Best systemic treatments for adults with atopic eczema over the long term (BEACON)

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Best Systemic Treatments for Adults with **A**topi**c** Eczema over the L**on**g Term (BEACON)
A phase IV, multi-arm multi-stage, assessor blind randomised control trial comparing the effectiveness, tolerability and cost effectiveness of systemic treatments for adults with moderate-severe atopic eczema

Trial Identifiers

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Research Study Centres

Participating research study centres are listed on the Beacon Trial Website: https://www.beacontrial.org/

General information

This protocol has been written in a modular format such that core elements of the trial are described in the main protocol, with arm-specific information detailed in investigational medicinal product (IMP) appendices (*e.g.* background to the arm, drug information, arm-specific eligibility requirements and treatment details). Appendices will be added and removed through the course of the trial as IMPs are added or removed by substantial amendment.

1 STUDY SYNOPSIS

TITLE OF CLINICAL TRIAL:	**Be**st systemic treatments for adults with **a**topi**c** eczema over the l**on**g term (BEACON): A phase IV, multi-arm multi-stage, assessor blind randomised control trial comparing the effectiveness, tolerability and cost effectiveness of systemic treatments for adults with moderate-severe atopic eczema
SHORT TITLE:	**Be**st systemic treatments for adults with **a**topi**c** eczema over the l**on**g term (BEACON)
Protocol Short Title/ Acronym:	BEACON
Study Phase:	4
Sponsor Name(s):	Guy's and St Thomas' NHS Foundation Trust and King's College London
Chief Investigator:	Dr Andrew Pink
IRAS:	1004703
ISRCTN number	ISRCTN11056540
REC number	**23/LO/0224**
Medical Condition or Disease Under Investigation:	Atopic eczema
Purpose of Clinical Trial:	Determine the effectiveness, tolerability and cost-effectiveness of systemic therapies used to treat moderate to severe atopic eczema in adults.
Intervention (Description, frequency, details of delivery)	i) Methotrexate s/c 15mg once weekly (increasing to 20mg after 3 months if required) ii) Dupilumab s/c 600mg week 0 followed by 300mg every two weeks iii) Abrocitinib orally 200mg daily
Comparator Intervention:	Ciclosporin orally 3mg/kg (increasing to 5mg/kg after 3 months if required)
Primary outcome measure (6 months):	Change in objective disease severity, presented as mean absolute change from baseline, using the Eczema Area Severity Index (EASI, blinded assessment).
Secondary outcome measures (collected over 12 months):	1. Eczema severity measured by: a. EASI b. Investigator Global Assessment (vIGA-AD) 2. Patient reported symptoms measured by: a. Patient Orientated Eczema Measure (POEM) b. 11-point peak pruritus numerical rating scale (NRS) c. Overall disease control (RECAP) d. Patient global assessment (PtGA)

	3. Quality of life measured by: a. Dermatology Life Quality Index (DLQI) 4. Depression and anxiety measured by: a. Patient Health Questionnaire 9-item (PHQ-9) b. Generalised Anxiety Disorder 7-item GAD-7) 5. Health economic outcomes will include: a. Resource use questionnaire b. EUROQOL Five Dimension Five level (EQ-5D-5L). 6. Safety outcomes will include: a. Adverse events b. Adverse events of special interest 7. Adherence and Tolerability a. Visual Analog Scale (VAS)[34] for Medications Taken (VAS) b. Tolerability non validated measure Likert scale
Exploratory analyses	1. Provide data on whether the carriage of *filaggrin* gene mutations (one or two) associate with treatment response (possible predictive biomarker). 2. Provide data on whether methotrexate polyglutamate measurement can be used as a biomarker for treatment response on methotrexate. 3. Examine whether baseline IgE and eosinophil levels are predictors of outcome on the different therapies. 4. Examine whether predominant head and neck (“exposed site”) eczema at baseline is a predictor of outcome on the different therapies. 5. Explore patient thoughts about participating in the trial, expectations of treatment, experience in the trial, experience on specific treatments and suggestions relating to the future implementation of these therapies in practice. 6. To assess the utility of photographs for monitoring eczema through deep learning-based severity assessments and accrue a comprehensive collection of photographs of skin, thereby establishing a critical resource for future use by investigators to improve outcomes in eczema.
Trial Design:	UK, multicentre, interventional, 1 year, assessor-blind, multi-arm, multi-stage, superiority, randomised controlled trial. Patients randomised 1:1:1:1 to methotrexate, dupilumab, abrocitinib or ciclosporin for 6 months (optional dose increase at 3 months for those on methotrexate or ciclosporin as per clinical practice). Responders (defined as those achieving a 50% improvement in their objective disease severity measured using the Eczema Area and Severity Index (EASI), and a ≥ 4 point improvement in quality of life score (Dermatology Life Quality Index (DLQI)) will continue treatment up to 1 year. Non-responders will switch treatment in a pre-defined way to reflect clinical practice (methotrexate to dupilumab, ciclosporin to dupilumab, dupilumab to methotrexate, abrocitinib to methotrexate) and continue this treatment for 6 months.
Sample Size:	536 (134 per group) Please note the number of participants will be updated for additional arms as required

Study Population:	Adults with moderate to severe eczema requiring systemic therapy.
Maximum Duration of Treatment of a Participant:	1 year
Version and Date of Final Protocol:	Version 3.1, 10/11/2025

Revision History

Protocol version	Description of changes from previous revision	Effective Date
Protocol Version 1.0	New protocol (submitted for combined approval)	08.02.2023
Protocol Version 1.1	Adherence VAS check at Month 1 visit removed; Addition of Nested Interview Study Data Flow (Appendix 4); Correction of Sponsor SAE reporting process; Minor wording amendments for clarity.	07.09.2023
Protocol Version 1.2	Addition of REC and ISRCTN numbers; Removal of Stephen Smith as a co-applicant; Footer formatting and paragraph spacing; Addition of Be Part of Research Volunteer Service to participant identification; Edit to participant schedule of events footnote A; Addition of participant surveys to schedule of events; Minor edits to drug specific study flow footnotes; Postcode and mobile number removed from pre-randomisation data collection; Section 13.3 amended to reflect updated sponsor phamacovigilance policy; Amended wording to clarify process around participant online surveys; Wording in long-term follow up section amended to accurately reflect A-STAR data sharing; Amended wording in section 21 to reflect change from 'BEACONomics' to 'Allied Mechanistic Study'; Removal of 'BEACONomics' from Appenix 2 Data Flow.	11.04.2024

Protocol Version 2.0	Addition of abrocitinib as a 4th arm in the trial (related changes throughout protocol); drug-specific information moved to drug-specific appendices; addition of optional skin photography to schedule of events and sections 3.3, 6.2.5, 6.4.3, 9.4, and 9.5.4; exclusion criterion 2 amended to exclude patients with prior exposure to systemic therapies with similar mechanisms of action to the IMPs; exclusion criterion 3b amended in line with amended criterion 2; addition of acne to skin examination; addition of 'method of participant identification' to be assessed pre-randomisation; addition of option to defer trial visit or EASI assessment when EASI is deemed not to be assessible due to temporary confounding skin condition; minor updates to DrDoctor data security; change to reporting of abnormal laboratory results as adverse events – all to be recorded in AE log post-consent; IGRA TB screening added to screening bloods; clarification that participants may be trained using a dummy device (methotrexate / dupilumab); clarification that prohibited medications are those contraindicated in the SmPC for the trial drug participants are taking (or due to switch to); internal pilot 'go'/'no go' criteria table removed as pilot phase elapsed; amended permitted timeframe for qualitative interviews; BEACON-omics changed to mySkinomics; Figure 3 updated; TMG member names removed from Table 3; details added on Pfizer funding; Appendix 6, 7 and 8: Data/ Sample/ Flow Diagrams updated.	12.11.2024
Protocol Version 2.1	Appendix 4: correction to abrocitinib flow diagram and schedule of events to clarify week 4 safety bloods required (in line with Table 1 - main schedule of events, and abrocitinib-specific safety bloods detailed in appendix text)	29.01.2025

Protocol Version 3.0	Study synopsis table: change to CI email address Table 1 (schedule of events) and individual IMP schedules of events in Appendices 1-4: addition of footnote to allow clinical blood results within 4 months prior to randomisation to be used as screening bloods Section 5: change to target site number; addition of information regarding the NIHR Be Part of Research Volunteer Service; clarification around withdrawals and IMP discontinuation Section 6: change to skin photography – to be acquired via mySkin app; addition of information on investigator monitoring of PROMs and management of psychological symptoms identified; in line with new footnote in Table 1, addition of timeframe within which clinical blood results can be utililised as screening bloods. Section 7: change to requirement to withdraw participants who take certain medications (previously 'prohibited' medications) now retaining them in trial (where participants willing to continue data collection) with documentation of new medication Section 9: amendment to the online platform to be used for skin photography, and inclusion of participant self-taken photography Section 10: addition of procedure for SAE reporting to Pfizer, for the abrocitinib arm only; addition of information around pregnancy reporting;	27.05.2025
Protocol Version 3.1	Section 6.7.1: Clarification added that it is not essential to have IgE result back prior to baseline visit Section 7.4.1; Appendix 1, section 1.4.4; Appendix 2 section 1.4.6; Appendix 3, section 1.4.4; Appendix 4, section 1.4.4: Removal of SmPC dates.	10/11/2025

2 GLOSSARY OF TERMS

AE/AR	Adverse Event/Adverse Reaction
ALT	Alanine Aminotransferase
AST	Aspartate aminotransferase
CA	Competent Authority
DCR	Data Clarification Request
CI	Chief Investigator
CONSORT	Consolidated Standards Of Reporting Trials
CRF	Case Report Form
CSV	Comma-Separated Values
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EQ-5D-5L	EuroQol – 5 dimensions – 5 levels
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
GGT	Gamma-glutamyl transferase
GP	General Practitioner
GCP	Good Clinical Practice
HEAP	Health Econmics Analysis Plan
hCG	Human chorionic gonadotropin
ICF	Informed Consent Form
ID	Identification
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ITT	Intention to Treat
JAK	Janus Kinase
KCTU	King's Clinical Trials Unit
KHP-CTO	King's Health Partners Clinical Trials Office
LLN	Lower Limit of Normal
MHRA	Medicines and Healthcare products Regulatory Agency
MTA	Material Transfer Agreement
NES	National Eczema Society
NIHR	National Institute for Health Research
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator (at site)
PIN	Participant Identification Number
PIS	Participant Information Sheet
PP	Per Protocol
R&D	Research and Development
RA	Regulatory Agency
REC	Research Ethics Committee
RN	Research Nurse
SAE	Serious Adverse Event/ Serious Adverse Reaction
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SDW	Source Data Worksheets
SmPC	Summary of Product Characteristics
SS	Senior Statistician
SUSAR	Suspected Unexpected Serious Adverse Reaction
TM	Trial Manager
TMG	Trial Management Group
TS	Trial Statistician
TSC	Trial Steering Committee
UK	United Kingdom
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WOCBP	Women of child bearing potential

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1 INTRODUCTION

1.1 BACKGROUND

Atopic eczema (here on in referred to as 'eczema') is very common, affecting 5.1-8.7% of adults in the UK[1]. It is characterised by intensely itchy, sore areas of inflamed skin associated with scratching, recurrent infection and chronic sleep loss. Extent can vary from localised flexural site disease to generalised forms. Refractory eczema in adults can run a protracted course with unpredictable disease flares. The high disease burden negatively impacts on mood, social interaction, daily function, quality of life and work capability (57% patients with moderate to severe disease reported missing at least one day of work per year due to their eczema[2]). The disability adjusted life years rate in eczema is 153/100000, higher than for rheumatoid arthritis (78/100000)[3]. 88% of adults with moderate to severe disease report that their eczema at least partly compromises their ability to face life[2].

Common co-morbidities include asthma (30%), allergic rhinitis (35%), allergic conjunctivitis and food allergy and there is an increased risk of adverse cardiovascular outcomes[4,5]. Eczema is triggered by environmental factors (e.g. weather, irritants, allergens and microbes) in genetically susceptible individuals who have a skin barrier dysfunction and exaggerated Th2 cell-mediated immune responses. Loss-of-function mutations in the *filaggrin* gene (*FLG*, chromosome 1q21.3) are the strongest known genetic risk factor (3x increased risk, 20% prevalence in the eczema population), and associate with earlier onset, more severe disease[6].

Most people with eczema have limited disease, manageable with topical therapy. Up to 10% of people suffer with moderate to severe disease requiring specialist care[1,5]. This group suffer a disproportionate impact on their quality of life and incur high health care costs driven by appointments, day care, inpatient episodes and complex therapeutic interventions including phototherapy and systemic therapies. This trial concerns the adult eczema population with moderate to severe disease requiring systemic therapy. Older, and commonly used so-called 'standard' (or conventional) systemic therapy options include immunomodulators such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil (NICE TA534). Ciclosporin is the only one of these that is licensed for eczema and methotrexate is the one most commonly prescribed in the UK[7]. The preferred first line systemic agent in our pre-trial UK clinician survey was methotrexate followed by ciclosporin (56% and 37% respectively). More recently, based on a growing understanding of the key molecular mechanisms underlying eczema, a number of novel targeted therapies have been introduced that are revolutionising the therapeutic landscape. The first of these was dupilumab, an interleukin (IL)-4 receptor antagonist (monoclonal antibody) that blocks the interleukin-4 and -13 signalling. Subsequently tralokinumab and lebrikizumab, monoclonal antibodies targeting interleukin 13, and three oral Janus kinase (JAK) inhibitors (baricitinib, abrocitinib and upadacitinib), which block multiple immune pathways driving atopic disease including interleukin-4, -13, and -31 signalling, have been licensed. All of these have been approved for use in the NHS (NICE TA534, TA681, TA814, TA986) in adult patients who have failed on at least one 'standard' immunomodulatory therapy.

1.1.1 CURRENT EVIDENCE BASE FOR SYSTEMIC TREATMENTS USED TO TREAT MODERATE-SEVERE ECZEMA IN ADULTS

There is good evidence that ciclosporin is of benefit versus placebo[5] but evidence for other 'standard' systemic options is limited (see section 1.4 for more detail)[5]. An HTA systematic review states that

the comparative effectiveness of systemic therapies is lacking and that “larger, clearly reported, clinically relevant studies are needed to properly compare the benefits of these drugs in adults and children with severe eczema”[5]. Dupilumab was the first licensed targeted (biologic) therapy for eczema and has a strong evidence base versus placebo but has never been compared with standard systemic therapy[8,9]. Likewise for the even newer agents tralokinumab, lebrikizumab and JAK inhibitors (abrocitinib, upadacitinib and baricitinib), there is a strong evidence base versus placebo[10,11], but there has been no comparison versus standard systemic therapy. There is also minimal available head to head data between the novel agents. Industry led head to head trials have been conducted between JAK inhibitors and dupilumab[12,13] however the early primary endpoints (as early as 2 weeks) are not optimal given that dupilumab can take 6 months to achieve maximum benefit[9]. A recent network meta-analysis suggested that there is an absence of well powered head-to-head trials, that dupilumab and ciclosporin may have better short term effectiveness than methotrexate and that “studies directly comparing established and novel treatments beyond 16 weeks are needed”[13]. Another recent systematic review states “to more directly compare medication efficacy, a standardised controlled trial comparing biologic and non-biologic systemic therapies is needed”[14].

Outwith efficacy and effectiveness, the standard and novel systemic therapies confer very different side effect profiles. Whilst the side effects of ciclosporin and methotrexate are well established, those of the more novel agents are less so and of those that we now know about, many were unexpected. Side effects on dupilumab such as ocular surface disease, facial flares and arthritis can affect tolerability for patients. Likewise on JAK inhibitors, infections (including herpes simplex and varicella zoster), acne, blood derangement and rarely venous thrombo-embolism impact patients. Safety is therefore a focus of increasing attention for those prescribing systemic therapies in this context and any informative head-to-head comparative data of the key agents if of clinical utility.

1.1.2 THE COST-EFFECTIVENESS OF SYSTEMIC TREATMENTS USED TO TREAT MODERATE-SEVERE ECZEMA IN ADULTS

Novel therapies, such as novel biologics and small molecules[15], for atopic eczema are increasingly available. The treatment cost with these drugs is significantly more than that seen for conventional systemic treatments[16] and for this reason technology appraisal guidance has leaned towards limiting their use to those with severe disease for whom conventional systemic treatment has stopped working or those for whom it is not well tolerated[17]. Since most studies to date are placebo-controlled there is a need for head-to-head randomised controlled trials comparing the cost-effectiveness of the newer biologics to conventional systemic therapies over a longer time frame[18].

1.2 RATIONALE FOR THIS TRIAL

There are currently important evidence gaps in the systemic treatment of adult eczema:

1. The comparative effectiveness and tolerability of standard and novel targeted systemic therapies is unknown.
2. The effectiveness and comparative effectiveness of these agents in treating severe disease, rather than moderate to severe disease, is unknown but important given the higher treatment need[18].

3. The cost effectiveness of standard and novel targeted systemic therapies is poorly described and important given the arrival of numerous high cost treatments which are licensed for long-term use.
4. The cost of eczema in adults in the UK is unknown (the only UK cost of illness study in adult eczema was in 1985[19], with a sample of just 19 patients aged >16), a gap highlighted in economic models for dupilumab[17].
5. Dermatologists do not currently know which treatment to start a patient on so as to optimise treatment continuation in the first year and avoid the need for treatment switches.
6. If a therapeutic switch is required, there is no current evidence to inform the optimal treatment pathway.
7. The mechanisms of drug action and cellular/ molecular mechanisms of drug benefit and adverse events (AEs) are poorly understood.

Doctors and patients want to know how the newer targeted treatments, such as dupilumab, compare with existing standard treatment. Indirect comparisons are not a substitute for key active comparator studies[18]. This trial will provide the first randomised evidence on the comparative effectiveness, tolerability and cost effectiveness of key systemic agents (covering the main mechanisms of action) used to treat moderate to severe adult eczema. It will address a priority identified by the James Lind Alliance priority setting partnership of patients, carers and health professionals: “What is the best and safest way of using drugs that suppress the immune system when treating eczema?”[19]. The trial will, for the first time, provide a comprehensive assessment of the healthcare costs related to the treatment of moderate to severe adult eczema. Additional subgroup analyses will be performed looking specifically at the severe and moderate subgroups, the impact of *filaggrin* status, methotrexate polyglutamate levels to ascertain if they can be used as a biomarker for treatment response, baseline IgE and eosinophil levels and head and neck “exposed site” involvement as a stratifier of response on the different treatments. Skin photography will also be collected, which may enable automation of disease severity assessments. Deep learning-based analysis of photographs has the potential to automate scoring severity in inflammatory skin diseases such as eczema, however there are a paucity of databases of prospectively-acquired photographic images (particularly of ethnically-diverse populations) with linked healthcare data[20].

