24 weeks of treatment will be summarised (to Day 365 [Week 52]).

The number and percentage of patients with TEAEs and the number of TEAEs will be summarised in each KY1005 treatment regimen and in the Placebo group.

The number and percentage of patients with TEAEs/AESIs will be further tabulated by causality and severity (mild, moderate and severe) in each KY1005 treatment regime and in the Placebo group.

In addition, the number and percentage of patients with SAEs, TEAEs leading to treatment discontinuation, TEAEs leading to study discontinuation and AEs leading to death will be summarised in each KY1005 treatment regimen and in the Placebo group.

Adverse events will be listed by treatment allocation, grouped by primary SOC and sub-grouped by PT and causality.

10.4.2.4.2 Concomitant Medications

Concomitant medications will be coded using the WHO Drug Dictionary and will be summarised in incidence tables by Drug Class and Preferred name, and by treatment regimen.

10.4.2.5 Vital Signs

At each timepoint, absolute values and change from Baseline of blood pressure, heart rate and temperature will be summarised with number of patients (n), mean, SD, median, minimum and maximum values. The number of available observations and out of range values (absolute and percentage) will be presented. Values outside the reference range will be flagged in the listing.

10.4.2.6 Safety Laboratory Tests

At each timepoint, absolute values and change from Baseline of clinical laboratory variables will be summarised with n, mean, SD, median, minimum and maximum values. The number of available observations and out-of-range values (absolute and in percentage) will be presented. All laboratory data (including re-check values if present) will be listed chronologically.

10.4.2.7 Virology

Positive samples for HIV, HBsAg, HBcAb and hepatitis C at the Screening Visit will be listed by patient.

10.4.2.8 12-lead Electrocardiograms

At each timepoint, absolute values and change from Baseline of ECG numeric variables will be summarised with n, mean, SD, standard error of the mean (SEM), median, minimum and maximum values. The number of available observations and out-of-range values (absolute and in percentage) will be presented. Values outside the reference range will be flagged in the listing. The Investigator's interpretation of 12-lead ECGs will be listed only.

10.4.2.9 Physical Examination

Physical examination findings will be listed by treatment regimen and by patient only.

10.4.2.10 Local Skin Reactions

Findings from examination of local skin reactions will be listed by treatment regimen and by patient only.

10.4.3 Pharmacokinetic Analysis

Serum KY1005 concentrations will be summarised by treatment group and visit using descriptive statistics. Serum concentration time profiles will be provided by treatment group. Additional plots will be prepared, as deemed necessary. Serum KY1005 concentrations might be used for population PK modeling if considered necessary and the results of population PK modeling will be reported separately from the CSR.

Further details will be provided in SAP.

10.4.4 Pharmacodynamic Analysis

The PD endpoint planned for this study is:

- Anti-KY1005 antibody titre and number of patients with positive response.

Data will be presented graphically, where applicable, and with summary statistics by visit and by treatment regime.

Statistical analysis of this endpoint will be defined in the SAP.

10.4.5 Handling of Withdrawals and Missing Data

[redacted]

Other details for handling missing data will be specified in the SAP.

10.4.6 Protocol Deviations

Any inadvertent protocol deviations that occur during the conduct of the study must be fully documented by the Investigator or authorised designee and the Sponsor notified. The statistical impact of important protocol deviations will be assessed, and the details provided in the SAP.

10.4.7 Other analysis

Data collected regarding the impact of the COVID-19 or other pandemics on the participants, will be summarized (eg, discontinuation due to COVID-19). Any additional analyses and methods required to investigate the impact of COVID-19 or other pandemics requiring public health emergency on the efficacy (eg, missing data due to COVID-19) and safety will be detailed in the SAP.

10.4.8 Interim analysis

An interim analysis will be planned when approximately [redacted] participants in each arm complete the Week 16 assessments. The interim analysis will evaluate the percentage change in EASI from baseline to Day 113 (Week 16) and proportions of participants with EASI 75 at Day 113 (Week 16), as well as the other available data as needed. [redacted] In order to maintain the further double-blinded conduct of the study, the Study Team will be kept blinded on the individual participant's treatment group assignment. An independent team will be formed to perform this analysis. More details will be specified in the statistical analysis plan for the planned interim analysis

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Monitoring

The Sponsor will ensure the approval of the assignment of an appropriately qualified monitor(s) who will be responsible for visiting the site at intervals throughout the study in order to verify adherence to the protocol, completeness and accuracy of the data entered in the eCRFs and to perform source data verification (SDV) of data recorded in the eCRFs, in accordance with applicable regulations, SOPs and the monitoring plan.

The monitoring plan will contain monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring).

The Investigator is responsible for the validity of all data collected at the site and should maintain adequate and accurate records and source data in accordance with the GCP principles of data integrity. Any source data changes should be traceable and original data not obscured.

The eCRF is expected to be completed on an ongoing basis to allow regular review by the study monitor, both remotely and during site visits.

The Study Monitor will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the Investigator and should ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented. Additionally, the Study Monitor will provide a written report, including copies of correspondence with the Investigator and site study staff, to the Sponsor, following each visit.