The trial will examine treatment pathways, establishing which therapy optimises treatment continuity over a year, and which pathway optimises outcomes at 12 months accounting for treatment continuity and those requiring a switch in treatment. There is a lack of understanding of the mechanism of action of currently available treatments. A parallel bioresource and mechanistic study will seek to elucidate the key cellular and molecular drivers of drug response and AEs. This could open important avenues for personalised data-driven management of eczema, whereby the optimum treatment can be selected for an individual patient and inform future therapeutic strategies.

1.3 RATIONALE FOR AN ADAPTIVE MULTI-ARM MULTI-STAGE (PLATFORM) TRIAL DESIGN

A multi-arm multi-stage adaptive trial design facilitates the simultaneous evaluation of multiple treatments against a common control arm and the incorporation of new trial arms over time. This is a time- and cost-efficient way to perform multiple comparisons, utilising a single trial infrastructure thus reducing cost and set up times. It ensures that comparators and associated research questions remain relevant as the therapeutic landscape in any condition evolves. Highly successful exemplars of this model include STAMPEDE and RECOVERY which changed the standard of care and

outcomes in prostate cancer and COVID respectively. This is a crucial time in eczema drug development with drugs in active phase II/III development spanning more than five new systemic therapeutic classes targeting IL13, IL31, OX40L, IL22, S1PR and CCR4. Adopting a MAMS design for BEACON is therefore appropriate and timely.

BEACON started with three arms with ciclosporin as the initial control because of its strong evidence base and license in eczema. Methotrexate is a key initial comparator as it is the most widely prescribed systemic treatment in the UK[7]. Dupilumab is another key initial comparator as it is a widely adopted, new, licensed, effective and targeted therapy, but has high costs, consequent NICE-defined access criteria and there is genuine clinical equipoise with the existing treatments[18]. Since first designing and initiating the trial oral JAK inhibitors have been licensed, NICE approved and are now widely used. As per dupilumab these are high cost, have defined access criteria and we do not know how they compare with existing treatments. Abrocitinib has been chosen as a JAKi class exemplar to be added to BEACON, representing the first additional arm. **Figure 1** is a schematic to show how BEACON could evolve into a multi-arm multi-stage platform. As indicated in this figure, the control arm (i.e. the platform 'standard of care') can change over time dependent on the trial results and any new treatments added after that change would thus be compared against the new control (see section 17 for further information).

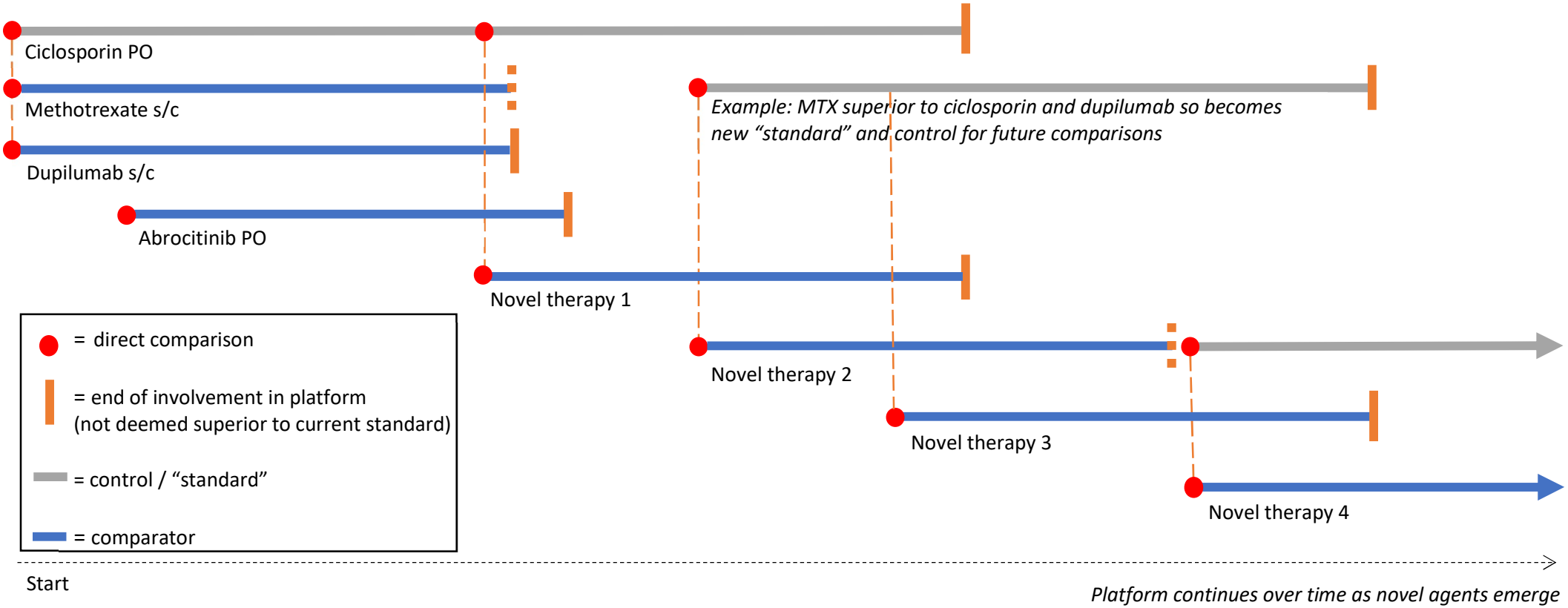


Figure 1 Schematic showing BEACON as a multi-arm multi-stage trial

1.4 SUMMARY OF FINDINGS FROM CLINICAL STUDIES OF THE IMPS

Ciclosporin is effective versus placebo for the treatment of moderate to severe AD in adults. Evidence for other standard systemic options is limited[5]. Methotrexate did not achieve non-inferiority versus ciclosporin at the 8 week stage (SCORAD as primary outcome) in one trial, but did achieve non-inferiority at 24 weeks with the EASI (EASI50 response, 87% methotrexate vs 80% ciclosporin)[21]. Limitations to this study included a small sample size, high and unbalanced dropout rates and a short treatment period. A small paediatric trial showed no statistically significant difference in effect between methotrexate and ciclosporin at 12 weeks[22]. Dupilumab has a strong evidence base versus placebo but has never been compared against standard active treatment (61-69% EASI50 vs 22-25% placebo, 44-52% EASI75 vs 12-14% placebo, at 16 weeks)[8,9]. Abrocitinib also has a strong evidence base versus placebo (76% EASI50 vs 22% placebo, 63% EASI75 vs 12% placebo, at 12 weeks)[10] but has also not been compared against standard treatments. Abrocitinib has demonstrated superiority versus dupilumab for both itch and objective disease severity primary endpoints in a head to head study at early time points (2 and 4 weeks respectively, 48% reported a ≥4 point improvement in itch NRS vs 26% dupilumab, 29% EASI90 versus 15% dupilumab)[13]. A network meta-analysis suggested that there is an absence of well powered head-to-head trials, that dupilumab and ciclosporin may have better short-term effectiveness than methotrexate and that "studies directly comparing established and novel treatments beyond 16 weeks are needed"[23].

2 TRIAL DESIGN

This is a UK, multicentre, one year, assessor-blind, randomised controlled trial assessing systemic treatments in adults with moderate to severe eczema. Three mechanistic classes of drugs are being tested against a control (ciclosporin). Further treatments and arms may be added in future amendments.

Participants will be randomised in a 1:1:1:1 ratio. **During the first stage of the trial (months 1-6), follow up will be face to face at 1, 3 and 6 months** for safety and effectiveness assessment (see Figure 2 for trial flow diagram and Table 1 for schedule of events). There are additional drug-specific safety only visits for some arms as shown in Table 1, Figure 2, and individual flow diagrams in drug specific Appendices 1-4, in line with routine care and national guidance. There is the **option to increase the treatment dose at 3 months for some arms if there has been an inadequate response** following which additional safety only visits may be required (see Table 1 schedule of events, Figure 2 trial flow diagram, and individual flow diagrams in drug specific appendices 1-4) . Dose reduction will be permitted at any stage as clinically indicated and according to standard clinical practice. Safety only visits (when no additional effectiveness measure is conducted) can be conducted in the community where deemed appropriate by the investigator (general practice). If participants attend study sites, contact with study staff should be minimised and staff will be trained to not provide additional support to minimise performance bias.

The primary outcome will be assessed at 6 months. Responders, defined as those achieving at least a 50% improvement in the objective EASI score (EASI50) and a ≥ 4 point reduction in Dermatology Life Quality Index (DLQI) **will continue the same therapy for a further 6 months (up to 1 year)** if they are tolerating the treatment and are happy to continue (in line with NICE guidance (NICE TA534[17])). **Non-responders will switch therapy** in a pre-determined way that mirrors real world practice (see Figure 2).

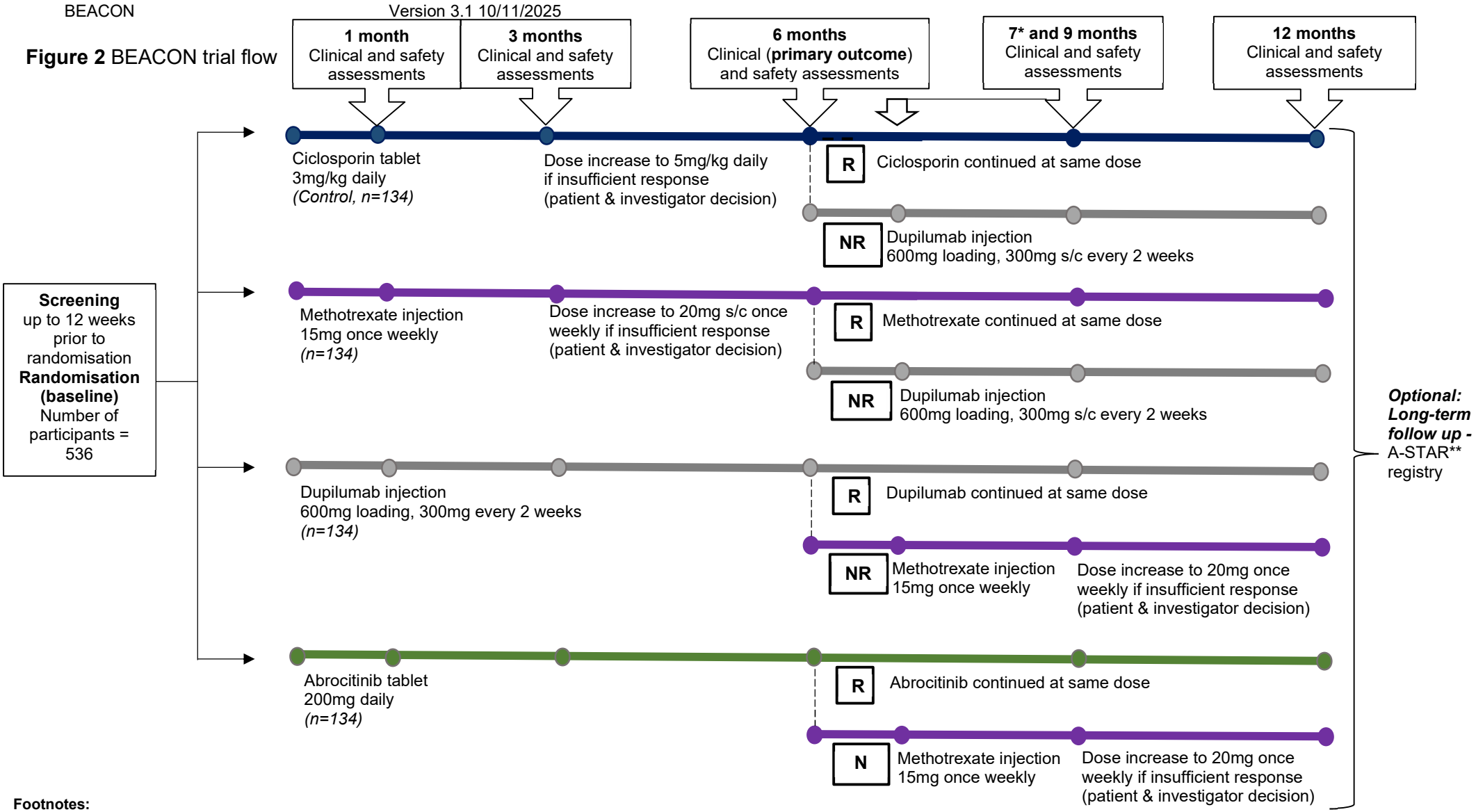
In the second stage of the trial (months 7-12) face to face safety and effectiveness assessments will be at 9 and 12 months. For those participants who have switched therapy there will be an additional telephone/ remote safety only visit (with bloods) at 7 months. Dependent upon

the drug that they switch to, additional safety bloods may be required and there may be the option to increase dose at 9 months (requiring further additional safety bloods, see Figure 2).

The pragmatic trial design mirrors routine care as closely as possible. Due to the different safety monitoring requirements of the trial drugs the number of times safety bloods are taken during the trial differs between arms. Patient reported outcomes will be collected via electronic questionnaires at trial visits using a secure online platform (DrDoctor). Topical treatment will be permitted throughout the trial.

This trial is an assessor-blind design. The primary outcome and assessor-rated secondary outcome will be conducted by an independent trained assessor at site, who is blinded to treatment allocation and not involved in the care of the patient. This may be a dermatologist or dermatology nurse who has received full training in using the instruments.

Figure 2 BEACON trial flow



Footnotes:

- Topical treatment permitted throughout, dose reduction permitted as per standard clinical care
- Additional safety bloods and blood pressure 2/6/8 weeks after starting ciclosporin and 2/4 weeks post-increment
- Additional safety bloods 2 weeks after starting or switching to methotrexate and 2/4 weeks post-increment
- * Only required for those who switch therapy, virtual review
- ** A-STAR = (British Association of Dermatology UK-Irish Atopic Eczema Systemic Therapy Register)

R = responder (achieved EASI50 **and** DLQI reduction ≥4 and patient/ investigator happy to continue)

NR = non-responder (not achieved EASI50 **and** DLQI reduction ≥4)

TABLE 1 SCHEDULE OF EVENTS

Event / form	Screening[A]	Baseline[B]	Week 2 Safety Visit[C]	Week 4 (Month 1)	Week 6 Safety Visit [D]	Week 8 Safety Visit [D]	Week 13 (Month 3)	Week 15 Safety Visit [E]	Week 17 Safety Visit [E]	PRIMARY OUTCOME Week 26 (Month 6)	Week 28 Safety Visit [F]	Week 30 Safety Visit [G]	Week 39 (Month 9)	Week 41 Safety Visit [H]	Week 43 Safety Visit [H]	Week 52 (Month 12) End of Study Visit	Ongoing
Informed Consent	X																
Registration Form	X																
Eligibility (confirmation only at baseline)	X	X															
Medical History and demographics	X																
Skin photography (*optional*)		X								X							
Randomisation Form (after all baseline data collected)		X															
Status Form				X			X			X			X			X	
Physical examination*	X	X		X			X			X			X			X	
Blood pressure	X	X															
Urinalysis	X																
Pregnancy test[+]		X								X[++]							
Eczema Area and Severity Index (EASI) **BLINDED ASSESSOR**		X		X			X			X			X			X	
Investigator Global Assessment (vIGA-AD) **BLINDED ASSESSOR**		X		X			X			X			X			X	
Patient Orientated Eczema Measure (POEM)		X		X			X			X			X			X	
Peak pruritus numerical rating scale (NRS)		X		X			X			X			X			X	
Eczema control (RECAP)		X		X			X			X			X			X	
Patient global assessment (PtGA)		X		X			X			X			X			X	
Dermatology Life Quality Index (DLQI)		X		X			X			X			X			X	
EQ-5D-5L		X					X			X			X			X	
PHQ-9		X								X						X	
GAD-7		X								X						X	
Resource use		X					X			X			X			X	
Adherence check (VAS) & Tolerability							X			X			X			X	
Participant Online Surveys		X														X	
Dispense medication		X					X			X			X				
Screening blood tests (+DNA for filaggrin status, *optional*)	X																
Safety Blood Tests (can be remote)		X	X	X[+++]	X	X	X	X	X	X	X	X	X[++++]	X	X	X	
Safety Blood Pressure (can be remote)**			X	X	X	X	X	X	X	X			X			X	
Safety urinalysis**				X			X			X			X			X	
Safety assessment (can be remote)***												X					
Methotrexate polyglutamate sample****				X			X			X							
Study medication switch review										X							
Study medication dose increment review							X						X				
Concomitant Medications Log																	X
Topical treatments		X		X			X			X							
Adverse Events Log																	X
Withdrawal Form																	X

* Physical examination (according to routine clinical care) required at screening and baseline, extent of physical exam during follow up as deemed appropriate by investigator
** Only required for those on ciclosporin
*** Only for those who switched treatment at 6 months
****Only required for those on methotrexate
+ Women of childbearing potential only. Urine test
++ Repeat pregnancy test at 6 months for patients changing treatment from dupilumab or abrocitinib to methotrexate
+++ Not required for those on dupilumab from the start (week 39 blood tests required for those who switch to dupilumab)
++++ Not required for those on dupilumab or abrocitinib from the start (week 39 blood tests required for those who switch to dupilumab)
A: Where there are no new risk factors, and at investigator's discretion, blood test results obtained in clinical practice within 4 months prior to randomisation can be used as screening bloods (required tests listed in section 6.7.1.1)
B: Baseline safety bloods for all treatments, at investigator discretion based upon timing of screening bloods. Baseline safety blood pressure check if randomised to ciclosporin only.
C: Week 2 Safety bloods and safety blood pressure check if randomised to ciclosporin, week 2 safety bloods if randomised to methotrexate
D: Week 6 & 8 Safety bloods and safety blood pressure check if randomised to ciclosporin only
E: Week 15 & 17 Safety bloods and safety blood pressure check if dose increased on ciclosporin, week 15 & 17 safety bloods if dose increased on methotrexate
F: Week 28 Safety bloods only if switched to methotrexate at 6 months
G: Week 30 Safety bloods only if switched to methotrexate at 6 months
H: Week 41 & 43 Safety bloods check for patients who switched to methotrexate and dose increased only

3 OBJECTIVES

3.1 PRIMARY OBJECTIVE

The primary objective of this trial is to determine the effectiveness of systemic treatments for moderate-severe eczema in adults compared with the control systemic treatment ('standard of care') over 6 months (including a pre-specified subgroup analysis examining moderate and severe groups separately).