The frequency and nature of monitoring will be agreed with the Sponsor and documented prior to commencement of the study. The monitor must have direct access to patient medical records and other study-related source documents. The Investigator and study staff will be expected to co-operate with the monitor, to be available during the monitoring visit to answer questions and to ensure that any problems detected are resolved in a timely manner.

11.1.1 Audits and Inspections

In accordance with the ICH E6(R2) GCP guideline, the Sponsor may select this study for audit. During the audit, the Sponsor/Sponsor representative will carry out an inspection of site facilities (eg, pharmacy, drug storage areas, laboratory) and review study-related records to evaluate the study compliance with the Sponsor/vendor SOPs, protocol, ICH E6(R2) GCP guideline, applicable parts of 21 CFR and local regulations. The Investigator must also agree to inspection of all study documents by the regulatory authorities and the IEC/IRB.

The Investigator and site personnel should be available to provide information and answer questions as necessary. Should the Investigator be notified of a regulatory inspection involving this study, they must notify the Sponsor immediately.

11.2 Data Quality Assurance

Quality assurance and quality control systems will be implemented and maintained using written SOPs to ensure that the trial is conducted, and that the data are generated, recorded and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

12 REGULATORY AND ETHICAL CONSIDERATIONS

The study will be conducted in compliance with the protocol, informed consent regulations, the general principles of the Declaration of Helsinki and the International Conference on Harmonisation (ICH) E6(R2) guidelines related to GCP. In addition, the study will adhere to all applicable local regulatory requirements. IEC/IRB Approval.

The study protocol, PIS, ICF, IB, available safety information, any patient-facing documents (eg, Patient Emergency Card), any patient recruitment materials (eg, advertisements), information about payments and compensation available to the patients and documentation evidencing the Investigator's qualifications and any other written information regarding this study to be provided to a patient or patient's legal representative will be submitted to the IEC/IRB for ethical review and approval if required by local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

The Investigator/Sponsor will follow all necessary regulations to ensure appropriate, initial, and ongoing, IEC/IRB study review. The Investigator/Sponsor (as appropriate) must submit and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by the Sponsor whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IEC/IRB.

If applicable, the Investigator will notify the IEC/IRB within 90 days of the end of the study (as defined in Section 3.4), or if the study terminates early, the Investigator must notify the IEC/IRB within 15 days of the termination. A reason for the early termination must be provided. The Sponsor will either prepare or review all submission documents prior to submission to the IEC/IRB.

Safety updates for KY1005 will be prepared by the Sponsor as required, for submission to the relevant IEC/IRB. Investigator/Sponsor will ensure all required safety updates including all

necessary SUSAR notifications are submitted to the IEC/IRB in accordance with relevant legislation and guidance.

The Investigator will inform the Sponsor if the IEC/IRB suspends or terminates the trial.

12.1 Regulatory Approval

As required by local regulations, the Sponsor will ensure approval of the appropriate regulatory bodies is obtained prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happens only after approval by the relevant regulatory authorities.

The Sponsor will notify the relevant regulatory authorities about end of study or early study termination within required timelines and in case of early termination will provide the reasons for it.

Safety updates for KY1005 will be prepared by the Sponsor as required, for submission to the relevant regulatory authority.

12.2 Patient Confidentiality and Data Protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy and Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The Sponsor is responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sponsor databases, including Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor will take all appropriate measures to safeguard and prevent access to this data by any unauthorised third party.

Protection of patient data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Patient race and ethnicity will be collected in this study because they may modify the drug response and are required by regulatory agencies. They will not be collected in countries where this is prohibited by local regulation.

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor or its service providers will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor. For all patients enrolled into the trial, the Investigator must maintain a list of names and identifying information (eg, date of birth, patient identification code, date of study enrolment). The patient identification code list will be kept by the Investigator in the ISF.
- The patient will be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.

- The patient will be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. The patient's consent to direct access to his/her original medical records for data verification purposes must be obtained prior to a patient's participation in the study.
- Patients must be informed that their study-related data will be used for the whole "drug development programme", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow the Sponsor to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any Sponsor service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sponsor (via link available on Sponsor website), although this may limit a professional's ability to participate in the study.
- Personal data can be communicated to the following recipients:
  - Personnel within the Sponsor or partners or service providers involved in the study;
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognised by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by the sponsor in accordance with the requirement of European law.
- Professionals have the possibility to lodge a complaint relating to data protection with a competent local regulatory authority.
- Personal data of professionals will be retained by the Sponsor for up to thirty (30) years, unless further retention is required by applicable regulations.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sponsor via the link provided on the Sponsor's website.

12.3 Protocol Amendments

The Investigator will not implement any changes to the protocol without approval from the Sponsor, the regulatory authority and IRB/IEC (and other approving bodies), if required, except where necessary to eliminate immediate hazards to the study patients, or when the changes involve only logistical or administrative aspects of the study.

The Sponsor will not permit or approve any waivers from the approved protocol.

Modifications to the protocol will be made as a protocol amendment.

Substantial amendments to the protocol are those likely to have a significant impact on:

- The safety, or physical or mental integrity of the patients.
- The scientific value of the trial.

Non-substantial amendments (eg, changes in telephone numbers, etc) will not require prior submission to the regulatory authority and the IRB/IEC or other approving body unless requested.