3.2 SECONDARY OBJECTIVES

1. Determine the effectiveness of systemic treatments compared with standard of care over 12 months
2. Determine the impact on symptoms, quality of life, daily function and mood of systemic treatments compared with standard of care over 12 months
3. Determine the safety / tolerability of systemic treatments compared with standard of care, and adherence to the medications over 12 months
4. Determine cost-effectiveness of systemic treatments compared with standard of care over 12 months
5. Collect data on which first line therapy optimises treatment continuity over the first year and in the event of a treatment switch, which of the tested pathways optimises treatment outcomes at one year.
6. Determine the incidence of AEs of special interest (see section 10.2 for further information) on systemic treatments compared with standard of care over 12 months
7. Collect clinical data and samples for use by the scientific community to understand atopic eczema disease biology and treatment response in order to improve outcomes in people with atopic eczema.

3.3 EXPLORATORY OBJECTIVES

1. Provide data on whether the carriage of filaggrin gene mutations (one or two) associates with treatment response (possible predictive biomarker).
2. Provide data on whether methotrexate polyglutamate measurement can be used as a biomarker for treatment response on methotrexate.
3. Examine whether baseline IgE and eosinophil levels are predictors of outcome on the different therapies.

4. Examine whether predominant head and neck (“exposed site”) eczema at baseline is a predictor of outcome on the different therapies.
5. Explore patient thoughts about participating in the trial, expectations of treatment, experience in the trial, experience on specific treatments and suggestions relating to the future implementation of these therapies in practice.
6. To assess the utility of photographs for monitoring eczema through deep learning-based severity assessments and accrue a comprehensive collection of photographs of skin, thereby establishing a critical resource for future use by investigators to improve outcomes in eczema.

4 OUTCOME MEASURES

4.1 PRIMARY OUTCOME

Objective eczema severity using EASI[24] (blinded assessment at 6 months, presented as mean absolute change from baseline).

4.2 SECONDARY OUTCOMES

1. Eczema severity measured by:
   a. EASI (blinded assessment)
      i. EASI50/ EASI75/ EASI90/ EASI100/ absolute EASI ≤ 7 (months 1,3,6,9,12, presented as proportion achieving these outcomes)
      ii. Change from baseline in EASI (months 1,3,9,12, presented as mean absolute change)
   b. Investigator Global Assessment[25] (vIGA-AD, blinded assessment, months 1,3,6,9,12, proportion clear/ almost clear)
2. Patient reported symptoms (months 1,3,6,9,12) measured by:
   a. Patient Orientated Eczema Measure[26] (POEM, mean absolute change from baseline)
   b. 11 point peak pruritus numerical rating scale[27] (NRS, mean absolute change from baseline)
   c. Overall disease control[28] (RECAP, mean absolute change from baseline)
   d. Patient global assessment (PtGA (5-point scale), proportion clear/ almost clear)
3. Quality of life measured by:
   a. Dermatology Life Quality Index[29] (DLQI, months 1,3,6,9,12, mean absolute change from baseline and proportion achieving DLQI ≤ 5)
4. Depression and anxiety measured by Patient Health Questionnaire 9-item[30] and Generalised Anxiety Disorder 7-item[31] (PHQ-9 and GAD-7, months 6,12, mean absolute change from baseline and proportion with score < 5)
5. Health economic outcomes will include (months 3,6,9,12):
   a. Resource use questionnaire
   b. 5-level EQ-5D[32,33] (EQ-5D-5L, months 3,6,9,12 mean utility by study arm at each time point. Used to estimate QALYs as described in the HEAP).
6. Safety outcomes will include (continuous to 12 months):
   a. AEs
   b. AEs of special interest
7. Adherence and Tolerability
   a. Visual Analog Scale (VAS)[34] for Medications Taken (VAS, months 3,6,9,12, mean scores)
   b. Tolerability non validated measure Likert scale (months 3,6,9,12, mean scores and frequency distribution)

5 PARTICIPANTS

5.1 STUDY SETTING & RECRUITMENT

The trial will be delivered in UK dermatology secondary care settings (30 centres), utilising the delivery infrastructure of the NIHR Clinical Research Network (CRN). Where local service agreements allow, blood test and blood pressure safety visits will occur at GP practices.

Partipants will be recruited from participating secondary care centres as well as via adverts in primary care, online and with partner bodies including the National Eczema Society (NES). Study sites have been identified via the UK DCTN, NIHR CRN and previous successful dermatology trial networks. The UK DCTN (http://www.ukdctn.org) has over 1000 members with an interest in conducting independent skin research and has a strong track record of successfully delivering large national multicentre trials in skin disease including eczema (14 completed trials, 8 ongoing trials). The Network has and will continue to identify experienced recruiting centres across the whole of the UK with a strong track record of recruiting to time and target.

The geographical spread of study sites and diverse recruitment strategies should expand access to participation so that research follows patient need (including under-researched areas, following INCLUDE principles for recruitment).

5.2 PARTICIPANT IDENTIFICATION

Participants will be recruited by health care professionals in secondary care via:

- Clinics
- Trial specific invitation letters mailed to patients referred to the dermatology services at participating sites
- Databases held within hospital/ pharmacy/ research units
- Study site recruitment websites
- Primary care networks / participant identification centres (PICs)
- The BEACON trial website
- Self referral in collaboration with the NES (via the BEACON website)
- NIHR Be Part of Research Volunteer Service / Registry

We will advertise the study on relevant websites (e.g. BEACON website, NES website) and social media to try to reach under-served communities. The NES, the UK patient organisation for people with eczema and their carers (2700 members), will help to publicise the trial and aid recruitment. It delivers information via its website, social media, publications and a nurse-supported Helpline and reaches hundreds of thousands of people through its wider communications, active social media communities and media engagement work.

Primary care: Support in the identification of suitable participating organisations will be sought from regional research delivery networks (RRDNs). RRDNs will also aid in the set-up and management of primary care PICs, which will use a database search to identify potentially suitable patients who will be alerted to the trial via SMS or letter. These patients will be directed to the trial website to engage with the trial and to be referred to their nearest recruiting site for screening.

NIHR Be Part of Research Service / Registry: The purpose of the Be Part of Research Volunteer Service (BPORVS) is to allow members of the public to become volunteers by creating an account, specifying the areas of research that they are interested in and give consent to be contacted by the Be Part of Research team. Those who consent will receive information about BPORVS, in particular to alert them to specific BPORVS registered studies that they may be interested in, based on their

volunteered details and study specific eligibility criteria, using an online self-registration service. The register is open to those that live in the UK, are over 18 and have an email address.

At the time of registration, volunteers are made aware that they are not signing up to take part in a specific health study when they join this register and that they will only be signposted to studies that have NIHR funding or are listed on the NIHR RDN Portfolio. If the volunteer is interested in the study there will be a link in the email to take them to the study team (e.g. website, pre-screener) where they will move into the study team's screening process and consenting process if they take part in the study.

The Be Part of Research Volunteer Service is funded by the Department of Health and Social Care and delivered by the National Institute for Health and Care Research (NIHR) in conjunction with Public Health Agency, Research & Development, Northern Ireland, NHS Scotland and Health and Care Research Wales. Further information on BPORVS is available here: https://bepartofresearch.nihr.ac.uk/volunteer-service/researchers

5.3 ELIGIBILITY CRITERIA

Assessment of the below eligibility criteria must be performed by a medical doctor.

5.3.1 INCLUSION CRITERIA

1. Patients must be deemed to have the capacity to provide fully informed consent to participate.
2. Adults (18 +) with a diagnosis of atopic eczema (UK Working Party Diagnostic Criteria – see Appendix 5)
3. Moderate to severe eczema requiring systemic therapy.
4. Objective measure of moderate to severe eczema based on an Investigator Global Assessment (vIGA-AD) score of ≥3 at baseline.
5. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.

5.3.2 EXCLUSION CRITERIA

1. Active dermatologic conditions that may confound the diagnosis of atopic eczema or interfere with assessment of treatment.
2. Prior exposure to any of the systemic therapies being investigated in the trial or those with a similar mechanism of action to the systemic therapies being investigated in the trial (see drug specific appendices for examples of excluded drugs and further information).
3. Receipt of any of the following:
    a. Phototherapy (UVB TL01, UVB, PUVA, UVA1), tanning beds, oral or parenteral traditional Chinese medicine or oral systemic immunosuppressant/ immunomodulatory agent that can help eczema (including but not limited to prednisolone, azathioprine, mycophenolate mofetil, tacrolimus, Janus kinase (JAK) inhibitor or phosphodiesterase 4 inhibitor) within 4 weeks prior to randomisation.
    b. Biologic therapy for eczema (including but not limited to amlitelimab, rocatinlimab and nemolizumab) within 3 months prior to randomisation.
    c. Receipt of a cell-depleting agent (e.g. rituximab, alemtuzumab, cyclophosphamide, chlorambucil) for 6 months prior to randomisation or until lymphocyte count returns to normal (whichever is longer)
4. Any medical condition that, in the opinion of the investigator, may compromise the safety of the participant in the trial, interfere with evaluation of the IMP, or reduce the participant's ability to participate in the trial.
5. Receipt of live/ live attenuated vaccine 30 days prior to the baseline visit date or expected need of live / live attenuated vaccination during the trial.

6. Participating in another clinical trial.
7. Women of child-bearing potential (WOCBP*) at risk of pregnancy during the trial (i.e. sexually active women not on effective contraception **)
8. Women who are pregnant or breastfeeding.

** WOCBP defined as: fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.*

***Effective methods of contraception include:*

- *combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:*
  - *oral*
  - *intravaginal*
  - *transdermal*
- *progestogen-only hormonal contraception:*
  - *oral*
  - *injectable*
  - *implantable*
- *intrauterine device (IUD)*
- *intrauterine hormone-releasing system (IUS)*
- *bilateral tubal occlusion*
- *vasectomised partner (only considered highly effective if partner is the sole sexual partner of the WOCBP and the vasectomised partner has received medical assessment of the surgical success).*
- *Male or female condom with or without spermicide*
- *Cap, diaphragm or sponge with spermicide*
- *A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods)*

5.3.3 DRUG-SPECIFIC EXCLUSION CRITERIA

See the individual drug appendices for the additional drug-specific exclusion criteria. **Please note, as long as a participant is eligible to take ciclosporin (control arm) and at least one of the other trial treatments they can be randomised** (i.e. they can meet exclusion criteria for one or more of the other treatments and still be randomised). If they fail to respond at 6 months, a pre-defined treatment switch (as per protocol) may or may not be possible depending on whether they still meet exclusion criteria for the relevant switch option. If the switch is not possible, they would be withdrawn from the trial at that stage.

5.4 INFORMED CONSENT

Informed consent will be obtained by the Principal Investigator or delegated physician at each site, following personal explanation of the trial procedures. If a participant is physically unable to sign the consent form, verbal consent in the presence of a witness can be documented on the consent form and the participant signature should be marked with an X. The following text should be written on the form: 'Participant physically unable to sign consent but has given verbal consent in the presence of [name, relationship to clinic or participant, contact information]'. The witness should sign the

witness line on the consent form and the physician should sign the consent form as normal. Participants who lack capacity to provide verbal consent are not eligible to participate.

5.5 PARTICIPANT WITHDRAWAL AND IMP DISCONTINUATION

A trial participant has the liberty to withdraw their consent at any time and for any reason, without penalty or loss of benefits to which they would otherwise be entitled. Participants who withdraw consent will discontinue their future participation in the trial, however, trial data obtained to the point of withdrawal will not be deleted and will be included in any future analysis. Prior to giving consent, recipients will be informed that they are able to request the destruction of stored blood biological samples upon withdrawal, and that this will only be possible for samples that have not been tested at the time of withdrawal. Participants will not be able to request the deletion of data generated from tested samples. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of participants should be avoided. The investigator will maintain a record of all participants who decide to withdraw from the study and will make every effort to report the reason for withdrawal as thoroughly as possible using the withdrawal form. Withdrawn participants will not be replaced.

The investigator has the right to discontinue the study drug for participants in the event of intercurrent illness, AEs, SAEs, SUSARs (see section 10), protocol violations, administrative reasons or any other reasons. Participants who discontinue trial medication (IMP) will be asked to confirm whether they are still willing to provide trial-specific data at follow-up visits including safety and AE monitoring. In such instances, the visit schedule will be adhered to but noting the participant is no longer taking trial medication within the medical notes /Source Data Worksheets and EDC database. A withdrawal form will not be completed for these participants, but discontinuation of IMP will be documented on the relevant visit status forms.

6 DATA COLLECTION & DATA ENTRY

6.1 TRIAL VISITS

Please see Table 1, Schedule of Events (section 2 Trial Design) for the tabulated trial visits and data collection.

6.1.1 VISIT WINDOWS

The screening visit can be scheduled up to 12 weeks prior to randomisation. Main trial visits are scheduled at month 1 post-randomisation and then months 3,6,9,12, with a visit window of 7 days either side (likewise for PROM data capture). In the event that a visit falls outside the target visit window of +/- 7 days, the visit should be scheduled as soon as possible and the data should be entered into the intended visit. Subsequent visits should be scheduled as per the original visit schedule. Investigators should ensure the month 6 visit (primary endpoint) falls within the visit window where at all possible. A timepoint is considered missed if the visit is not conducted by the start of the subsequent visit window.

6.1.2 SCREENING VISIT

Participants will be screened for the study only after signing the current approved Informed Consent Form. Screening data will be collected as per the Schedule of Events (Table 1) for the screening visit and ongoing visits. Patients can be re-screened at the principal investigator's discretion.

6.1.3 BASELINE VISIT

Eligibility criteria will be confirmed at the Baseline visit (Week 0). Laboratory results must be reviewed by a physician prior to randomisation. Study medication should be dispensed and started on the day of randomisation, or as close as possible. If IMP has not commenced within 2 weeks of randomisation, the site team should inform the central study team via email. Baseline data will be collected as per the Schedule of Events (Table 1).

6.1.4 WEEK 2, 6, 8, 15, 17, 28, 30, 41, 43 SAFETY VISITS

For additional drug-specific safety visit requirements please see the individual drug appendices.

6.1.5 MONTH 1, 3, 6, 9 VISITS

Follow up data will be collected as per the Schedule of Events (Table 1) for the relevant quarterly visits. At each follow up timepoint, a status form is completed; in the event of a missed visit, the status form must be completed.

6.1.6 MONTH 12 OR END-OF-STUDY VISIT

Month 12 data will be collected as per the Schedule of Events (Table 1) above for the month 12 visit and ongoing section. In cases where the participant completes the study to month 12, a withdrawal form should be completed at the final visit to indicate the participant did not withdraw from the trial.

In the event a participant wishes to stop study medication and withdraw from further data collection prior to month 12, a withdrawal form must be completed (see section 5.5), and where possible a withdrawal visit should be scheduled to collect unused medication and undertake a final set of outcome assessments. If the participant continues data collection, the visit schedule should be followed per protocol and a withdrawal form should not be completed (see section 5.5).

6.2 DATA ENTRY

6.2.1 RANDOMISATION

Randomisation of participants will be undertaken as per the instructions in the Randomisation User Guide provided separately.

6.2.2 MACRO ECRF

Authorised staff at sites will transcribe baseline and follow up participant data directly from the participants medical records or from source data into the study eCRF by going to www.ctu.co.uk and clicking the link to access MACRO. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

Study site staff will be delegated by the site PI to access the eCRF and randomisation systems via a Study Site Delegation Log. The request for user access must go to the Trial Manager, who will submit user requests for all sites to the KCTU team upon receipt of completed Study Site Delegation Logs. Requests for user access will be processed within a maximum of 5 working days.

Training videos for data entry staff, study site monitors and trial managers / trial co-ordinators are available at www.ctu.co.uk under the ‘Training’ section. Users can self-register and should select the MACRO related training videos.

6.2.3 PATIENT ONLINE DATA ENTRY (DRDOCTOR)

Data will be entered directly by the participant onto a secure online platform (DrDoctor). Site staff and monitors will be able to check if data has been entered and view the data only. Training for patients and site staff regarding the remote data capture platform (DrDoctor) will be provided.

6.2.4 SAMPLE DATA ENTRY (CAPTURE)

Clinical and sample data will be entered onto a secure web-based forms system used to capture clinical research data for use in research studies and clinical trials 'CAPTURE' (ChArting PaTient outcomes Using an online REsource). CAPTURE has been developed by the NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Trust (GSTT) and King's College London (KCL). Participants will not have access to the CAPTURE system. Data will be entered directly by the site staff and the CAPTURE team. Users will be added/managed by the CAPTURE team.

6.2.5 SKIN PHOTOGRAPHY DATA ENTRY

Participants who provide consent for skin photography will be invited to provide skin photographs (including self-taken) at timepoints as shown in Table 1 (Schedule of Events) via the mySkin online self-report platform/Smartphone application (app). The online mySkin platform is housed on a secure web-based system used to capture clinical research data. Participant-led photography may be completed using the patient's own device; for patients who do not wish to use their own phone and/ or where clinician support is required and/ or where device-standardised image capture is required, study specific devices will be used to support participant-led photography and upload via the mySkin app. Skin photographs will be used by trained members of the research team to quantify disease severity, to complement current objective disease measures and patient-reported outcomes collected in BEACON and to inform the development of accurate digital skin assessment methods.

6.3 PRE-RANDOMISATION DATA COLLECTION

6.3.1 REGISTRATION

When the participant has signed consent, the study site staff should register the participant in the MACRO eCRF system. Upon registration, the system will assign a unique study PIN to be used for the participant throughout the study.

6.3.2 ELIGIBILITY

All eligibility checks must be completed and a physician must confirm eligibility prior to randomisation.

6.3.3 MEDICAL HISTORY

Relevant medical history must be recorded including:

- Date of onset
- Co-morbidities/ past medical history
    - including history of:
        - atopic conditions such as asthma, allergic rhinoconjunctivitis (hay fever), atopic eye disease, eosinophilic oesophagitis, food allergy
        - other eye disorders (including dry eye, conjunctivitis, keratitis, blepharitis, , previous ocular surgery, contact lens wear)

        - skin infections (bacterial and viral including herpes simplex virus and shingles)
        - pain in and around joints
        - acne requiring systemic treatment (e.g. antibiotics/ isotretinoin)
    - diagnosis, date of onset, active or in remission
- Treatment history for eczema (topical/ phototherapy/ systemic therapy)
- Current eczema treatment
    - start date, effect
- Concomitant medications
    - If the participant is taking any medications at baseline, the relevant condition should be recorded in the medical history.
- Smoking history
- Alcohol consumption
- Conception/ pregnancy plans (men and women, relevant to men in case of methotrexate)

6.3.4 DEMOGRAPHICS

Relevant demographic information will be collected prior to randomisation including initals, age (date of birth), sex at birth, ethnicity, weight, and height.

6.3.5 SKIN EXAMINATION

This will cover:

- Skin type (type I-VI)
- Flexural eczema (and sites)
- Non-flexural eczema (and sites)
- Presence of head and neck eczema/ exposed site eczema
- Vesicular hand eczema
- Discoid eczema
- Nodules
- Follicular eczema
- Ichthyosis
- Keratosis pilaris
- Palmar hyperlinearity
- Erythroderma
- Acne
- Eye signs

6.3.6 METHOD OF PARTICIPANT IDENTIFICATION

The method of participant identification (for example, referred to the trial by a clinician, self-referred via the trial website) will be assessed at screening. Furthermore, for patients self-referring via the website, the route through which they identified the trial and self-referral pathway will be explored (for example, social media, NIHR newsletters, poster advertising).

6.3.7 RANDOMISATION

Sites must confirm in the eCRF system whether participants were randomised into the study or not. The randomisation procedure and access to the randomisation system is described in the Randomisation User Guide provided separately.

6.4 EFFECTIVENESS

The core outcome set for eczema recommended by the Harmonising Outcome Measures for Eczema (HOME) initiative (http://www.homeforeczema.org/) is included in this trial.

6.4.1 Objective measures (blinded assessor)

6.4.1.1 Eczema area and severity index (EASI)

The EASI is an objective disease severity score that assesses clinical signs in eczema across four body sites (arms, face/neck, trunk, legs) including erythema, induration, excoriation, lichenification (each on a 4 point scale) as well as area of involvement, with a maximum score of 72. This will be assessed by a nominated blinded-assessor at site, who may not be delegated to or involved in any other trial activities. Site staff will only be delegated to complete this assessment if they have completed the relevant training and are certified to complete the assessments. If the investigator feels that there is a temporary confounding skin condition that will significantly affect the ability to obtain an accurate EASI (e.g. severe sunburn) then they should defer the visit / blinded assessment as appropriate, within the visit window where at all possible (see section 6.1.1).

6.4.1.2 Investigator global assessment (vIGA-AD)

The IGA is an objective global disease severity measure (validated Investigator Global Assessment scale vIGA-AD, 5-point scale - clear/ almost clear/ mild/ moderate/ severe). This will be assessed by a nominated blinded-assessor at site.

6.4.2 Patient-reported outcome measures (PROMs)

Participants should be informed to complete self report measures in the absence of any caregiver prior to each visit as instructed, and will input directly into DrDoctor using a phone, laptop or tablet. Site investigators will check all PROM answers promptly following completion of questionnaires and will follow local guidance for the management of low mood, anxiety, self-injurious or suicidal ideation, or any other concerns raised in PROM responses.

6.4.2.1 Patient Orientared Eczema Measure (POEM)

The POEM is a patient-assessed 7-point instrument to measure patient-reported symptoms including itch, sleep, bleeding, weeping, cracking, flaking and dryness (scored 0-4) with a maximum score of 28.

6.4.2.2 Peak pruritis numerical rating scale (PPNRS/ NRS11)

The PPNRS is a single item, patient assessed measure of peak pruritis, or worst itch, over the previous 24 hours (numerical scale of 0-10).

6.4.2.3 Recap

RECAP is a 7-item patient assessed quiestionnaire to measure AD control. Domains include general perception of eczema, itching, intense itching, sleep disturbance, impact on activities, feelings and acceptibility (each scored 0-4, maximum score 28)

6.4.2.4 Patient global assessment (PtGA)

The PtGA is a patient assessed global measure of their eczema (5 point scale, clear/ almost clear/ mild/ moderate/ severe).

6.4.2.5 Dermatology Life Quality Index (DLQI)

The DLQI is a 10-point (each scored 0-3) patient assessed measure to determine how much a participants skin condition is affecting their life, encompassing symptoms, embarrassment, daily activities, clothes, sport, work, relationships, sexual activities and burden.

6.4.2.6 PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

The PHQ-9 is a patient assessed 9 question (each scored 0-3) instrument to screen, diagnose and measure the severity of depression. It incorporates pleasure from activities, feeling low or hopeless, sleep patterns, energy levels, eating habits, self-perception, concentration, speed of talking and moving and thoughts of self-harm or suicide.

6.4.2.7 GENERALISED ANXIETY DISORDER - 7 (GAD-7)

The GAD-7 is a patient assessed 7 question instrument to screen for generalised anxiety disorder. It incoroprates feeling on edge, not being able to control worrying, worrying too much about things, trouble relaxing, restlessness, irritability and feeling afraid.

6.4.2.8 EUROQOL (EQ-5D-5L)

The EQ-5D-5L is a 5-item participant self-report measure that assesses the health status in terms of five dimensions: mobility, self-care, usual activities, pain/ discomfort and anxiety/ depression.

6.4.2.9 TOPICAL TREATMENTS

At baseline, months 1, 3 and 6, participants will be asked about their current use of topical eczema treatments.

6.4.3 SKIN PHOTOGRAPHY

Participants will be asked to optionally consent to provide photographs (including self-taken) of their skin at baseline and at month 6 via the mySkin app. At some sites, study specific devices will be used to capture participant-led photographs and upload via the mySkin app to standardise image capture for initial validation.

6.5 SAFETY DATA

6.5.1 PHYSICAL EXAM

The general physical examination will be conducted by a qualified physician at screening and baseline according to routine clinical care. The extent of subsequent examinations will be at the discretion of the physician, as clinically indicated. Any examinations not required should be recorded as ‘not done’.

6.5.2 BLOOD PRESSURE

Blood pressure will be measured at screening and baseline. The need for any drug-specific additional safety assessment blood pressure readings is stated in the individual drug appendices (Appendices 1-4). Blood pressure should be measured in an upright position after the participant has been rested for five minutes

6.5.3 ADVERSE EVENTS

During each visit, participants will be asked about adverse events (see section 10). All adverse events will be recorded in an ongoing adverse event log stating start/ end date, severity, serious adverse event, relatedness to study medication, relatedness to study procedure, impact on treatment and outcome. Adverse events of special interest will be captured in more detail (see section 10.2).

6.5.4 CONCOMITANT MEDICATIONS

During each visit, participants will be asked about their current medication. All concomitant medication will be recorded in an ongoing concomitant medication log.

6.5.5 DOSE INCREMENTS AND THERAPEUTIC SWITCHES

All dose increments or reductions will be recorded with any corresponding clinical reason/ comment. All treatment switches (as per the pre-defined 6 month switch criteria) will be recorded with corresponding clinical reason/ relevant comment (see section 7 Interventions).

6.5.6 WITHDRAWAL

A withdrawal form must be completed in the event of participant death, at month 12, or where the participant has stopped taking study medication and is no longer prepared to provide any follow up data. Every effort will be made to continue data collection for participants who stop taking study medication (see also sections 5.5 and 6.1.6). Where the participant has stopped study medication but is still being followed for outcome data, a withdrawal form should not be completed, but a status update must be recorded in the eCRF (status form) every 3 months as documented in section 5.5.

6.6 TREATMENT ADHERENCE

6.6.1 VISUAL ANALOG SCALE FOR MEDICATION ADHERENCE (VAS)

The VAS for medication adherence was developed as an adjunct self-report measure of medication adherence[34]. The VAS asks individuals to mark a line at the point along a continuum showing how much of each drug they have taken in the past 3 months.

6.7 LABORATORY DATA

All tests listed below will be performed as per the time points indicated in the participant timeline in Table 1 (Section 2, Study Design). In addition, laboratory safety tests may be performed at unscheduled times, if deemed necessary by the investigator and abnormal results recorded as an adverse event if clinically significant. Trial sites will use the routine local laboratories. If samples are requested elsewhere (eg via a community based doctor) the laboratory results report should be requested. Results must be reviewed and signed by a physician, the local PI is responsible for ensuring appropriate documentation. After consent is obtained, clinically significant abnormal laboratory results will be recorded in the adverse events log. Individual result values will not be transcribed to the eCRF unless outside the normal range.

Blood samples for methotrexate polyglutamate and filaggrin analysis will be sent to the KCL 9th floor St John's Institute of Dermatology Laboratory, Guy's Hospital, for processing – see sample flow diagrams (Appendix 7) and lab manual for logistical arrangements and sample analysis plans. Where optional consent is provided by participants, there will be long term storage of DNA samples in the St John's Research Tissue Bank (part of Guy's Research Tissue Bank, Ethics Committee ref: 07/H10712/106; HTA License Number 12521).

6.7.1 BLOOD TESTS

6.7.1.1 SCREENING BLOODS

At PI discretion, the following blood tests collected in routine care up to 4 months prior to randomisation will be accepted as screening bloods, assuming no new risk factors. If these tests have not been conducted in the 4 months before randomisation, or in the presence of new risk factors, they should be repeated during the screening visit.

Serology
HIV
Hepatitis B and C
IgE*

Interferon-gamma release assay (IGRA) – e.g. T-SPOT**
VZV (if no history of chicken pox)

HAEMATOLOGY
Haemoglobin
Haematocrit
Total and differential leukocyte count
Red blood cell count
Platelet count

BIOCHEMISTRY

Creatinine
Potassium
Liver function tests (LFTs)
Lipids
Urate
Creatinine kinase

* Not essential to have IgE result back prior to baseline

** TB screening should be performed as per local guidance at individual sites (**but blood testing is an essential requirement**)

6.7.1.2 SAFETY BLOODS

The timing of post-randomisation drug-specific safety tests (including bloods, blood pressure and urinalysis) is shown in the main schedule of events (Table 1, section 2) and drug-specific schedules of events (at the beginning of each of the drug-specific appendices 1-4). The nature of drug-specific safety blood tests is detailed in the relevant drug appendices (section 1.4 in each appendix).

6.7.1.3 METHOTREXATE POLYGLUTAMATE LEVEL (MONTHS 1,3,6)

This is only required in those randomised to methotrexate. Please refer to the methotrexate-specific drug appendix (Appendix 2), section 1.4.4 for details.

6.7.1.4 BLOOD FOR DNA

All patients who consent for optional samples, at screening visit (collection at any visit permitted): 2 x 6ml of blood will be collected in EDTA Vacutainer tube (purple top) for DNA extraction to check FLG status and for future genomic interrogation. Please refer to lab manual for full procedure on how to collect, store and send samples.

6.7.2 URINALYSIS (BASELINE, MONTHS 1,3,6,9,12)

A urine protein:creatinine ratio is required at screening. This is only required as part of ongoing safety visits for those on ciclosporin. Please see Appendix 1 (ciclosporin-specific drug appendix) section 1.4.2.4 for timing and further details of required safety urinalysis.

6.7.2.1 URINE PREGNANCY TEST

Urine beta-hCG test will be used for the female participants of child-bearing potential during the baseline visit prior to randomisation to allow the site pharmacy adequate time to prepare the study medication for dispensing on the same day post-randomisation. The urine test beta-hCG test will be repeated at the 6-month visit only for female participants of child-bearing potential switching treatment from dupilumab or abrocitinib to methotrexate. Please refer to methotrexate-specific drug appendix (Appendix 2) section 1.4.3.3 for details.

6.8 IMP DOSING DATA

6.8.1 STUDY MEDICATION PRESCRIBED DOSE LOG

Study medication dosing, including any active temporary or permanent discontinuation of study medication, will be recorded on the Study Medication Prescribed Dose Log.

6.9 MEASURES TO PROMOTE PARTICIPANT RETENTION

Where possible data collection will be via routine follow up clinics, minimising the need for additional research visits. Much of the data are collected in routine care in recruiting sites and are not time consuming to complete. In the event a participant wishes to stop taking study medication, follow up visits should still be completed with participant agreement (see sections 5.5, 6.1.6 and 6.5.6). Where appropriate, safety visits (blood sampling +/- blood pressure measurement) can happen remotely in the community. The week 30 safety assessment for those who switch on to methotrexate or dupilumab at 6 months could be remote (if easier for participant and local blood testing available in the community where needed).

7 INTERVENTIONS

7.1 CHOICE OF COMPARATORS

In the first iteration of the platform two different classes of systemic therapy (methotrexate and dupilumab) were tested against a control (ciclosporin). Abrocitinib is the first new treatment arm to enter the platform and has been included as an exemplar of the new class of JAK inhibitors licensed for and increasingly used to treat adult atopic eczema.

Further treatments and arms will be added in future amendments. The Trial Management Group (TMG) are responsible for proposing those treatments and related dosing to the Trial Steering Committee (TSC) for ratification.

Patients will be randomised 1:1:1:1 to one of the following trial arms:

1. Ciclosporin (PO)
2. Methotrexate (SC)
3. Dupilumab (SC)
4. Abrocitinib (PO)

For detailed information on each IMP please refer to the relevant individual drug appendix (Appendices 1-4). Information regarding side effects and administration is provided in those appendices and in the Participant Information Sheet (PIS).

7.2 INTERVENTION AND COMPARATOR DESCRIPTION, DOSING, PACKAGING, LABELLING, STORAGE AND ACCOUNTABILITY

Sites should not randomise patients unless they have sufficient drug available on site for all trial arms.

Investigators will be encouraged to adhere to the suggested dose increases for ciclosporin and methotrexate, but changes of dose outside of this schedule where clinically indicated will be permitted and recorded.

Dispensed trial medicines will be collected from pharmacy by the patient or their representative. At the baseline visit, the research team will train the patient on how to administer their new treatment using either their dispensed medication or a dummy device and counsel them on the new medication.

Participants should start the medication the day of their baseline visit, but if that is not possible as soon as possible thereafter. If there is a delay of more than 2 weeks then the site must contact the BEACON team to clarify how to proceed.

7.3 DISCONTINUING ALLOCATED INTERVENTIONS

Participants may temporarily or permanently stop taking study drug at their discretion or that of the site investigator. In all cases every effort should be made to ensure follow up data is collected per protocol to the end of the trial, unless the participant is formally withdrawing from further data collection (see section 5.5, 6.1.6, and 6.5.6). The clinical study report will include reasons for participants discontinuing study medication.

7.4 CONTRAINDICATED TREATMENTS AND REPORTABLE TREATMENTS THAT CAN IMPACT ECZEMA SEVERITY

7.4.1 CONTRAINDICATED TREATMENTS

Medications listed as contraindicated in the Summary of Product Characteristics (SmPC) for the trial drug that the participant is on (or, where relevant, for a trial drug that they are due to switch to) should be avoided, but should the IMP be discontinued as a result of starting a contraindicated medication, the participant should not be withdrawn from the trial (unless specifically requested by the participant or in the event of a death) and data collection should continue wherever possible (see also section 5.5 and 6.5.6).

The following contraindicated medications are listed in the current SmPC's for the IMPs on the Electronic Medicines Compendium (EMC), but investigators are advised to refer to the most up to date SmPC on the EMC when assessing a participant's concomitant medications:

- Ciclosporin (Neoral oral solution / soft gelatin capsules): products containing *Hypericum perforatum* (St John´s Wort); medicines that are substrates for the multidrug efflux transporter P-glycoprotein (P-gp) or the organic anion transporter proteins (OATP) and for which elevated plasma concentrations are associated with serious and/or life-threatening events, e.g., bosentan,

dabigatran etexilate and aliskiren. Investigators are advised to refer to the most up to date SmPC on EMC for a more comprehensive list of medications that utilise these pathways.

- Methotrexate (Metoject 15mg / 20mg solution for injection pre-filled pen: concurrent vaccination with live vaccines
- Dupilumab (Dupixent 300mg solution for injection pre-filled pen / syringe: no contraindicated medications listed
- Abrocitinib (Cibinqo 200mg film-coated tablets: no contraindicated medications listed

7.4.2 REPORTABLE TREATMENTS THAT CAN IMPACT ECZEMA SEVERITY

Exposure to medicines/ treatments that may impact eczema severity should be avoided where possible during the trial. These include:

- UV treatment (e.g. UVB, UVB TL01, PUVA, UVA1, tanning beds)
- Immunosuppressants/immunomodulatory agents that can help eczema (e.g. prednisolone, azathioprine, mycophenolate mofetil, tacrolimus, Janus kinase (JAK) inhibitors, biologics therapies that can help eczema, and therapies involved in the trial if they have not been randomised to them)

Should exposure to these medications/ treatments be unavoidable during the trial, they must be flagged on the concomitant medications log as a reportable medication that might impact eczema severity, in line with guidance on CRF and database completion (provided separately to research teams). Any adverse events leading to the commencement of these treatments should also be documented on the AE log (and AESI logs if relevant). Participants who commence a concomitant medication/treatment that may impact eczema severity should remain on trial (and on trial medication where PI feels appropriate) and continue data collection per protocol wherever possible. They should not be withdrawn from the trial unless specifically requested by the participant or in the event of a death (see section 5.5 and 6.5.6).

Topical corticosteroids and topical calcineurin inhibitors will be permitted throughout the trial as per standard practice.

All other usual care therapy is allowed during the trial.

7.5 PROVISIONS FOR POST-TRIAL CARE

Patients on methotrexate or ciclosporin at trial end will be able to continue treatment where deemed appropriate by the PI. Patients on dupilumab or abrocitinib will be able to continue treatment where in line with NICE criteria (including participants who switched from methotrexate or ciclosporin to dupilumab at the 6 month stage and participants on dupilumab or abrocitinib throughout the trial who had received previous systemic therapy for eczema pre-trial (e.g. azathioprine, mycophenolate mofetil) or are contraindicated to standard systemic treatments/ it would be inappropriate to switch). Any participant who suffers harm from trial participation has access to all services and relevant compensation offered by their participating institution.

8 ASSIGNMENT OF INTERVENTIONS

8.1 RANDOMISATION METHOD

Randomisation is by the method of minimisation, balanced by recruiting study site and disease severity (moderate/ severe) and with a random component.

8.2 CONCEALMENT MECHANISM

Randomisation and treatment allocation will be via the web based KCTU randomisation system, maintained by the King's Clinical Trials Unit for the duration of the project. A random component and a simple randomisation run in period will both be implemented within the minimisation algorithm to assure allocation concealment of subsequent participants.

8.3 RANDOMISATION IMPLEMENTATION

8.3.1 ALLOCATION SEQUENCE GENERATION

The randomisation sequence will be generated dynamically by the KCTU team via the KCTU web based randomisation system, in accordance with the specification agreed with the CI and Senior Statistician. The Chief Investigator, Senior Statistician and TMG will be blinded to the sequence generation.

8.3.2 ENROLMENT OF PARTICIPANTS

Participants will be enrolled in the study for the purpose of CONSORT reporting at the point of signing a consent form to being screened for eligibility and will be part of the target at the point of randomisation.

8.3.3 ASSIGNMENT OF PARTICIPANTS TO INTERVENTIONS

Recruiting sites will assign participants to interventions by logging into the 'KCTU randomisation and IMP management system' at www.ctu.co.uk (click 'randomisation' and select 'BEACON') and entering the participant's initials, date of birth and stratifiers (see Randomisation User Guide). The system will randomise the participants to one of the study medications in a ratio of 1:1:1:1.

8.3.4 RANDOMISATION PROCEDURE

See Randomisation User Guide.