12.4 Principal Investigator Responsibilities

Principal Investigator responsibilities are set out in the ICH E6(R2) Guideline for GCP, applicable parts of 21 CFR and in the local regulations. Sponsor staff or an authorised representative will evaluate and approve all Investigators who in turn will select their staff.

The PI must show that they are appropriately qualified, registered and have the time, resources and expertise needed to carry out the study.

If there are changes to the Investigator's status or a change in PI, the Sponsor should be informed.

The PI must ensure that all persons assisting with the study are appropriately qualified and trained for the role they will perform and are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The PI must ensure that the facilities and number of staff available are adequate to conduct the trial properly and safely.

The PI is responsible for supervising any individual or party to whom he/she delegates trial related duties and functions and will maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

If the PI contracts any vendors to work on the study, he/she must ensure appropriate oversight of said vendors and must obtain approval from the Sponsor for such work to be subcontracted.

The PI is responsible for the validity of all data collected at site (see Section 13).

13 DATA HANDLING AND RECORD KEEPING

13.1 Data Capture

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported and should ensure that study staff are adequately trained and have sufficient time to fulfil their responsibilities.

The PI must ensure that adequate and accurate records and source data are maintained in accordance with the GCP principles of data integrity. Any source data changes should be traceable and original data not obscured.

An eCRF, Rave, a 21 CFR Part 11-compliant data capture system provided by Medidata will be used for this study.

In addition, patients will be asked to enter data into electronic patient-reported outcome (ePRO), which will form patient diaries and enable recording of patient daily assessments.

The results from screening and data collected during the study will be entered into Medidata Rave by the Investigator or delegate. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. The Investigator will electronically sign the eCRF indicating that the data in the eCRF have been assessed and agreed.

At the Sponsor's discretion, SDV may be performed on all data items or a percentage thereof. The study monitoring plan will document the approach to be taken for SDV.

13.2 Data Management

Detailed data entry instructions will be provided in the eCRF Completion Guidelines.

Data management and handling of the data will be conducted according to Data Validation Manual, the CRO equivalent of the study-specific data management plan (DMP), ICH guidelines and PPD SOPs.

The electronic data capture (EDC) system, Medidata Rave will be used to capture data on eCRFs in the study. Authorised study site personnel will perform data entry. Changes to the data in the eCRF will be made at the site by study site personnel. The PPD Data Management Team will perform data cleaning and handling of queries. The data will be subjected to data review according to PPD SOPs to ensure accuracy of the collected data.

Medidata Rave includes full audit trail with functionality for data capture, tracking and documentation of any changes to identify the person and timing of entering or changing the data. Electronic signatures will be used to sign off the eCRFs.

Results of clinical laboratory and PK analyses will be sent electronically to PPD and merged with the clinical datasets for inclusion in Study Data Tabulation Model (SDTM) transfers.

Before database lock, a reconciliation will be performed between the SAEs entered in the safety database and the study clinical database. After the database has been declared complete and accurate, the database will be locked and the database will be exported as SAS® datasets for statistical analysis. Any deviations (ie, discrepancies and additions from the process defined in the DMP) will be described in an appropriate study plan).

13.3 Record Archiving and Retention

The PI and study staff are responsible for maintaining a comprehensive ISF of all study-related (essential) documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced at the site.

In addition, all original source documents supporting entries in the eCRF must be included in the patient's medical file and retained so that integrity and accessibility are maintained for at least 5 years after the end of the study and in accordance with the maximum period of time permitted by the hospital, institution or private practice. This requirement applies to both hardcopy (paper) and electronic source data.

The ISF must be retained in accordance with ICH E6(R2) GCP, 21 CFR 312.62(c) or longer if required by applicable regulatory requirements or by the Sponsor. The PI or his/her institution should retain essential documents until written instructions for their destruction are obtained from the Sponsor and must take adequate measures to prevent accidental or premature destruction of trial related records. If the PI wishes to assign the study records to another party or to another location, they must obtain prior approval in writing from the Sponsor. Any transfer of records must be fully documented.

14 FINANCING AND INSURANCE

The financing and insurance for this study will be subject to a separate written agreement between the Sponsor and applicable parties.

This study will be financed by Kymab Ltd, a Sanofi Company, the Sponsor of the study. Individual site financing and insurance will be subject to a separate written agreement between the Sponsor and applicable parties. Patients will not be paid for participating in this study; however, allowances and reimbursements for patient and family travel may be provided, as included in the site-specific written agreement/budget/Clinical Trial Agreement.

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the end of the study.

15 PUBLICATION POLICY

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential.

The Sponsor is committed to publish the data arising from this study at a suitable time irrespective of the study outcome. Results from the study will be published/presented at scientific meetings as per the Sponsor's publication policy.

This is a multi-site study, and publication of the results of the study conducted at any individual site may not be made before multi-site publication(s) by Sponsor. Once the Sponsor's multi-site publication(s) have taken place, each site will have the right to publish its results from the study, subject to the following notice requirements:

- At least 60 days prior to submitting or presenting a manuscript relating to the study for publication a copy must be provided to the Sponsor for review and comment.

- The Sponsor may request further delay to publication or presentation for a period of up to 120 days to allow the protection of any proprietary information, intellectual property or inventions.
- If there is no multi-site publication within 18 months after the study has been completed or terminated at all study sites, and all data has been analysed, sites will have the right to publish their own results from the study.
- Any publication made by a site must refer to the relevant Multi-Centre Trial publication where applicable.