8.4 BLINDING STATUS OF RESEARCHERS*

TABLE 2 BLINDING STATUS

Individual blinding status	Blinded	Unblinded
Chief Investigator		X
Academic Lead		X
Principal Investigators and all other staff at site		X
Trial Manager/Trial Co-ordinators		X
Senior Statistician	X	
Junior Statistician		X
Pharmacists at site		X
Trial Pharmacist		X
Trial Participants		X
EASI and IGA outcome assessors	X	
Local research teams (excluding outcome assessors)		X
Treating Clinicians		X
Sponsor (CRA/Monitor)		X
Trial Steering Committee (TSC)	X	
Data Monitoring Committee (DMC)		X

**For roles not listed please refer to study delegation logs*

The blinding status of the research team with respect to an individual patient's allocation is detailed in Table 2 above.

Only the Junior Trial Statistician will see summary data split by intervention allocation, as this is required for the preparation of reports to the DMEC. No other members of the trial team will have access to this information until the primary analysis is complete. This information will be available to the DMEC members in closed reports.

9 DATA MANAGEMENT

There are five datasets in the trial: the KCTU randomisation system, KCTU Ennov Macro eCRF system dataset, DrDoctor platform, GSTT CAPTURE system, and the dedicated research database for skin photography. The CI will act as custodian for the trial data.

9.1 RANDOMISATION SYSTEM AND MACRO

A web based electronic data capture (EDC) system will be designed, using the InferMed Macro system. The EDC will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL.

The CI or delegate will request usernames and passwords from the KCTU. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g Trial Manager) in the first instance.

Participant initials and date of birth will be entered on the EDC. NHS number, email address, participant names, addresses and full postcodes will not be entered into the EDC. No data will be entered onto the EDC system unless a participant has signed a consent form to participate in the trial. Source data will be entered by recruiting site staff, typically within 7 days of data collection by authorised staff onto the EDC by going to www.ctu.co.uk and clicking the link to access the MACRO EDC system. A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

The CI team will undertake appropriate reviews of the entered data, in consultation with the project analyst for the purpose of data cleaning and will request amendments as required. No data will be amended independently of the study site responsible for entering the data.

Prior to formal trial comparisons the site PI will review all the data for each participant and provide electronic sign-off to verify that all the data are complete and correct. At this point, all data for formal trial comparisons can be locked for analysis.

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate

Optional source data worksheet templates will be available to all recruiting sites if helpful. These will be prepared after the database specification is finalised and database testing is complete. Participating sites will complete source data location lists defining the source data at their site, specifying which, if any, source data worksheets will be used.

9.2 DRDOCTOR

DrDoctor, a commercial web-based patient engagement platform, will facilitate the collection of patient reported outcome measures. Patient reported outcome measures will be collected in their validated format. Participants will be able to directly input data at the required time points (up to 1

week before each scheduled trial visit, except baseline where assessments will only be available that day). Site staff need to check that assessments have been completed at each study visit and request completion of any outstanding forms during the appointment. Study site staff experiencing issues with system access or functionality should contact a CI delegate (e.g Trial Manager). Patients experiencing issues with the system should contact the research team at the study site, who will seek advice from the CI delegate (e.g. Trial Manager).

Participant's mobile number will be entered on to DrDoctor; the name, date of birth, post code, and hospital number entered onto DrDoctor are determined by 'patient tokens' that include no real participant data. No data will be entered onto the DrDoctor system unless a participant has signed a consent form to participate in the trial. To login into the staff portal, staff will be invited to create a username and account. Data entry will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

At the end of the trial, DrDoctor will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate.

9.3 CAPTURE

The GSTT CAPTURE system will be used to track all samples collected for the study. Patient demographics (initials, gender, ethnicity and date of birth) and study ID, along with the date of the study visit and the samples collected at that visit will be added via the CAPTURE front-end into the CAPTURE database. Along with this, details regarding the use of the samples will also be stored in the database.

A pre-defined report will be created by the CAPTURE team and made available to the appropriate users, so that all data entry can be monitored in real time by the CI team.

Users will be added/managed by the CAPTURE team.

9.4 SKIN PHOTOGRAPHY

Participants who provide consent for skin photography will provide photographs (see section 6.4.3 for further information) of their skin via the mySkin app, access to which will be linked with the participant ID. Photographic data will be hosted on secure servers with our cloud provider, Amazon Web Services, and managed by GSTT in compliance with best practice. After de-identification, images will be transferred (under an appropriate data sharing agreement) from the GSTT network to KCL data management and processing servers via a secure protocol. See Appendix 6 for data flow diagram.

9.5 DATA SECURITY

9.5.1 MACRO

Data Management Plans will be provided to the Trial Manager for the Trial Master File, detailing relevant security information about both data systems. Systems access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested and a request for access to be revoked must be requested when staff members leave the project.

Participant initials and date of birth will be entered into the systems. No more identifiable data will be entered into the eCRF system. Trial sites will maintain a master participant log linking participant identifiers to study numbers. No data will be entered unless a participant has signed a consent form to participate in the trial.

9.5.2 DrDoctor

Data Management Plans will be provided to the Trial Manager for the Trial Master File, detailing relevant security information about DrDoctor systems. Systems access will be strictly restricted through user-specific passwords to patients and authorised research team members. It is a legal requirement that passwords are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested and a request for access to be revoked must be requested when staff members leave the project.

Participants' mobile number will be entered into the system. No identifiable data will be entered into the DrDoctor system. Trial sites will maintain a master participant log linking participant identifiers to study numbers. No data will be entered unless a participant has signed a consent form to participate in the trial.

DrDoctor is based in secure premises with door locks, security alarms, motion detectors and CCTV. DrDoctor received 'standards exceeded' for their 2023-2024 Data Security and Protection Toolkit submission and is registered with the ICO. DrDoctor has Cyber Essentials Plus certification and is ISO27001 accredited.

Protection from cyber attack: DrDoctor data centre providers must be able to evidence their plan for and resilience to cyberattacks, particularly denial of service events and malicious code that might target critical components or devices (such as routers and switches).
Back-up and recovery: DrDoctor maintains a prioritised focus on Business Continuity Planning & Disaster Recovery in the event of an unexpected disruption in service or business operations.

DrDoctor complies with the following industry standards:

- DSPT Standards exceeded
- Data centres used as part of the DrDoctor system are ISO27001 accredited
- DrDoctor is ISO27001 accredited
- Encryption standards – SSL/TLS for data in transit and AES 128/256 bit for data at rest
- ICO registration number (Z3313550) (edited)

DrDoctor is compliant with the current Data Protection Legislation, the Data Protection Act, as well as relevant guidance and codes of practice on data protection. ICNH Ltd, trading as DrDoctor, is registered with the Information Commissioner's Office. There are, in addition, regular spot checks, resilience and external penetration testing, disaster recovery and business continuity plans in place to ensure the confidentiality and protection of patient and hospital data.

- Data in transit/at rest SSL/TLS (transit), AES 128/256 (at rest)
- Monitoring of system performance and availability
- Auditing of user logins, interactions and system modifications (patient, clinical and admin)
- IG policies are in place and DrDoctor staff are spot checked tested annually.

Microsoft Azure data centres used as part of the DrDoctor system are ISO27001 accredited;
Microsoft Azure - https://www.microsoft.com/en-us/TrustCenter/Compliance/ISO-IEC-2700.

9.5.3 CAPTURE

Data Management Plans will be provided to the Trial Manager for the Trial Master File, detailing relevant security information about the system.

CAPTURE sits on the GSTT servers behind the NHS firewall and data stored within CAPTURE is therefore afforded the same security controls as any clinical data held within the GSTT servers. Data stored on CAPTURE will be kept in compliance with the Research Governance Framework issued by the Department of Health, which specifies that the data be kept for at least 5 years. Personal information stored within CAPTURE that could identify individuals will remain strictly confidential. Access to the information will be restricted at all times to researchers with clear purpose or need to access it. All data held within CAPTURE is processed in accordance with the Data Protection Act 2018 and UK GDPR.

CAPTURE will be used by GSTT/KCL staff members onsite as well as third-party collaborators. Security to the application is managed at a number of different layers.

- **Web Application Proxy**: In order for users to access the system over the internet, CAPTURE is published through the DMZ Web Application Proxy (WAP) gateway. This is a secure way of publishing web-based content out over the internet. Any request for https://capture.gstt.nhs.uk will need to be authenticated – and the WAP layer depends on internally managed ADFS servers for authentication. This layer is owned and managed by the IT Infrastructure team.
- **ADFS & SafeNET 2-Factor Auth**: When accessing CAPTURE internally on the GSTT network, each user authenticates against ADFS, supplying their normal GSTT credentials to be authenticated against the Trust Directory. All external user accounts will be created and managed in a separate Active Directory. The external directory is also supported by the Service Desk. Any member of staff accessing CAPTURE externally, or a non-GSTT staff member accessing CAPTURE will also need to authenticate via SafeNET 2-factor authentication. This is a fully supported solution implemented by GSTT. Any user wishing to access the system externally will need to be enrolled on SafeNET and supplied with a token. They then connect that token to the SafeNET mobile app on their personal smartphone device. When logging in they supply their account credentials along with the SafeNET “OTP” (One-time-passcode), given to them via the app. This ensures that even if a malicious user is able to gain access to a staff member’s username and password, they will not be able to gain unauthorised access to CAPTURE.

9.5.4 SKIN PHOTOGRAPHY

Photographs will be collected at baseline and month 6 via the mySkin app (either on participants’ own device or a study specific device). These data are hosted on secure servers with the sponsor cloud provider, Amazon Web Services and managed by the sponsor organisation, GSTT in compliance with best practice. Security certifications for our provider includes ISO and CSA STAR certifications for information security in cloud-based environments. The data are encrypted in transit while being captured from the patients and at rest. All data are processed in accordance with the Data Protection Act 2018 and UK GDPR. Personal information that could identify individuals will remain strictly confidential and any analysis will occur in a highly secure data environment (i.e. Trusted Research Environment). Access to the information will be restricted to research personnel with clear need to access it. Data will be kept in compliance with the Research Governance

Framework issued by the Department of Health, which specifies that the data should be kept for at least 5 years.

After de-identification of the photographs, the data will be transferred from the GSTT network to the KCL School of Biomedical Engineering and Imaging Sciences (BMEIS) data management and processing servers via a secure protocol. The data management system implemented in BMEIS relies on XNAT, an online archiving system (http://xnat.org). XNAT provides secure access via tailored permissions based on user credentials. The data are stored on a dedicated storage solution, access to which is also managed via user credentials, and access will only be granted to research personnel with a clear need for access. All data transfers are done through a secure restful API using the https protocol and a dedicated certificate. The system itself and Unix server running it are kept up to date by the BMEIS dedicated IT team. No external IT supplier has access to the BMEIS systems. All data access is logged by the system. The system is only accessible from within the BMEIS network that is enclosed within a firewall within the KCL firewall. As a result, only users with BMEIS credential can access the system, which is otherwise hidden from other KCL members. As part of their induction, KCL members receive training about data protection and governance policy

9.6 DATA QUALITY PROCESSES

9.6.1 MACRO

At the database design stage, validations were programmed into the systems to minimise data entry errors by querying the data entered in real time with sites.

The CI and central trial team will undertake appropriate reviews of the entered data in consultation with the project analyst where appropriate for the purpose of data cleaning and will request amendments to the MACRO eCRF system data as required. No data will be amended independently of the study site responsible for entering the data.

No data can be amended in the randomisation system, however CI or delegate (e.g., Trial Manager) may request King's Clinical Trials Unit to add notes against individual participant entries to clarify data entry errors. Any errors should be reported by site staff to the Trial Manager as soon as possible once they are detected. The trial manager will onward report errors to KCTU and retain records in the TMF.

The KCTU will provide the Trial Manager with Data Management Plans for both the Ennov Macro eCRF system and the randomisation system once the systems are made live. Those documents will be filed in the Trial Master File.

A regular Data Management Report will be produced by KCTU and passed to the Trial Manager, who will raise Data Clarification Requests (DCRs) with sites in the eCRF system. Study sites will periodically review raised DCR's and respond to the queries raised.

During site monitoring visits, the CRA will raise any queries with sites.

9.6.2 DRDOCTOR

Data will be collected on the DrDoctor platform which will enable the system to collect longitudinal clinical data using PROMs – also known as electronic clinical outcome measures (eCOAs). The study site teams will undertake appropriate reviews of the data at each visit to ensure patient reported outcomes are completed. DrDoctor will provide the Trial Manager with a Data Management Plan for the system which will be filed in the Trial Master File. Data Management Reports will be downloaded by the Trial Manager.

9.6.3 CAPTURE

A pre-defined report showing all data that has been entered into the CAPTURE database will be created on the CAPTURE application and access will be granted to the appropriate users. Any data changes made by users is tracked and recorded, and there are several validation rules setup within the front-end of the application to ensure the cleanest dataset possible.

9.7 DATABASE LOCK

9.7.1 RANDOMISATION SYSTEM AND MACRO

At the end of follow up for each intervention, the site PI's will review all the data for each participant in the MACRO eCRF system and provide electronic sign-off to verify that all the data are complete and correct.

The Trial Manager and KHP-CTO CRA will confirm all checks are complete and all monitoring queries have been resolved prior to database lock. No data will be released without the approval of the Senior Statistician.

Before the final data extract for each arm is requested, the Trial Manager will lock each individual participant in the relevant arm(s). When the study in its entirety ends, KCTU will remove all relevant data entry user access prior to data extract and will retain only 'monitor' access for site PI's and other relevant individuals. Until that time, all sites will retain access to the system.

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute to sites as appropriate. Once sites have received copies of their individual datasets and confirmation of receipt has been received, the Trial Manager will request that relevant user access is removed from the MACRO eCRF system for any sites no longer participating in the future arms or at the end of the study in its entirety. A copy of the dataset will be stored in the TMF.

9.7.2 DRDOCTOR AND CAPTURE

The Trial Manager and KHP-CTO CRA will confirm all checks are complete and any issues have been resolved prior to database lock for any given arms. No data will be released without the approval of the senior statistician.

When the final data extract is requested, DrDoctor will remove all relevant data entry user access prior to data extract and will retain only access for site PI's and other relevant individuals.

Upon request, DrDoctor will provide a copy of the final exported dataset to the CI/senior statistican and the CI will onward distribute to sites as appropriate. Once sites have received copies of their individual datasets and confirmation of receipt has been received, the Trial Manager will request that relevant user access is removed from the system. A copy of the dataset will be stored in the TMF prior to archiving.

10 ADVERSE EVENT MANAGEMENT AND REPORTING

All adverse events will be recorded from consent to the end of study visits in the participants medical notes, the AE source data worksheets and the eCRF. SAE's will be additionally reported, within 24 hours of site becoming aware of the event, to the KHP-CTO.

All SAEs, SARs and SUSARs will be reported immediately (and certainly no later than 24hrs) by the Investigator to the KHP-CTO for review in accordance with the current Pharmacovigilance Policy and as per the instructions on the SAE report form.

All SAEs in participants randomised to abrocitinib will additionally be reported to Pfizer by the CI within 24 hours of becoming aware of the event, or immediately for fatal or life-threatening events. Reporting to Pfizer will follow specific guidance provided by Pfizer and will use the Pfizer AE reporting form, which will be emailed to the relevant contact. All SAEs in participants on abrocitinib will also be reported to the KHP-CTO following the procedure described in this section.

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

- Adverse Event (AE): Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
- Adverse Reaction (AR): Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.
- Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) for that product.
- Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:
  - results in death
  - is life-threatening
  - required hospitalisation or prolongation of existing hospitalisation (excluding elective or planned procedures)
  - results in persistent or significant disability or incapacity
  - consists of a congenital anomaly or birth defect
- Important Medical Events (IME): Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.
- Adverse Event of Special Interest (AESI): Pre-specified adverse events of interest for which more detailed information will be collected

Pregnancy: Although not a serious adverse event, any unplanned pregnancy in female participants will also be reported via the SAE reporting system. The outcome of the pregnancy will be reported as a follow-up report to the SAE. Pregnancies in female partners of male participants will not be reported, in line with standard clinical practice with these medications.

10.1 EVALUATING AES AND SAES

10.1.1 ASSESSMENT OF INTENSITY

The Investigator will make an assessment of intensity for each AE and SAE reported during the study. The assessment will be based on the Investigator's clinical judgement. The intensity of each AE and SAE recorded in the eCRF should be assigned to one of the following categories:

- Mild; An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities
- Moderate; An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe; An event, which is incapacitating and prevents normal everyday activities

An AE that is assessed as severe should not be confused with an SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

10.1.2 ASSESSMENT OF CAUSALITY

The Investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.

The causal relationship to the study product assessed by the Investigator (or medically qualified delegate) should be assessed using the following classifications:

- Not Related: In the Investigator's opinion, there is not a causal relationship between the study product and the AE.
- Unlikely: The temporal association between the AE and study product is such that the study product is not likely to have any reasonable association with the AE.
- Possible: The AE could have been caused by the study participant's clinical state or the study product.
- Likely: The AE follows a reasonable temporal sequence from the time of study product administration, abates upon discontinuation of the study product and cannot be reasonably explained by the known characteristics of the study participant's clinical state.
- Definitely: The AE follows a reasonable temporal sequence from the time of study product administration or reappears when study product is reintroduced.

There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the report is submitted within 24 hours of becoming aware of the event. The Investigator must always attempt to assess causality for every event prior to transmission of the SAE form to the Sponsor, however the initial report should be sent without this information if needed to meet reporting timelines. The Investigator may change his/her opinion of causality considering follow-up information, documenting this on an SAE follow up form and sending to the sponsor accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.1.3 ASSESSMENT OF EXPECTEDNESS

A reasonable possibility of a relationship conveys that there are facts, evidence and/or arguments to suggest a causal relationship, rather than a relationship that cannot be ruled out.

- Expected: An adverse reaction, the nature or severity of which is consistent with the applicable Reference Safety Information (RSI) in the Summary of Product Characteristics for an approved medicinal product
- Unexpected: An adverse reaction, the nature or severity of which is not consistent with information in the relevant reference document.

Section 4.8 of the SmPC's will form the RSI for the IMPs in this trial. Please refer to the drug-specific appendices 1-4 for the SmPC versions currently approved as the RSI for assessing expectedness.

10.1.4 FOLLOW-UP OF AES AND SAES

After the initial AE/SAE report, the Investigator is required to proactively follow each participant and provide further information to the Sponsor on the participant's condition. All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts. All AEs and SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the participant is lost to follow-up. Once resolved, the adverse event log will be updated. The Investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. New or updated information will be recorded on anSAE follow up form,signed and dated by the Investigator. The follow up SAE form should be sent to the Sponsor.

10.1.5 POST-STUDY AES AND SAES

A post-study AE/SAE is defined as any event that occurs outside the AE/SAE detection period. Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including death, at any time after a participants has been discharged from the study, and he/she considers the event reasonably related to the investigational product, the Investigator will promptly notify the Sponsor.

10.2 ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

The AESI listed below will be recorded in more detail via AESI report forms throughout the trial. A template document outlining the information to be recorded will be provided to sites, to be recorded onto Source Data Worksheets or directly into the participants medical records for transcribing into the MACRO eCRF system:

- Ocular surface disease – e.g. conjunctivitis/ blepharitis/ keratitis/ dry eye/ keratoconus
- Pain in or around joints
- Facial skin rashes (including acne)

10.3 ADVERSE EVENT PROCESSING RESPONSIBILITIES

The Sponsor has delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004) to the KHP-CTO.

The KHP-CTO will report SUSARs to the relevant ethics committee and to the MHRA. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days;
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

The Chief Investigator and King's Health Partners Clinical Trials Office (KHP-CTO) (on behalf of the co-sponsors) will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to

the MHRA and REC annually.

The Trial Statistician will report relevant adverse events to the Data Monitoring Committee.

11 ETHICS AND REGULATORY APPROVAL

The KHP-CTO will be responsible for preparing the submission packs for regulatory approval. The CI will be responsible for preparing the submission packs for ethics approval.

Individual participants will consent to participate. The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996)[35], the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments[36].

This protocol and related documents will be submitted for review to Health Research Authority (HRA), Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation in the UK.

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the co-sponsors) and the REC within the timelines defined in the Regulations.

11.1 PROTOCOL AMENDMENTS AND VERSION CONTROL OF STUDY DOCUMENTS

The Trial Manager and the KHP-CTO CRA will be responsible for preparing and submitting protocol amendments to the ethics committee and the MHRA.

Participant-facing documents (e.g. PIS, consent form) will be prepared by the co-ordinating centre and the co-ordinating centre is responsible for maintaining version control.

All correspondence, including submission packs with attachments and approvals, will be filed in the Trial Master File.

Recruiting study sites are responsible for communicating relevant information to participants.

The Trial Manager will be responsible for updating the ISRCTN register subsequent to relevant protocol amendments.

12 STATISTICAL METHODS

12.1 SAMPLE SIZE JUSTIFICATION

This study is designed to test separate pair-wise comparisons of methotrexate, dupilumab and abrocitinib for superiority against ciclosporin. The minimum clinically important difference for EASI is 6.6[37]. In order to detect a mean absolute difference of 6.6 (assuming a standard deviation of 13.6 (pooled SD=13.6 for EASI at 24 weeks in the pivotal industry trial LIBERTY AD CHRONOS[9]), 20% loss to follow up at primary endpoint, with 90% power and conservative type 1 error rate of 2.5% per comparison) we will need to randomise at least 134 participants per arm. This will have 94% power to test a difference between each comparator and ciclosporin of 6.6 on EASI, 90% for a difference of 6 points, and 80% for 5.2 points. In the subgroup of ~30% participants with severe disease at baseline (n=40 per arm), there is 80% power for a difference of 9.6 points and 50% power for 6.6 points. In order to enable a powered comparison between new arms (e.g. abrocitinib) and the current control arm (ciclosporin) using contemporaneously recruited participants, we will need to extend recruitment to the current control arm.

12.2 STATISTICAL ANALYSIS PLAN

A full Statistical Analysis Plan (SAP) will be drafted in accordance with the KCTU Standard Operating Procedures authored and approved by the Trial Steering Committee and Data Monitoring and Ethics Committee.

The Junior Trial Statistician will be fully blind until the first version of the SAP is approved by the Data Monitoring Committee (DMC).

After the first version of the SAP is approved by the DMC, the Junior Trial Statistician will become unblinded and access participant level data by arm. The Junior Statistician will then have access to the adherence data and be able to monitor and inform the DMC of the trial adherence of the participants. They will present the closed DMC report to the DMC members.

The Junior Trial Statistician will not take part in any discussion that influences the early stopping of the trial at any TMG, TSC, or DMC meetings.

12.3 GENERAL PRINCIPLES

We will report data in line with the Consolidated Standards of Reporting Trials (CONSORT) for multi-arm trials showing attrition rates and loss to follow-up. This will include the number of eligible patients, number of patients agreeing to enter the trial, number of patients refusing, then by intervention arm: the number of patients compliant/non-compliant with treatment, the number continuing through the trial, the number withdrawing, the number lost to follow-up and the numbers excluded/analysed at each time point.

Analyses will be carried out using the intention to treat principle: participants will be analysed in the group they are randomised to, and available data from all participants are included, including those who do not complete therapy. Every effort will be made to follow up all participants in all arms for research assessments. For estimates of treatment effects in each comparison, only participants who could have been randomised to either arm (i.e. not contraindicated to either drug and contemporaneously randomised) will be included in that comparison.

Analysis will be conducted in Stata version 17.0 or later.

12.4 BASELINE CHARACTERISTICS

No statistical significance tests or confidence intervals will be calculated for the difference between randomised groups on any participant level baseline variables. The randomisation of participants to intervention groups means that any imbalance over all measured and unmeasured baseline characteristics is by definition due to chance.

Appropriate summary statistics will be applied to describe demographic and clinical measures: mean and standard deviation for all symmetric (non-skewed) distributed measures; median, 25th and 75th quartiles for skewed distributions. QQ plots and histograms will be used to assess data distributions of continuous measures. Categorical outcomes will be described using both numbers and proportions (percentage).

12.5 STATISTICAL METHODS FOR PRIMARY AND SECONDARY OUTCOMES

12.5.1 STATISTICAL METHODS FOR PRIMARY OUTCOME

For the repeated measures of the continuous EASI score, linear mixed models will be fitted to the outcome variable at all time points. We will use a linear mixed model, with fixed effects of trial arm, time and a time*arm interaction term, baseline values of the EASI score and minimisation factors (recruitment centre, severity). Random intercepts will be fitted at the participant level.

Marginal treatment effects will be estimated for the EASI score at 6 months and reported as adjusted mean difference in scores between the comparative groups, its standard error, 97.5% confidence intervals and p-value. Significance level (type 1 error) will be two-sided at 0.025.

12.5.2 STATISTICAL METHODS FOR SECONDARY OUTCOMES

For continuous secondary outcomes, the same modelling approach will be followed as for the primary outcome.

For binary secondary outcomes logistic mixed models will be estimated. We will report the treatment effect estimate as the conditional odds-ratio, the 97.5% confidence interval and p-value.

12.6 INTERIM ANALYSES (STATISTICAL)

Following discussion with the oversight groups, sponsor and funder as the study progresses, we may include one interim analysis for futility and efficacy. This will control the type 1 error rate for each pairwise comparison and have minimal impact on the power for the final analyses.

12.7 INTERNAL PILOT 'GO'/'NO GO' PROGRESSION

The initial 10 months of recruitment forms the internal pilot phase, to enable NIHR HTA to confirm progression criteria are met.

12.8 METHODS TO ACHIEVE TARGET SAMPLE SIZE

Trial recruitment will be monitored closely by the Trial Manager and reported at the TMG meetings. Anonymised participant pre-screening logs will be requested from sites and assessed on an ongoing basis. Section 5.2 outlines how participants will be identified for inclusion in the trial.

Additionally, the KCTU Standard Operating Procedures (SOPs) will guide the Trial Statistician's reports outlining recruitment numbers across the trial and at site level to the DMC. The DMC will be asked to advise on strategy where there are recruitment difficulties i.e., including but not limited to; modifications to the inclusion/exclusion criteria, targeted recruitment drives, escalation at site level to PI/R&D or site closure.

12.9 METHODS FOR ADDITIONAL ANALYSES (E.G. SUBGROUP ANALYSES)

For subgroup analysis (moderate and severe groups), treatment effect estimates will be estimated for each subgroup and formally tested by including an interaction between subgroup and treatment as a fixed effect in the analysis models.

In a secondary analysis, to identify the optimal treatment pathways adjusting for non-responders who switch treatments, we will use Q-learning to identify the pathway that maximises the expectation of the outcomes at 12 months, and if these differ by patient characteristics. Q-learning is a popular, regression-based approach for estimating treatment pathways involving treatment switching over time, as is permitted in this study after 6 months for non-responders. It involves defining the quality of treatment functions (Q-functions) at each time point. For the clinician-assessed eczema severity (EASI) outcome at 1 year, this is the expectation of the outcome conditional on treatment and covariate history from 6 months and baseline, estimated through linear regression. The maximum argument of the expectation with respect to the choice of treatments at 6 months is then regressed on the baseline randomisations and covariates. The optimal treatment pathway for an individual is

then defined as the pathway that maximises the Q-function at both time points, and this will be estimated for different subgroups of participants.

We will additionally explore whether the carriage of filaggrin-null mutations, baseline IgE and eosinophils and predominant head and neck eczema predicts treatment response on the three treatments and whether methotrexate polyglutamate measurement can be used as a biomarker for treatment response in those on methotrexate.

If two comparators (A, B) are both found to be superior to the current control (C) in each respective pair-wise comparison, we may make a direct comparison between A and B. There is limited power for such a comparison, and the results of this direct comparison will be presented as opportunistic and exploratory. Only participants that could have been randomised to both A and B will be included in this opportunistic comparison (i.e., will exclude participants that were contraindicated to 1 or both arms, and will exclude participants that were randomised when 1 arm was not yet available).

12.10 METHODS TO HANDLE MISSING DATA

For missing outcome data, the results from the linear mixed models are valid under a missing at random (MAR) missing data generating mechanism that allows for fixed effects and earlier outcome values to predict missingness of later ones.

Considering incomplete baseline measures: although baseline data should be complete prior to randomisation, there may be some limited missing data. Descriptive baseline summaries will be presented as complete case. The proportion of missing data will be summarised by scale/assessment. If any of the baseline measures are found to relate to missing primary outcome at 6 months we will consider adjusting for them in models for the primary outcome. To allow for this, any baseline measure considered as a covariate in the main model would best be imputed to a full single dataset. Missing baseline covariate data will therefore be imputed using the missing indicator method where a dummy variable for missingness will be included as a covariate in the model for binary data, and mean imputation for continuous data, as per the recommendations of White and Thompson (2005).

12.11 PLANS TO GIVE ACCESS TO THE FULL PROTOCOL AND PARTICIPANT LEVEL-DATA

It is anticipated that the full protocol and all results will be available as open access according to the rules of the funding body, the National Institute of Health Research (NIHR).

13 MEASUREMENT OF COSTS AND OUTCOMES

13.1 WITHIN-TRIAL HEALTH ECONOMIC EVALUATION

This will:

a. Estimate resource use and costs in each arm over 1 year in adults with moderate to severe eczema.
b. Estimate QALYs in each arm over 1 year in adults with moderate to severe eczema.
c. Undertake a within-trial cost-utility analysis to assess the value for money of different treatment options for moderate to severe atopic eczema in adults for NHS provision.
d. Estimate uncertainty levels associated with the decision about treatment provision.

13.1.1 ECONOMIC DATA COLLECTION

Resource use associated with the treatment options (drug use, monitoring and adverse events) will be recorded during the 12-month treatment period. Wider resource use (primary care visits, prescriptions, other health contacts) will be regularly collected via the patient facing electronic tool (baseline and months 3, 6, 9 and 12) and participants will be offered study diaries to act as an aide memoire.

13.1.2 ECONOMIC EVALUATION ANALYSIS

Costs will be estimated from the perspective of the NHS and Personal Social Services[38], by attaching published unit costs for the most recent price year (example sources include Jones et al 2024, NHS England 2021/22, NHSBSA 2022/23)[39-41]. Wider resource impacts on the participants, in terms of employment and out of pocket costs, will be analysed separately. The utility score from the EQ-5D-5L will be used to estimate QALYs for the trial period using linear interpolation and area-under-the-curve analysis with and without adjusting for baseline differences[42]. We will value the EQ-5D-5L in our primary analysis in line with NICE recommendations at the time of analysis.

The economic evaluation will estimate the mean incremental cost and mean incremental QALYs of the comparator drugs at 6 and 12 months (given the timeframe costs and benefits will not be discounted). A regression-based approach (for instance seemingly unrelated regression equations if assumptions are met[43]) will be used to estimate the mean incremental cost and effects with and without adjusting for difference in baseline characteristics (EASI score, costs, EQ-5D, duration of disease) and minimisation factors (recruitment centre, severity). In line with the guide to handling missing data in within trial cost-effectiveness analysis[44], the pattern and nature of the missingness will be explored using descriptive analyses (e.g. amount of missing data by trial group at each time point; missing patterns; association between missingness and baseline variables; and association between missingness and observed outcomes). We will use this analysis to choose an appropriate method to handle any missing data.

Since cost data are likely to be skewed, we will use non-parametric bootstrapping to estimate mean (95% CI) incremental cost and mean (95% CI) incremental QALY. Treatment options will be ranked from least to most costly, any option that is strongly dominated (i.e. options which are inferior in terms of both cost and outcome) will be ruled out before estimating incremental cost effectiveness ratios (ICERs) and/or net monetary benefits as appropriate (NMBs). These will then be examined for extended dominance, where treatment options with a higher ICER than options that follow, will be removed and ICERs/NMB re-estimated. Bootstrapping will also be used to explore the level of uncertainty associated with the decision to adopt a treatment through the estimation of cost-effectiveness acceptability curves (CEAC)[45]. A range of ceiling ratio (or willingness-to-pay per QALY) values will be tested, including the £20,000 and £30,000 per QALY indicative thresholds used by NICE[38]. We will conduct sensitivity analysis in relation to key assumptions, including alternative assumptions in relation to missing data. A health economics analysis plan (HEAP) will be finalised before the trial database is locked.

13.2 LONG-TERM HEALTH-ECONOMIC ANALYSIS

A disease-based decision-analytic model will be developed to evaluate the expected long-term costs and health consequences of moderate to severe eczema in adults. This will incorporate periods of disease relapse and remission, adverse events related to treatment and drug specific prescribing guidelines (e.g. ciclosporin use not recommended for >1 year). Sensitivity analysis will be used to explore assumptions made (i.e. about treatment duration, costs, disease severity and relapse rates post-treatment). The model form is likely to be a Markov-type model, where groups of patients move

between defined health states (e.g. healthy skin, mild eczema, moderate eczema, severe eczema, death) using estimated probabilities of disease progressions for fixed time intervals. Model design will be finalised after: a) an updated review of existing eczema economic models[46]; b) multi-disciplinary input on model structure and data sources; and c) review of evidence for source data for model parameters. This process will be documented to interrogate the proposed model and reach agreement amongst those involved. Identification, selection and synthesis of relevant evidence sources will follow recommended methods and will use the primary data collected within BEACON and expert clinical input amongst the team. The Markov model will be developed in an open-source framework (excel/visual basic/R) to enable sharing. To demonstrate model credibility we will ensure transparency, face validity, internal validity (including sensitivity analysis using a broad range of values for all parameters to ensure the model behaves as expected according to the theoretical model) and model corroboration (a discussion of similarities and differences between the model produced and those already in the literature). An economic evaluation will be performed for an appropriately long-time horizon in line with the within trial analyses except all costs and benefits will be discounted at recommended rates to reflect the longer timeframe.

14 NESTED PROCESS EVALUATION

The process evaluation will consist of two distinct elements: (i) semi-structured 1:1 interviews with a sample of trial participants; and, (ii) an online survey of all those screened for inclusion.

14.1 INTERVIEW STUDY

14.1.1 PURPOSE

This nested study will seek insight from participants about the ongoing practical delivery of this platform trial as well as future implementation of systemic, immunomodulatory treatment in moderate to severe eczema. Specifically, it will investigate participants' expectations (including perceived benefits and risks of 'standard' vs targeted treatments) and experience of trial procedures (recruitment, data collection (including via the online platform), clinical tests including biological sample collection and ongoing involvement) and of treatment (benefits, side-effects, medication transitions).

This insight will support the maintenance of the trial, offering contextualised information about how best to approach, recruit and retain participants. It will provide important insight about how to support treatment changes at month 6. It will offer insight that will support the extension of this platform as additional drugs and/or treatments for moderate to severe eczema are subsequently identified for inclusion.

Appreciating participant's expectations and experiences of systemic treatment will support the design and implementation of novel treatment pathways for moderate to severe eczema.

14.1.2 SAMPLE AND SELECTION

In the first instance a purposive sample of approximately 30 trial participants will be recruited to take part in this element of the research. As the trial proceeds, with each additional arm, 10 to 15 extra participants may be recruited. Participants will be selected to ensure that individuals from each arm of the trial are included. We will use baseline demographic and clinical data to ensure a diverse study population including 'hard to reach' populations (male/female, younger/older, ethnicity). Selecting

participants in this way will ensure that findings are reflective of, and responsive to, a broad range of perspectives and experiences.

In addition, we will responsively recruit participants should any emergent issues arise in the delivery of the trial – such as difficulties with specific treatments or with particular research processes. In these cases, we will seek to interview those who withdraw from the trial or those who experience difficulties with treatment/research processes.

Participants who are selected for and willing to take part in the interview study following review of the PIL will be asked to complete and return the paper consent form prior to the first interview.

14.1.3 Data Collection and Management

Most participants will be interviewed at two time-points – as soon as possible after of randomisation (ideally within 8 weeks), and then at the completion of the study, in order to gain insights into expectations prior to or at the start of treatment and experience following trial treatment completion. Some of these may be asked to take part in an additional interview should they change medication at month 6. Those participants recruited to explore an emergent issue may only be interviewed once.

All interviews will be semi-structured and 1:1 with open questions (see Interview Topic Guide provided separately) used to guide a discussion of experiences and opinions. Interviews will be flexible to allow participants the opportunity to introduce new topics and to focus in areas which they think are important. All interview data will be audio-recorded, transcribed in full and handled using the NVivo 12 software package.

Please see Appendix 8 for pre-consent data flow for the nested interview study.

Initial interview:

Initial interviews will explore patients' experience of eczema, their expectations of treatment (specifically considering whether the different treatments offered are typified by different expectations); and thoughts about participating in this trial, particularly around treatment allocation.

Interviews will explicitly explore knowledge of treatment options, feelings about their allocated treatment and their expectations for clinical outcomes and safety. Initial experience of treatment will also be discussed.

Later interview (on completion of participation):

Later interviews will reflect upon participants' experience of the trial, their experience of treatment(s) such as the benefits or difficulties of self-injection compared to oral treatment, adherence, or their experience of multiple treatments and the process of switching treatments.

Recommendations for future treatment use in the implementation of the findings of the study will be sought. Data generated (insight offered) in the early interviews will be revisited at later interviews to consider how participant expectations had been fulfilled or changed. Insight generated in this way will illuminate perceptions about systemic treatments for eczema, will help to identify common misapprehensions, and will support better clinical / research communication about systemic treatments in eczema management.

Ad hoc interviews (emergent issues):

Interview topic guides will be developed to explore ad hoc issues which emerge in the process of the trial. This might include a concern for participant withdrawal, for side-effects and medication difficulties, or for some other reason.