The Sponsor will ensure that any applicable requirements to register the study or publish the results arising on public databases are met.

16 REFERENCES

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17 APPENDICES

17.1 Appendix 1 - Protocol Amendments

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the STUDY PERSONNEL.

This is the ninth version of the protocol. Details of the key changes made in each version are provided below.

[redacted]

17.1.2 Amended Clinical Trial Protocol 04 (14 December 2021)

This amended clinical trial protocol 04 is considered non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reason for this amendment to Protocol KY1005-CT05 is to fulfil requirement from Pharmaceuticals and Medical Devices Agency (PMDA), Japan.

[redacted]

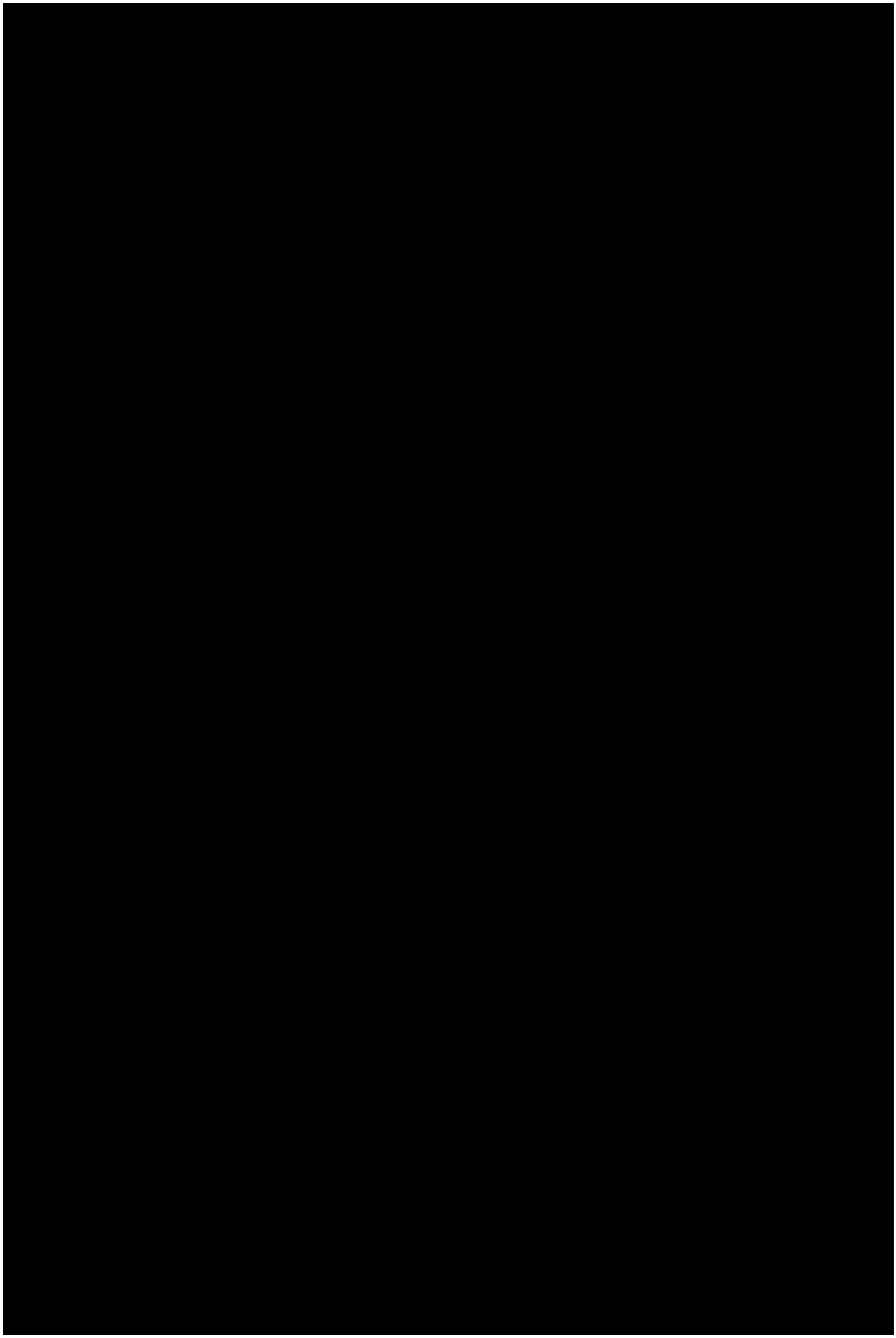
17.1.3 Amended Clinical Trial Protocol 05 (18 January 2022)

This amended clinical trial protocol 05 is considered substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reason for this amendment to Protocol KY1005-CT05 is to fulfil requirement from the Medicines and Healthcare products Regulatory Agency (MHRA), UK.

[redacted]



[redacted]

17.1.4 Amended Clinical Trial Protocol 06 (03 February 2022)

This amended clinical trial protocol 06 is considered non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reason for this amendment to Protocol KY1005-CT05 is to fulfil requirement from the Hungary Ethics Committee for Clinical Pharmacology, Emberi Erőforrások Minisztériuma, Ministry of Human Capacities.