Patient contact details forms (referral forms for interview study received from hospital sites) and interview study consent forms will be kept alphabetically within a locked filing cupboard during the project. Within the electronic data, patients will only be referred to using study ID and so effectively interview recordings will be pseudonymised. Patient name and study ID are only linked on the referral forms that are received from the hospital sites (following consent to be contacted regarding the qualitative interviews) and the interview study consent forms.

We will use University of Nottingham (UoN) provided storage for our working data. UoN licenses Microsoft Teams, allowing for secure and controlled sharing of data among the research team only. Microsoft Teams encrypts data both in transit and at rest and is approved against the University's Handling Restricted Data Policy. The service provides several layers of automatic back up and, in a disaster scenario, files can be recovered. Access to data stored in MS Teams is via secure log-in with multi-factor authentication. There is a Teams channel for the BEACON study at the University of Nottingham with restricted access for only BEACON study team members.

Audio files will be stored with the following filename format: BEACONAUDIO_PID (PID=participant identification number) within the "Interview recordings" folder on the BEACON Microsoft Team. Transcription files will be stored with the following filename format:BEACONTranscript_PID in the "Transcripts" folder on the BEACON Microsoft Team. NVivo analysis files will the stored as "BEACON qualitative interviews" in the "Analysis" folder on the BEACON Microsoft Team.

14.1.4 Data Analysis

We will build upon previous qualitative eczema research by providing a detailed, contextualised assessment of individuals' experience of systemic treatment for moderate/severe disease.

An external audio transcription company will be assigned to transcribe and anonymise the interview recordings (other than study ID, no other identifiable information about participants will be shared with the transcription company). Data will not be transferred to the third-party transcription vendor until a service level agreement is in place to ensure confidentiality of the data. Interview transcripts will be reviewed and coded thematically using the NVivo 12 software package – identifying key insight, experiences or opinions. Coded interviews will be reviewed and compared to characterise recurrent and/or prioritised ideas about disease, treatment and the platform trial. Interview transcripts will be stored within a separate study file.

The perspectives of different participants will be compared and synthesised in this process in order to reflect upon similar and different experiences associated with the different treatments included in this trial. Participant assessment of their experiences (and treatment benefits / difficulties) will support conclusions about which treatments are most accepted and best tolerated.

Analytic codes and themes will be tested and refined as new data is considered. This process will cease when these codes/themes are considered stable and no longer growing or evolving.

14.2 BEACON PARTICIPANT ONLINE SURVEY

14.2.1 PURPOSE

Developed in collaboration with our PPI partners to gain a broad insight about participants' expectations of the medications included in this study, and to explore issues of medication adherence and acceptability.

14.2.2 SAMPLE AND SELECTION

All individuals who consent to screening and are eligible to take part will be provided with a link to a BEACON participant online survey (start of study) to complete via DrDoctor prior to randomisation at the baseline visit. At the 52 week clinical and safety assessment all participants will be provided with a link to a second BEACON participant online survey (end of study).

Any participant that leaves the study prior to the 52 week assessment will also be provided with a link to the second online survey.

14.2.3 DATA COLLECTION

Each online survey will include a small number of questions which broadly consider the acceptability of the medications being investigated here.

In the first survey potential participants will be asked about their knowledge of the medications, their expectations of benefits associated with them, perceived challenges associated with them, and any preference that they may have.

In the final survey they will be asked about their experience of taking the medications, to identify any difficulties associated with the medication, to indicate any strategies that they developed to support medication adherence, and any retrospective preference for specific medications.

14.2.4 DATA ANALYSIS

Data will be uploaded from DrDoctor to the NVivo 12 Software package and analysed alongside the qualitative interview data. To reflect that data will be generated digitally (online) and might vary in quality (some offering more detail than others) an iterative approach to analysis will be adopted. Keyword and keywords in context will offer a broad, summative form of content analysis; a more conventional thematic analysis will complement this with greater depth of insight where responses allow.

Analysis will consider each medication separately and will bring together insight from the screening and later online surveys. For each it will summarise participants' knowledge and expectations of the medication and will review issues of adherence and acceptability. For each medication a unique 'model' will be constructed.

Comparison of these models will allow comment on participants views of the different medications, and assessment about which is broadly considered more appropriate and acceptable.

15 LONG TERM FOLLOW UP

All trial participants will be invited to enrol into the UK-Irish Atopic Eczema Systemic Therapy Register (A-STAR). Participation in A-STAR will be optional. A-STAR is an observational study running in the UK and Ireland, collecting data on the short and long-term safety and effectiveness of systemic treatments for people with eczema (https://astar-register.org/) funded by the British Skin Foundation and the British Association of Dermatologists. Patients will be offered the chance to consent to A-STAR upon enrolment in BEACON. Data would subsequently be collected for BEACON and A-STAR, with no additional data collection needed for A-STAR over and above that required for BEACON in the first 12 months. This will contribute to this large-scale effort to establish the long-term safety and clinical outcomes of systemic treatments.

16 Allied Mechanistic Research

Our allied mechanistic research study, mySkinomics, will characterise the events underpinning eczema drug actions and outcomes to treatment, with a view to informing the design of novel therapeutics and personalised medicine approaches to management. The governance framework for this observational research is separate to BEACON, with independent consent. BEACON participants on methotrexate or dupilumab at participating sites will be invited to participate (their participation is optional).

17 CONTINUATION AS A MULTI-ARM MULTI-STAGE PLATFORM

This trial has adopted an adaptive multi-arm multi-stage platform trial design to facilitate the incorporation of new treatments and arms in the future as they emerge (see section 1.3 for information).

17.1 STATISTICAL CONSIDERATIONS

Each additional arm will be considered as a new parallel-group comparison against the nominated standard of care (currently ciclosporin). The advantages of considering these new comparisons in a future platform are multiple:

a. statistical efficiency from the use of a single control group
b. operational efficiency from adding a new arm into an existing protocol and database
c. cost efficiency compared to setting up an independent parallel-group trial

Design considerations for MAMS trials include controlling the type 1 error rate. If the additional trial arms are different, the emphasis should be on controlling the pairwise error rate and powering each research arm separately, as though an independent trial[47]. Therefore, there are no additional considerations for the three-arm trial at this stage, which already has a conservative pairwise adjustment of 0.025. If new arms are added late during the course of this study, there will be little overlap in shared control arm information, which will further reduce the correlation between the pairwise comparisons, and the need to change the type I error for the current arms. However, the timing of new arms will impact on the length of the study required to randomise a concurrent control group with the same eligibility criteria, and we may adjust the randomisation ratio to produce results from each comparison at a similar time.

17.2 DECISION RELATING TO THE "STANDARD OF CARE" (I.E. CONTROL)

Factors that will be considered prior to proposing a change in standard of care (i.e.the control) in this platform are summarised in Figure 3. The TMG will propose any change to the "standard" which will require ratification by the TSC. Members with relevant conflicts of interest can comment but will leave the meeting prior to a decision being made.

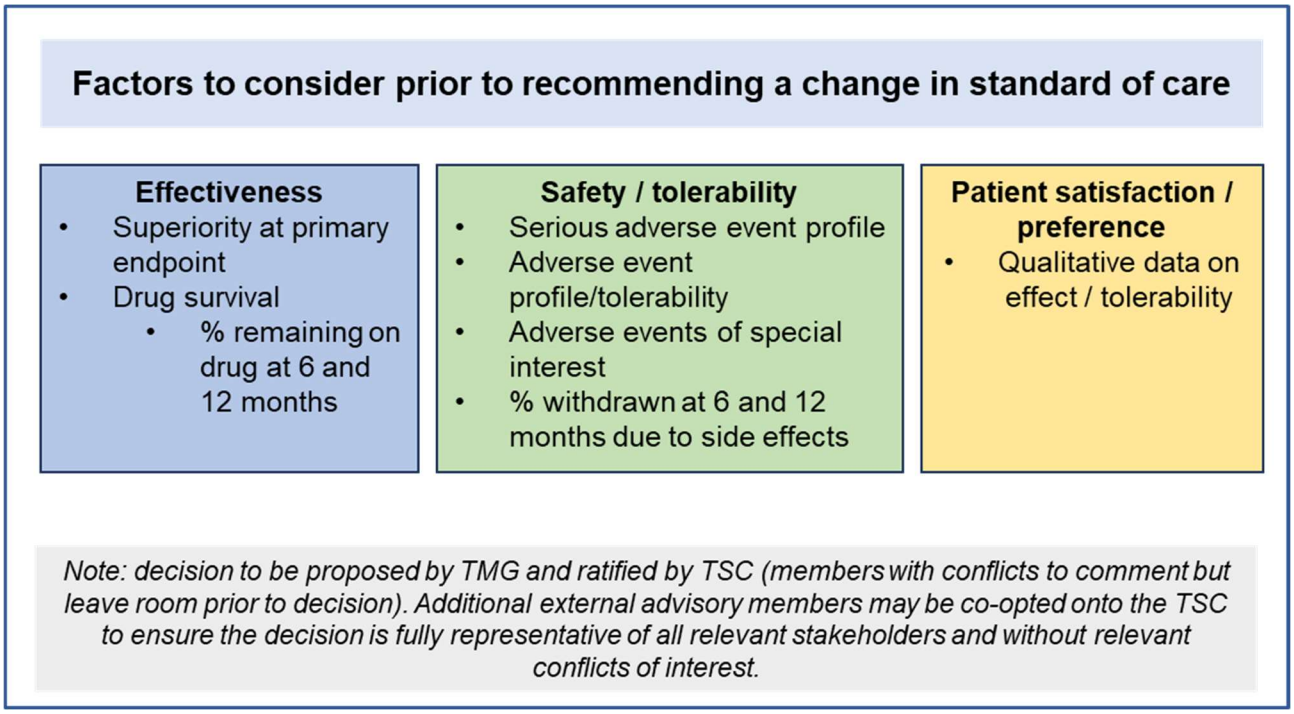


Figure 3 Factors to consider prior to recommending change in standard of care

18 OVERSIGHT AND MONITORING

18.1 TRIAL MANAGEMENT GROUP (TMG)

Members of the TMG are listed in Table 3. Changes in individuals filling these roles will not require a protocol update but will be documented in the TMG minutes.

TABLE 3 TRIAL MANAGEMENT GROUP MEMBERSHIP IN BEACON TRIAL

Title	Role
Chief Investigator	Chair
Programme Lead	Member
BEACON Senior Statistician	Member
BEACON Junior Statistician	Member
KCTU Senior Trial Manager	Member
KCTU Trial Manager	Member
KCTU Trial Manager	Member
KCTU Pharmacist	Member
KCTU Director of Operations	Member

KCTU Data Centre Lead	Member
Nested Process Evaluation Lead	Member
Health Economist – Within Trial Evaluation	Member
Health Economist – Economic Modelling	Member
PPI Member	Member
PPI Member	Member
mySkinomics (affiliated mechanistic research) Chief Investigator	Member
National Eczema Society Chief Executive	Member
KHP-CTO Clinical Research Associate for BEACON	Observer

18.2 PATIENT LIASION ADVISORY GROUP (PLAG)

There are three patients in the BEACON trial development team (co-applicants), all with lived experience of moderate to severe eczema, systemic therapy and/or trial therapy. They are reflective of the planned trial population and have provided in-depth viewpoints to the team by drawing on their personal experience. In addition to our patients, Andrew Proctor, Chief Executive of the National Eczema Society, is also a member of the trial development team (co-applicant), bringing a third-party perspective of a much wider group of patients.

To reduce burden the PLAG will only be invited to relevant TMG meetings or consulted separately throughout the lifetime of the trial thereby contributing to all the key decisions including but not limited to input into patient facing materials such as information leaflets, newsletters and the website to ensure information is understandable, comprehensive and focussed on the aspects that matter to participants.

18.3 TRIAL STEERING COMMITTEE (TSC)

The TSC will be composed of five independent members. The TSC is an executive committee, reporting to the funder (NIHR) and the sponsor. The TSC is formally appointed by NIHR and members will receive individual letters from NIHR confirming their role. Independent members will be independent of the Sponsor organisation and of any recruiting study sites.

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Data Monitoring Committee, Trial Steering Committee, regulatory authority or ethics committee.

If the trial is prematurely discontinued, active participants will be informed, and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

18.4 DATA MONITORING COMMITTEE (DMC)

The DMC will be composed of three independent members: a statistician and two clinicians. The DMC is an advisory committee, reporting to the TSC. The DMC is formally appointed by NIHR and members will receive individual letters from NIHR confirming their role. Members will be independent of the Sponsor organisations and of any recruiting study sites. The DMC will work to the DAMOCLES guidance[48].

18.5 MONITORING

Monitoring of this trial to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained by the KHP-CTO Quality Team at KCL.

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g., participants' case sheets, blood test reports etc.).

The KHP-CTO will prepare a site monitoring plan in accordance with local regulatory and REC requirements. At the site initiation visit, the Trial Manager will provide the recruiting site with a BEACON-specific investigator site file and a site pharmacy file to be maintained for the duration of the study.

19 INVOLVEMENT OF PATIENTS AND THE PUBLIC

Patients have been involved from initial conception of this research proposal. The Eczema Priority Setting Partnership of patients and clinicians prioritised the research question: "*What is the best and safest way of using drugs that suppress the immune system when treating eczema?*" Patients have subsequently been involved in all relevant aspects of BEACON to ensure that the study design is acceptable. The PLAG have contributed to the original funding application, pre-trial surveys and the BEACON trial design.

Direct input from these individuals has been supplemented with two online patient surveys promoted through the National Eczema Society, to address specific areas of concern that required a wider range of viewpoints. We had 97 and 51 respondents to these surveys, of which 95% had eczema that was moderate or severe and therefore closely reflected our anticipated trial participants. Through a dedicated workshop session on 12th October 2020, we have also benefitted from the UK Dermatology Clinical Trials Network patient panel input into the trial design. The trial was discussed three times at the UK Dermatology Clinical Trial Network meetings and at UK Translational Research Network in Dermatology meeting, both of which include patient representatives as well as clinicians and researchers.

Having patients involved has meant that the trial has been designed in a way that is acceptable to patients. For example, we were strongly encouraged to minimise any additional patient burden through extra visits, so the follow-up schedule reflects normal practice and our patient survey showed the proposed schedule did not deter many from considering participating. We were unsure of how long patients were likely to be prepared to continue on a medication that was not providing the hoped for levels of effectiveness and it was clear that 3-6 months was acceptable which enabled us to design the trial with a dose adjustment point at 3 months and a switch point at 6 months.

We will continue to work with our existing patient partners throughout the trial i.e. our three patient co-applicants, the UK Dermatology Clinical Trials Network patient panel and wider input via the National Eczema Society.

20 MISCELLANEOUS

20.1 PLANS FOR INDEPENDENT AUDIT

There are no current plans to commission an independent audit study.

20.2 DISSEMINATION PLANS

The results of the BEACON trial will be of great interest to patients and the public, dermatologists (national/ international), GPs, nurses, pharmacists, scientists interested in eczema and healthcare commissioners. Our dissemination will take into account these different audience types and capitalise on the considerable reach through national clinical networks (British Association of

Dermatologists (BAD), UK DCTN (and Centre for Evidence Based Dermatology monthly evidence updates), UK Translational Research Network in Dermatology (UK TREND), British Dermatological Nursing Group (BDNG)), international networks (European Society of Dermatological Research (ESDR), HOME, International Eczema Council), and health economic networks and links.

The primary and secondary outcomes will be published in a peer reviewed open-source medical journal within 12 months of the close of each comparison regardless of the magnitude or direction of effect. We will submit summary articles where possible, including the Dermatological Nursing Journal and the National Eczema Society quarterly magazine “Exchange”. The health economic analysis will be presented as a separate publication(s). Additional potentially high impact publications are likely to arise around lessons learned from the trial conduct and setting up the trial as a platform for future trial arms. We will publish the trial protocol.

We will submit the BEACON trial results to key international dermatology conferences including the BAD Annual Meeting (35% of UK dermatologists attend), ESDR, the European Academy of Dermatology and Venereology, the American Academy of Dermatology (AAD), the International Symposium on Atopic Dermatitis and the World congress of Dermatology. Results will be submitted to the BDNG and the Society for Academic Primary Care (SAPC) Dermatology Specialist Interest Group meeting to reach other professional healthcare groups. We will hold a stakeholder workshop with the National Eczema Society (NES) to disseminate the results of the trial as soon as available. Dermatologists and other healthcare professionals from recruiting sites will be invited, as well as other prominent UK dermatologists, patients, dermatology nurses, and commissioners. In addition to publicising results to key stakeholders, this workshop will provide a platform to understand how the patient and clinical community view the results, informing the proceeding wider dissemination strategy. Results will additionally be shared at information days for patients and study days for clinicians, both routinely run by the NES.

In collaboration with the NES, we will produce digestible plain language summaries in a range of formats to publicise the trial results to different target groups. Infographics will be produced to disseminate our trial findings to a clinical and a wider lay audience. We will produce summaries of the results in written, audio (podcast) and video format involving patient and healthcare professional members of the trial team. Brief versions will be targeted to a lay audience and more detailed versions to the healthcare professional audience. We will provide suggested text and images that can be used for social media posts. The NES will review and amend as necessary its existing patient information resources on systemic treatments, to reflect the research findings. In addition to what is planned, we will seek out ideas for different formats that may emerge over the lifetime of this trial. The trial website will describe the results and link to the summaries in different formats. We would also hope that an NIHR signal would be produced to support our dissemination.

We will ensure that the results of this trial are available for updates to key UK and European guidelines. These will include Technology Appraisal Guidance, Primary Care Dermatology Society and BAD Guidelines for the management of atopic eczema**,** Scottish Intercollegiate Guidelines Network (SIGN) Management of atopic eczema in primary care and European Guidelines for treatment of atopic eczema.

We will invite a small number of trial participants to provide short testimonials and/or blogs about their participation in the trial. With their permission, we will use these in our publicity materials and website to encourage others to participate and increase retention. We will invite participants of under-represented ethnic groups or gender to contribute to these.

20.3 END OF TRIAL

The end of the trial will be defined as final database lock.

20.4 CONFIDENTIALITY

When consent forms are signed, a copy will be provided to the participant, a copy will be filed in the medical records and the original will be retained in the Investigator Site File. Participant initials and date of birth will be entered into the study database but no more identifying information will be collected outside of the recruiting study site.

When the study is complete, a data sharing dataset will be created from the raw data by the study analyst, which will not include participant initials, date of birth or any other identifiable data and study PIN will be altered so that individuals are not recognisable from the dataset.

The study will comply with the General Data Protection Regulations (GDPR)[49].