[redacted]

17.1.5 Amended Clinical Trial Protocol 07 (10 February 2022)

This amended clinical trial protocol 07 is considered non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The primary reason for this amendment to Protocol KY1005-CT05 is to fulfil requirements from the German authorities Paul-Ehrlich-Institut (PEI) and Ethics Committee (EC) of the State of Berlin (Ethik-Kommission des Landes Berlin).

[redacted]

17.2 Appendix 2 - Eczema Area and Severity Index

Table 1. Eczema area and severity index: calculation for patients 8 years of age and older[1]

Body region	EASI Score[2,3]
Head/Neck (H)	(E+I+Ex+L)×Area×0.1
Upper limbs (UL)	(E+I+Ex+L)×Area×0.2
Trunk (T)	(E+I+Ex+L)×Area×0.3
Lower limbs (LL)	(E+I+Ex+L)×Area×0.4
EASI =	*Sum of the above 4 body region scores*

[1]For children aged 0–7 years, proportionate areas were head/neck, 20%; upper limbs, 20%; trunk, 30%; and lower limbs, 30%.
[2]E=Erythema, I=induration/papulation, Ex=excoriation, L=lichenification.
[3]Where area is defined on a 7-point ordinal scale: 0=no eruption; 1=<10%; 2=<10%–29%; 3=<30%–49%; 4=<50%–69%; 5=<70%–89%; and 6=>90%–100%.

Source: Hanifin et al (2001) [Hanifin Exp Dermatol 2001]; reproduced with permission of Wiley (© Munksgaard 2001, managed by Wiley).

How to Use EASI

The EASI scoring system uses a defined process to grade the severity of the signs of eczema and the extent affected:

1. Select a body region

Four body regions are considered separately:

- Head and neck
- Trunk (including the genital area)
- Upper extremities
- Lower Extremities (including the buttocks)

2. Assess the extent of eczema in that body region

Each body region has potentially 100% involvement. Using the table below, give each respective body region a score of between 0 and 6 based on the percentage involvement. Precise measurements are not required.

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

To aid in your body region grading you can use the diagrams in Appendix 1.

3. Assess the severity of each of the four signs in that body region:

1. Erythema
2. Edema/papulation
3. Excoriation
4. Lichenification

Further explanations of these terms can be found in FAQ's (Appendix 4)

Grade the severity of each sign on a scale of 0 to 3:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved region.
- ✓ Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild (1)
- ✓ Palpation may be useful in assessing edema/papulation as well as lichenification

To aid your severity grading, a photographic atlas of suggested categories is available in Appendix 2

Remember: *Include only inflamed areas in your assessment; do not include xerosis (dryness), ichthyosis, keratosis pilaris, urticaria, infection (unless there is underlying eczema), or post inflammatory pigmentation changes.*

Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. Exp Dermatol. 2001 Feb;10(1):11-8

EASI - United States/English
EASI_AU2.1_eng-USorl.doc

How to record your scores

The assessed parameters are inserted into a table (example shown below for age≥8 years). The final EASI score ranges from 0-72.

Body region	Erythema	Edema/ papulation	Excoriation	Lichenification	Area score	Multiplier	Score
Head/neck	(+	+	+	)	x	X 0.1	
Trunk	(+	+	+	)	x	X 0.3	
Upper extremities	(+	+	+	)	x	X 0.2	
Lower extremities	(+	+	+	)	x	X 0.4	
The final EASI score is the sum of the 4 region scores							_____ (0-72)

Two forms of the EASI scoring system are available depending on the age of the patients. The multipliers for the region score are different in the under 8's version to reflect the relative proportion of body regions in young children:

- Patients 8 years or above
- Patients under 8 years of age.

The forms can be found in appendix 3.1 and 3.2 and also as word documents on the HOME website (www.homeforeczema.org)

17.3 Appendix 3 - Investigator Global Assessment Scale

Investigator Global Assessment scale for Atopic

Investigator's Global Assessment (IGA)

Please refer to the instructions below and place a checkmark next to the appropriate score below:
_____ 0 Clear
_____ 1 Almost Clear
_____ 2 Mild Disease
_____ 3 Moderate Disease
_____ 4 Severe Disease

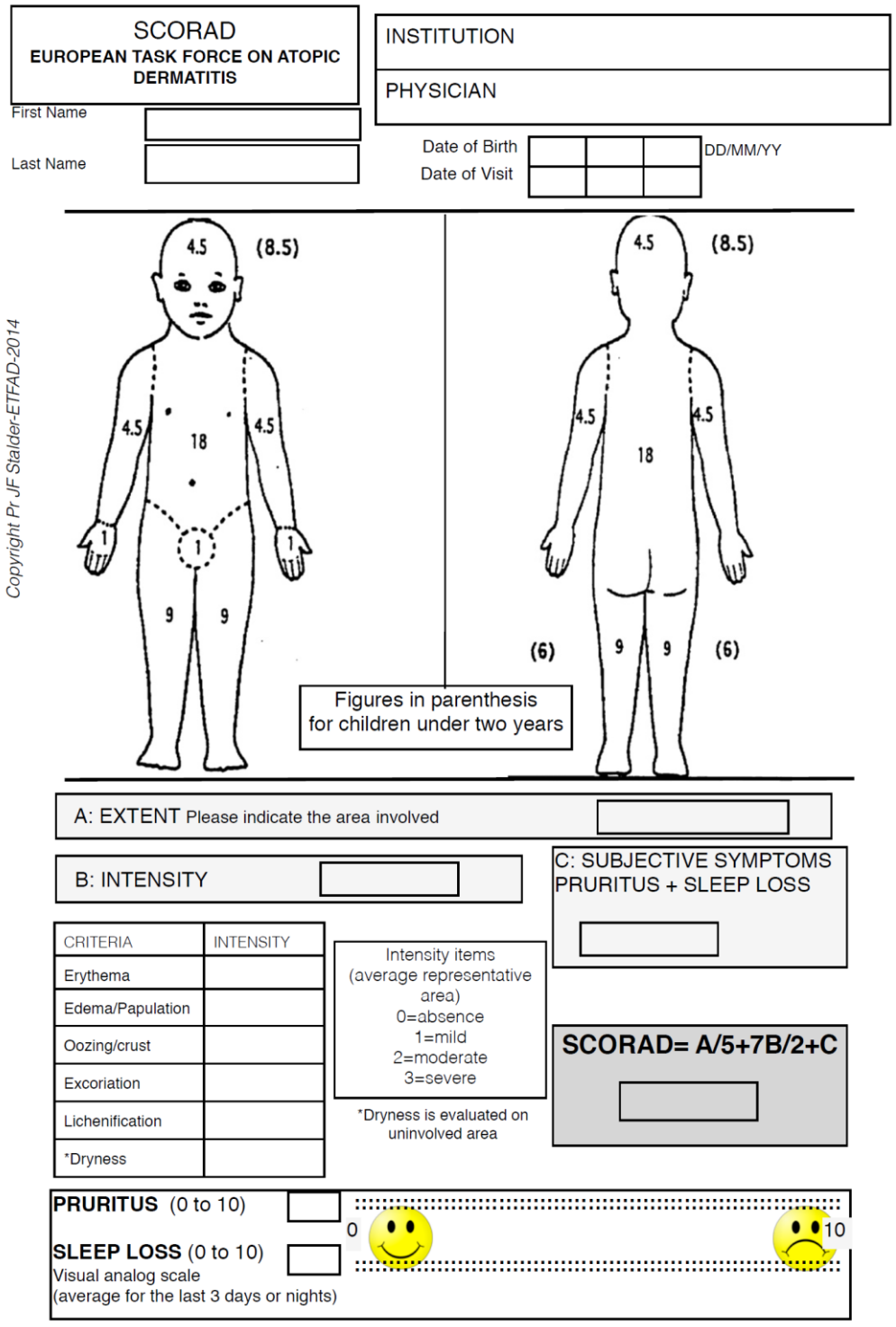
Print Name (First/Last) of Investigator Completing Assessment **Signature** **Date**

Instructions:

The Investigator's Global Assessment is a static 5-point measure of disease severity based on an overall assessment of the skin lesions.

IGA: Disease Severity Scale and Definitions of the scoring:	**Investigator's Global Assessment (IGA) Standard Definitions**	**Investigator's Global Assessment (IGA): Proposed Morphological Descriptors**
Score		
0 = Clear	No inflammatory signs of atopic dermatitis	No inflammatory signs of atopic dermatitis
1 = Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration	Barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration)
2 = Mild disease	Mild erythema and mild papulation/infiltration	Visibly detectable, light pink erythema and very slight elevation (papulation/infiltration)
3 = Moderate disease	Moderate erythema and moderate papulation/infiltration	Dull red, clearly distinguishable erythema; clearly perceptible elevation (papulation/infiltration), but not extensive
4 = Severe disease	Severe erythema and severe papulation/infiltration	Deep/dark red erythema; marked and extensive elevation (papulation/infiltration)

17.4 Appendix 4 - SCORing of Atopic Dermatitis Index (SCORAD Index)



Source: European Task Force on Atopic Dermatitis (2003)

17.5 Appendix 5 - Patient Oriented Eczema Measure

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POEM for self-completion

Please circle one response for each of the seven questions below about your eczema. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your skin been itchy because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

2. Over the last week, on how many nights has your sleep been disturbed because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

3. Over the last week, on how many days has your skin been bleeding because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

4. Over the last week, on how many days has your skin been weeping or oozing clear fluid because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

5. Over the last week, on how many days has your skin been cracked because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

6. Over the last week, on how many days has your skin been flaking off because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

7. Over the last week, on how many days has your skin felt dry or rough because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

Total POEM Score (Maximum 28): _____

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POEM for self-completion

How is the scoring done?

Each of the seven questions carries equal weight and is scored from 0 to 4 as follows:

No days	= 0
1-2 days	= 1
3-4 days	= 2
5-6 days	= 3
Every day	= 4

Note:

• If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 28

• If two or more questions are left unanswered the questionnaire is not scored

• If two or more response options are selected, the response option with the highest score should be recorded

References
Charman CR, Venn AJ, Williams HC. The Patient-Oriented Eczema Measure: Development and Initial Validation of a New Tool for Measuring Atopic Eczema Severity From the Patients' Perspective.
Arch Dermatol. 2004;140:1513-1519
Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods.
Br J Dermatol. Dec 2013; 169(6): 1326–1332.

17.6 Appendix 6 - Dermatology Quality of Life Index

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

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

Please check you have answered EVERY question. Thank you.

17.7 Appendix 7 - Atopic Dermatitis Control Tool

Atopic Dermatitis Control Tool

Please answer the following questions thinking about your experiences with eczema, sometimes called "atopic dermatitis."

1. Over the last week, how would you rate your eczema-related symptoms (for example, itching, dry skin, skin rash)?
   0☐ None 1☐ Mild 2☐ Moderate 3☐ Severe 4☐ Very Severe

2. Over the last week, how many days did you have intense episodes of itching because of your eczema?
   0☐ Not at all 1☐ 1-2 days 2☐ 3-4 days 3☐ 5-6 days 4☐ Every day

3. Over the last week, how bothered have you been by your eczema?
   0☐ Not at all 1☐ A little 2☐ Moderately 3☐ Very 4☐ Extremely

4. Over the last week, how many nights did you have trouble falling or staying asleep because of your eczema?
   0☐ No nights 1☐ 1-2 nights 2☐ 3-4 nights 3☐ 5-6 nights 4☐ Every night

5. Over the last week, how much did your eczema affect your daily activities?
   0☐ Not at all 1☐ A little 2☐ Moderately 3☐ A lot 4☐ Extremely

6. Over the last week, how much did your eczema affect your mood or emotions?
   0☐ Not at all 1☐ A little 2☐ Moderately 3☐ A lot 4☐ Extremely

1/1
ADCT – US/English

ADCT - United States/English - Mapi.
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17.8 Appendix 8 - Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression Scale (HADS)

GL assessment

Name:_____ Date: _____

FOLD HERE

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

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

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

FOLD HERE

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

Now check that you have answered all the questions

	A	D
TOTAL		

17.9 Appendix 9 - Pruritus Numeric Rating Scale

V1.0 29May2020 English (United Kingdom)
Update on copyright: 01Mar2021

Pruritis (itch) NRS

On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?

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

Page **1** of **1**

PP-NRS_AU1.1_eng-GB

17.10 Appendix 10 - Contraceptive and Barrier Guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.* Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly effective methods[b] that are user dependent *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation - oral - intravaginal - transdermal - injectable
Progestogen-only hormone contraception associated with inhibition of ovulation - oral - injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction)

17.11 Appendix 11 - Reporting of Serious Adverse Events

SAE reporting to the Sponsor via an electronic data collection tool

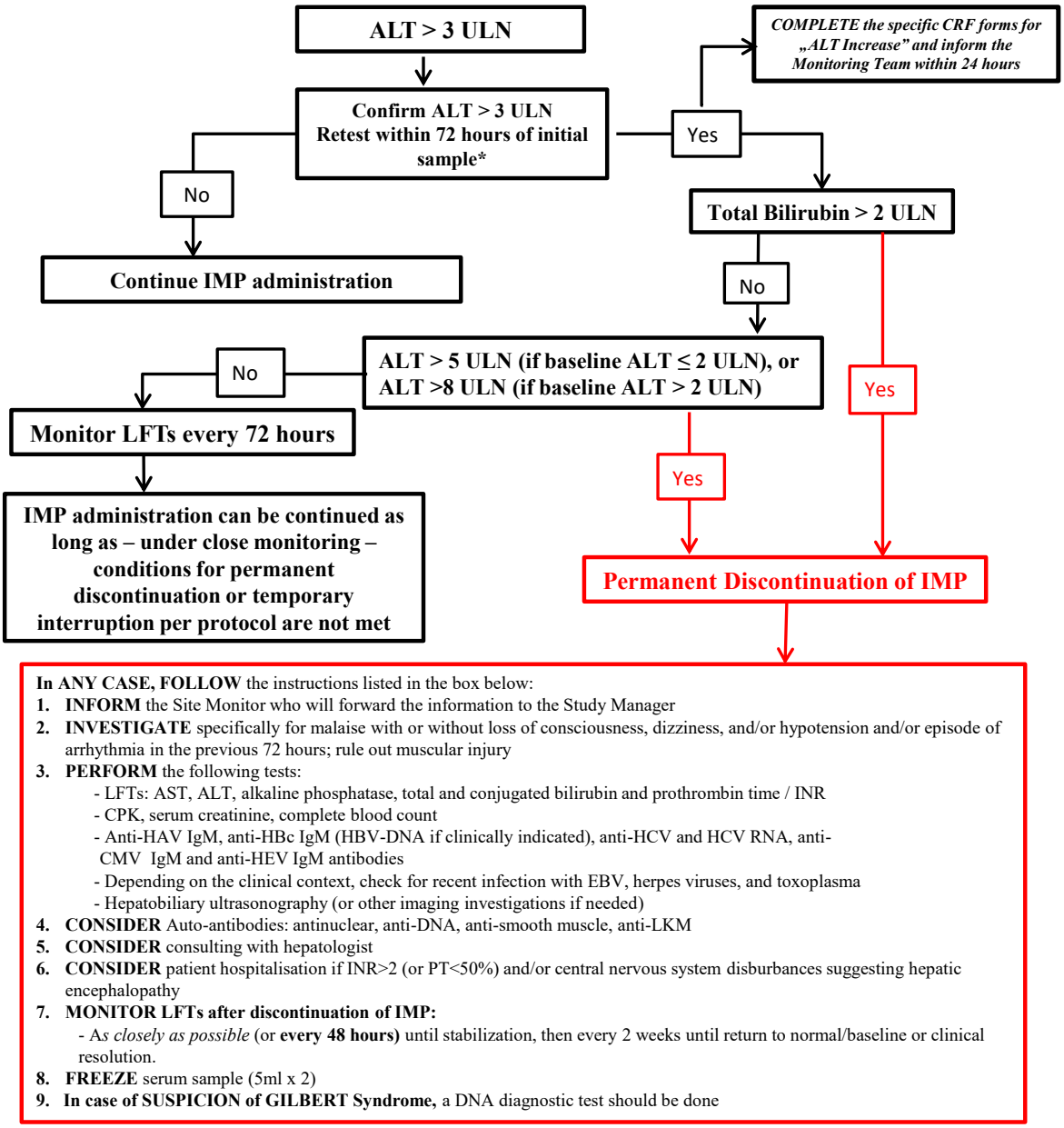
- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the Investigator Site File.

Serious adverse event reporting to the Sponsor via paper data collection tool (In case of failure of electronic reporting of SAE via the EDC system**)**

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Investigator Site File.

17.12 Appendix 12 - Liver safety: suggested actions and follow-up assessments

INCREASE IN ALT



*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
Note:
"Baseline" refers to ALT sampled at the Baseline Visit; or if the Baseline value unavailable, to the latest ALT sampled before the Baseline Visit. The algorithm does not apply to the instances of increase in ALT during screening.
See Section 17.10 (Appendix 10) for guidance on safety reporting.
Normalisation is defined as ≤ ULN or baseline value, if the Baseline value is > ULN.

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

17.14 Appendix 14 - Contingency Measures for a Regional or National Emergency That is Declared by a Governmental Agency

Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the patients, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance.

The following contingencies may be implemented for the duration of the emergency (after Sponsor agreement is obtained). Contingencies implemented due to emergency will be documented.

Informed consent

In exceptional circumstances, such as a regional or national emergency declared by a governmental agency, consent may be collected through a remote solution if allowed through country and site regulations and following approval by the Independent Ethics Committees (IEC)/ Institutional Review Boards (IRB). Implementation must have prior approval from the Sponsor (or its designee). Contingency procedures may be implemented for the duration of the emergency.

The patient or their legally authorised representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension).

Study drug administration

During the initial part of the study (up to and including Day 57 [Week 8]), study drug must be administered in accordance with Section 1.5.4, Section 1.7 and Section 5.2. At all other times, consideration may be given to administration of study drug at home if all conditions in the Pharmacy manual are adhered to and prior Sponsor agreement is obtained.

Temporary IMP discontinuation may apply in exceptional cases, under regional or national emergencies (eg, natural disaster, epidemic diseases, terrorist attack) due to which a visit at the clinical study site is no longer feasible.

In the case of an exceptional temporary treatment discontinuation, the discontinuation should be approved by the Sponsor. The Sponsor should also be notified to determine if treatment should be resumed. If deemed safe, the treatment can be resumed at the next scheduled or unscheduled visit. During the discontinuation period, remote checks (eg, telephone/video calls) will take the place of on-site visits per the Schedule of Assessments (Section 6.1).

Study assessments and procedures

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by a government declared regional or national emergency, focus should be given to assessments necessary to ensure the safety of patients and those important to preserving the main scientific value of the study.

Use of local clinic or laboratory locations may be allowed when central labs analyses cannot be performed due to a government declared regional or national emergency. These local laboratory results will only be performed to ensure patient safety and will not be used for the purpose of statistical analyses.

If onsite visits are not possible the implementation of remote visits (eg, phone call, virtual consultation, televisit, etc) or home visits (eg, home nurses, etc) may be planned for the collection of possible safety and/or efficacy data.

A Televisit is defined as a videoconference, video call or telephone call.

The following conditions must be met at a site level before such visits can be authorised.

- The visit must be performed by appropriately delegated study site staff or a home healthcare service.
- The correct equipment necessary to perform the required assessments must be taken to the visits.
- Home visits or televisits must be permitted by the site, local regulations, relevant ethics committee, relevant regulatory authority.
- The patient must have given consent via informed consent.
- Prior to implementing remote study visits for patients, notification to the Sponsor (or its designee) must be provided. The notification should include justification and expected patients and visits that may be impacted.

Visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely. Possibility of visit extension and duration of such extension must be discussed on a case-by-case basis with the Sponsor considering first of all patients' safety and best interests.

If the above emergency scenario occurs during the follow-up period, one or more follow up visits can be performed remotely (eg, via telephone calls or video calls), but at least one follow-up visit should be performed on site (EOS visit), even if the visit window needs to be extended. Remote follow-up should be conducted according to local regulations and approved by the Sponsor.

If the above emergency scenario leads to site closure or complete regional or national lock-down, the study may be suspended for the affected sites.

17.15 Appendix 15 - Country-specific Requirements

[redacted]

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