20.5 COVID-19 CONTINGENCIES

The recent COVID pandemic has impacted clinical trial work. BEACON trial visits should be conducted face to face. Safety visits for bloods/ blood pressure can be conducted in the community where appropriate and the week 30 safety assessment for those who switch to methotrexate or dupilumab after 6 months can be conducted remotely. If face to face review is not possible then month 1, 3 and 9 visits could be conducted remotely (after notification to the trial team/ manager) if supporting blood tests and blood pressure readings can be safely arranged locally but this is obviously not optimal for the completeness of data collection. Face to face review is essential for screening, baseline, month 6 and month 12.

20.6 FUNDING

This study is funded by the NIHR HTA Programme (NIHR 129926). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. Additional specific funding is provided by Medac, who are supplying methotrexate (IMP) and funding to support methotrexate polyglutamate analysis, and Pfizer, who are providing funding for the addition of the fourth (abrocitinib) arm and supplying abrocitinib. Free of charge abrocitinib supply will end following full enrolment to and completion of the abrocitinib arm. Post-trial, participants on abrocitinib will be transitioned on to commercial supply with prescribing within licence and reimbursement as per national (NICE)/ local formulary requirements (see section 7.5 for information).

20.7 AVAILABILITY OF DATA AND MATERIALS

In those patients that give consent, data and materials will be stored on a on a secure NHS database and in the St. John's Research Tissue Bank (Ethics Committee ref: 07/H10712/106; HTA Licence number: 12521) respectively. De-identified data and materials (relating to patients who have specifically given consent) will be available for sharing upon request for future scientific research, subject to approval by the Chief Investigator and Programme Lead. This may involve data and study samples being transferred outside the UK and to commercial partners and/or vendors for the purposes of research.

20.8 INSURANCE AND INDEMNITY

This study is co-sponsored by Guys and St Thomas' NHS Foundation Trust (GSTFT) and King's College London (KCL). The co-sponsors will, at all times, maintain adequate insurance for the

design, management and conduct of the study: (a) GSTFT through NHS Resolution cover, in respect of any claims arising as a result of negligence by its employees, brought by or on behalf of a study participant; and (b) KCL through its' own professional indemnity (Clinical Trials) & no fault compensation policy.

20.9 ARCHIVING

At the end of the trial, all trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the 2018 Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the KHP-CTO Archiving SOP. Recruiting sites will be responsible for archiving the source data, Investigator Site Files and Pharmacy Site Files.

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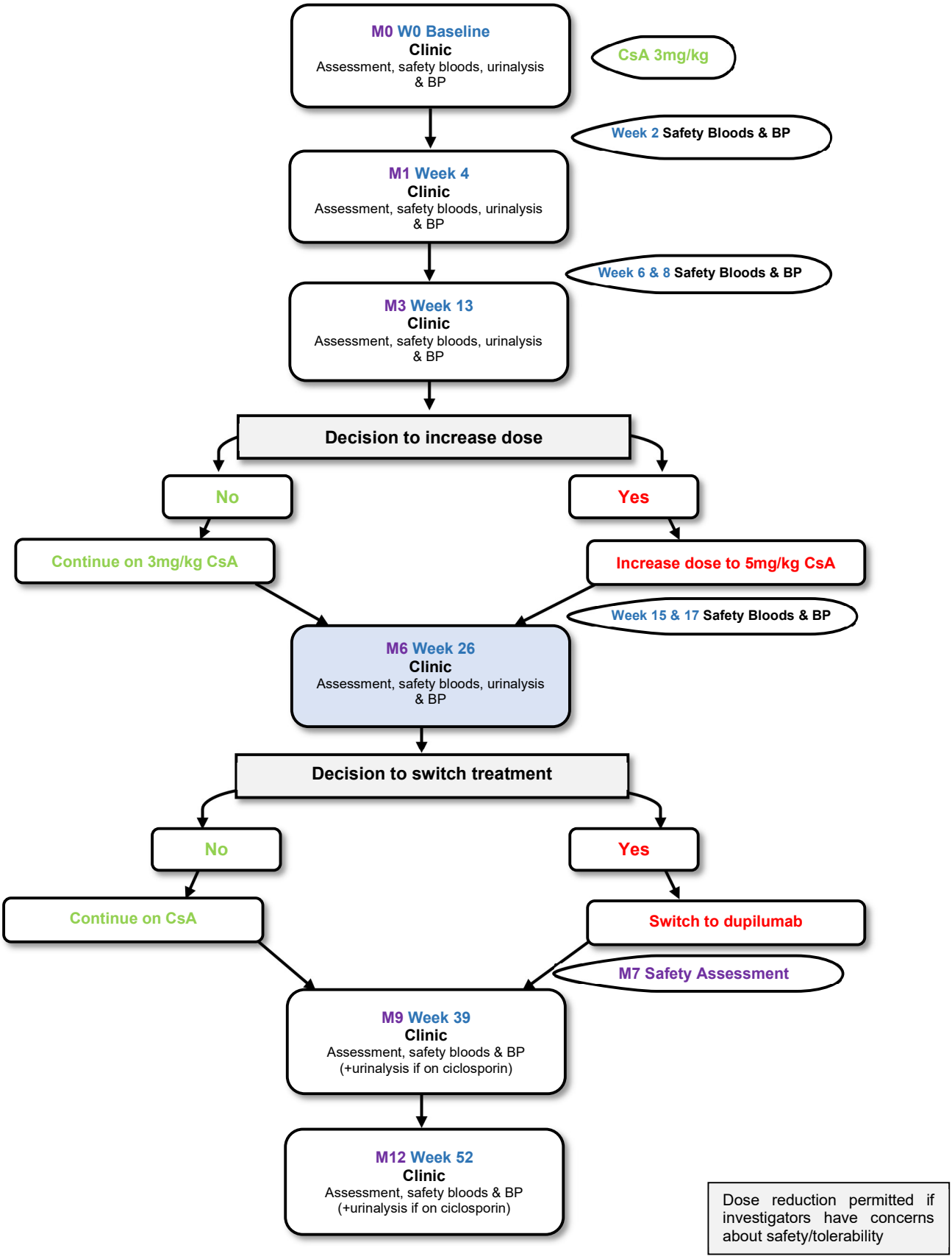
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APPENDIX 1 DRUG-SPECIFIC INFORMATION: CICLOSPORIN

TRIAL PARTICIPANT FLOW AND SCHEDULE OF EVENTS: CICLOSPORIN



CICLOSPORIN SCHEDULE OF EVENTS													
Event / form	**Screening[A]**	**Baseline[B]**	**Week 2 Safety Visit**	**Week 4 (Month 1)**	**Week 6 Safety Visit**	**Week 8 Safety Visit**	**Week 13 (Month 3)**	**Week 15 Safety Visit[C]**	**Week 17 Safety Visit[C]**	**PRIMARY OUTCOME Week 26 (Month 6)**	**Week 39 (Month 9)**	**Week 52 (Month 12) End of Study Visit**	**Ongoing**
Informed Consent	X												
Registration Form	X												
Eligibility (confirmation only at baseline)	X	X											
Medical History and demographics	X												
Skin photography (*optional*)		X								X			
Randomisation Form (after all baseline data collected)		X											
Status Form				X			X			X	X	X	
Physical examination*	X	X		X			X			X	X	X	
Blood pressure	X	X											
Urinalysis	X												
Pregnancy test+		X											
Eczema Area and Severity Index (EASI) **BLINDED ASSESSOR**		X		X			X			X	X	X	
Investigator Global Assessment (vIGA-AD) **BLINDED ASSESSOR**		X		X			X			X	X	X	
Patient Orientated Eczema Measure (POEM)		X		X			X			X	X	X	
Peak pruritus numerical rating scale (NRS)		X		X			X			X	X	X	
Eczema control (RECAP)		X		X			X			X	X	X	
Patient global assessment (PtGA)		X		X			X			X	X	X	
Dermatology Life Quality Index (DLQI)		X		X			X			X	X	X	
EQ-5D-5L		X					X			X	X	X	
PHQ-9		X								X		X	
GAD-7		X								X		X	
Resource use		X					X			X	X	X	
Adherence check (VAS) & Tolerability							X			X	X	X	
Participant Online Surveys		X										X	
Dispense medication		X					X			X	X		
Screening blood tests (+DNA for filaggrin status, *optional*)	X												
Safety Blood Tests (can be remote)		X	X	X	X	X	X	X	X	X	X	X	
Safety Blood Pressure (can be remote)			X	X	X	X	X	X	X	X	X	X	
Safety urinalysis				X			X			X	X	X	
Study medication switch review										X			
Study medication dose increment review							X				X		
Concomitant Medications Log													X
Topical treatments		X		X			X			X			
Adverse Events Log													X
Withdrawal Form													X

* Physical examination (according to routine clinical care) required at screening and baseline, extent of physical exam during follow up as deemed appropriate by investigator

+ Women of childbearing potential only. Urine test

A: Where there are no new risk factors, and at investigator's discretion, blood test results obtained in clinical practice within 4 months prior to randomisation can be used as screening bloods (required tests listed in section 6.7.1.1)

B: Baseline safety bloods for all treatments, at investigator discretion based upon timing of screening bloods

C: Week 15 & 17 safety bloods and safety blood pressure check if ciclosporin dose increased at week 13

***Please note**: if IMP is switched at 6 months, the schedule of events for the second IMP must be followed for the second 6 months of the trial.*

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1 CICLOSPORIN-SPECIFIC INFORMATION

1.1 BACKGROUND

1.1.1 BACKGROUND AND MECHANISM

Ciclosporin is a highly effective and rapidly acting potent inhibitor of T-cell function. Ciclosporin is a prodrug that forms a complex with the intracytoplasmic protein cyclophilin. This complex inhibits calcineurin phosphatase, an enzyme which normally facilitates dephosphorylation of NF-ATc and subsequent transcription of pro-inflammatory cytokines including IL-2, IL-4, IFN-γ, transforming growth factor-β and up-regulation of receptors such as IL-2R (CD25). Ciclosporin thereby inhibits T-cell function (IL-2 and IL-2R are key regulators of T-cell activation) and additionally reduces histamine release and down-regulates high-affinity immunoglobulin E (IgE) receptors on mast cells and basophils[1].

1.1.2 RATIONALE FOR USE OF CICLOSPORIN

Ciclosporin is the control in this trial because of its strong evidence base (see section 1.1.1 and 1.4 in main protocol for further background information) and as the only licensed 'standard' systemic treatment for treating atopic eczema.

1.1.3 CICLOSPORIN DOSE JUSTIFICATION

Ciclosporin will be initiated at 3mg/kg and increased to 5mg/kg when required, consistent with dose ranges in previous RCTs[2,3], SmPC, national guidance, and a UK wide clinician survey that we carried out via the UK Dermatology Clinical Trials Network (UK DCTN, dosing schedule preferred by > 50%, all respondents happy to use this regimen). In psoriasis (where there is better evidence for using ciclosporin), an RCT and a meta-analysis suggested that doses of > 5mg/kg increase the risk of adverse events (AEs) but with little increase in efficacy, < 2.5mg/kg have low rates of AEs but a significant drop in efficacy, and 3 mg/kg or less were less likely to be associated with AEs than doses >5 mg/kg[4]. These data support a 3mg/kg starting dose, to optimise effect and minimise risk. As there is no data to suggest that 4mg/kg is less likely to result in AEs than 5mg/kg, and in line with clinical practice (>80% clinicians surveyed reported using 5mg/kg as their maximum dose, preferred dosing schedule 3 to 5mg/kg), a 5mg/kg higher dose was chosen to optimise effect.

1.1.4 RATIONALE FOR 6 MONTH SWITCH OPTION FROM CICLOSPORIN (DUPILUMAB)

For those participants on ciclosporin who do not meet response criteria to continue at 6 months they can switch to dupilumab. Dupilumab was chosen as the switch option to most closely mirror clinical practice (in line with NICE TA534).

1.2 CICLOSPORIN TOXICITY AND SAFETY

Administration of ciclosporin for this study is not anticipated to induce any potential risk other than the known potential side effects listed below (please refer to the SmPC of the branded drug dispensed).

1.2.1 COMMON SIDE EFFECTS

Diarrhoea; electrolyte imbalance; fatigue; fever; flushing; gastrointestinal discomfort; gingival hyperplasia; hair changes; headaches; hepatic disorders; hyperglycaemia; hyperlipidaemia; hypertension; hyperuricaemia; leucopenia; muscle complaints; nausea; paraesthesia; peptic ulcer;

renal impairment (renal structural changes on long-term administration); seizure; skin reactions; tremor; vomiting.

1.2.1.1 RENAL IMPAIRMENT

Renal impariment is a frequent and potentially serious complication that can occur during ciclosporin therapy. These functional changes are dose-dependent and are initially reversible, usually responding to dose reduction. During long-term treatment, some patients may develop structural changes in the kidney (e.g. interstitial fibrosis).

1.2.2 UNCOMMON SIDE EFFECTS

Anaemia; encephalopathy; oedema; thrombocytopenia; weight increase.

1.2.3 RARE SIDE EFFECTS

Gynaecomastia; haemolytic anaemia; idiopathic intracranial hypertension; menstrual disorder; multifocal motor neuropathy; muscle weakness; myopathy; pancreatitis.

1.2.4 DRUG INTERACTIONS

Investigators should check for any relevant drug interactions in the Ciclosporin SmPC. Contraindicated medications include products containing *Hypericum perforatum* (St John´ s Wort) and medicines that are substrates for the multidrug efflux transporter P-glycoprotein (P-gp) or the organic anion transporter proteins (OATP) and for which elevated plasma concentrations are associated with serious and/or life-threatening events, e.g. bosentan, dabigatran etexilate and aliskiren (Investigators are advised to check the most recent SmPC for a more comprehensive list of medications that utilise these pathways).

1.3 SELECTION OF PARTICIPANTS

1.3.1 PARTICIPANT CORE INCLUSION AND EXCLUSION CRITERIA

To be eligible for randomisation, all participants must fulfil the core inclusion criteria and none of the exclusion criteria stated in section 5.3 of the main protocol in addition to the arm-specific criteria below.

Please note, as long as a participant is eligible to take ciclosporin (control arm) and at least one of the other trial treatments they can be randomised (i.e. they can meet exclusion criteria for one or more of the other treatments and still be randomised). If they fail to respond at 6 months, a pre-defined treatment switch (as per protocol) may or may not be possible depending on whether they still meet exclusion criteria for the relevant switch option. If the switch is not possible, they would be withdrawn from the trial at that stage.

1.3.2 CICLOSPORIN-SPECIFIC EXCLUSION CRITERIA

In addition to the core inclusion and exclusion criteria documented in the main protocol, the following arm-specific exclusion criteria apply for the ciclosporin arm.

1. Any contraindication to ciclosporin according to standard clinical care and/or the opinion of the investigator.

1.4 TREATMENT AND MONITORING OF PARTICIPANTS

1.4.1 PRODUCT INFORMATION

Dose: 3mg/kg orally daily increasing to 5mg/kg after 3 months if required (joint patient/investigator decision, as per standard practice). A dose reduction is permitted at any point and will be documented in the participants medical notes/Source Data Worksheets and CRF. Dosing is to be calculated per body weight, not lean body weight.

Description of product: Ciclosporin 25mg, 50mg, 100mg capsules and 100mg/ml solution (for patients who are unable to swallow capsules or require solution for another reason). Any brand can be used. Ciclosporin must be prescribed and dispensed by brand name (MHRA/CHM advice). Where patients are stabilised on one brand and then switch to another brand (e.g. supply issues with contracted brand), close monitoring of the patient would be required in accordance with standard practice.

Packaging: Commercial/licenced packaging.

Prescription: Trial-specific prescription. Prescription template to be provided by sponsor..

Source of product: Hospital stock. No reimbursement from the Sponsor.

Storage: Store in accordance with the storage conditions outlined in the relevant SmPC. Store in the original package. In the event of a temperature excursion, manage according to local pharmacy practice.

Labelling: Attach a dispensing label in addition to a Sponsor label. Refer to the pharmacy manual for further details.

Accountability: The pharmacy clinical trials team must maintain accurate accountability records including, but not limited to, the number of packs/capsules received, the number of packs/capsules dispensed to which participant, the number of unused packs/capsules in quarantine or destroyed, as well as a record of the batch number and expiry date. It must be clearly documented in the medical notes and CRF when a prescription is issued. There will be no patient diaries, consistent with the pragmatic trial design and real world practice. Adherence should be discussed at each trial visit. A record of study drug returns is not required. Patients should be advised to take any medication that is no longer needed to a pharmacy (community/hospital) for disposal.

1.4.2 SAFETY VISITS AND MONITORING REQUIREMENTS

Timing of post-randomisation safety tests (bloods, urine, blood pressure and safety assessment) are shown in the main protocol schedule of events (Table 1, section 2 Trial Design), and in the drug-specific schedule of events at the beginning of each drug-specific appendix. Further details, including the exact laboratory tests required, are provided below.

1.4.2.1 SAFETY VISITS (ADDITIONAL TO MAIN TRIAL VISITS)

All participants randomised to ciclosporin will be followed up for safety at week 2 with additional visits at weeks 6 and 8. In addition, if their dose is increased at 3 months, they will be seen at weeks 15 and 17. In the event of dose reduction, additional safety assessments should be arranged at the discretion of the investigator.

1.4.2.2 SAFETY BLOOD PRESSURE READINGS

Safety assessment blood pressure readings will be measured at weeks 2, 4, 6, 8, 12, 24, 39 and 52 for those on ciclosporin. For those who dose increment on ciclosporin at month 3 additional blood pressure measurements will be taken at weeks 15 and 17 (see schedule of events, main protocol Section 2). Blood pressure should be measured in an upright position after the participant has been rested for five minutes

1.4.2.3 SAFETY BLOODS

The following safety bloods will be performed at weeks 2, 4, 6, 8, 13, 26, 39 and 52. For those who dose increment on ciclosporin at month 3 additional safety bloods will be performed at weeks 15 and 17 (see schedule of events, main protocol Section 2).

HAEMATOLOGY
Haemoglobin
Haematocrit
Total and differential leukocyte count
Red blood cell count
Platelet count

BIOCHEMISTRY
Creatinine
Potassium
Liver function tests (LFTs)
*Lipids
*Urate

*screening and at months 3, 6, 9 and 12 only

1.4.2.4 URINALYSIS (BASELINE, MONTHS 1,3,6,9,12)

Urine protein:creatinine ratio will be performed at months 1,3,6,9,12.

1.4.3 MANAGING TOXICITY WITH CICLOSPORIN

Ciclosporin is licensed for use in this study population (adults with moderate to severe eczema). Investigators should refer to the summary of product characteristics in the event of toxicity.

Further British Association of Dermatologists drug related guidance for the safe and effective prescribing of ciclosporin can be found here:

Ciclosporin: https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjd.17587

1.4.4 EVALUATING AE'S AND SAE'S – ASSESSMENT OF EXPECTEDNESS

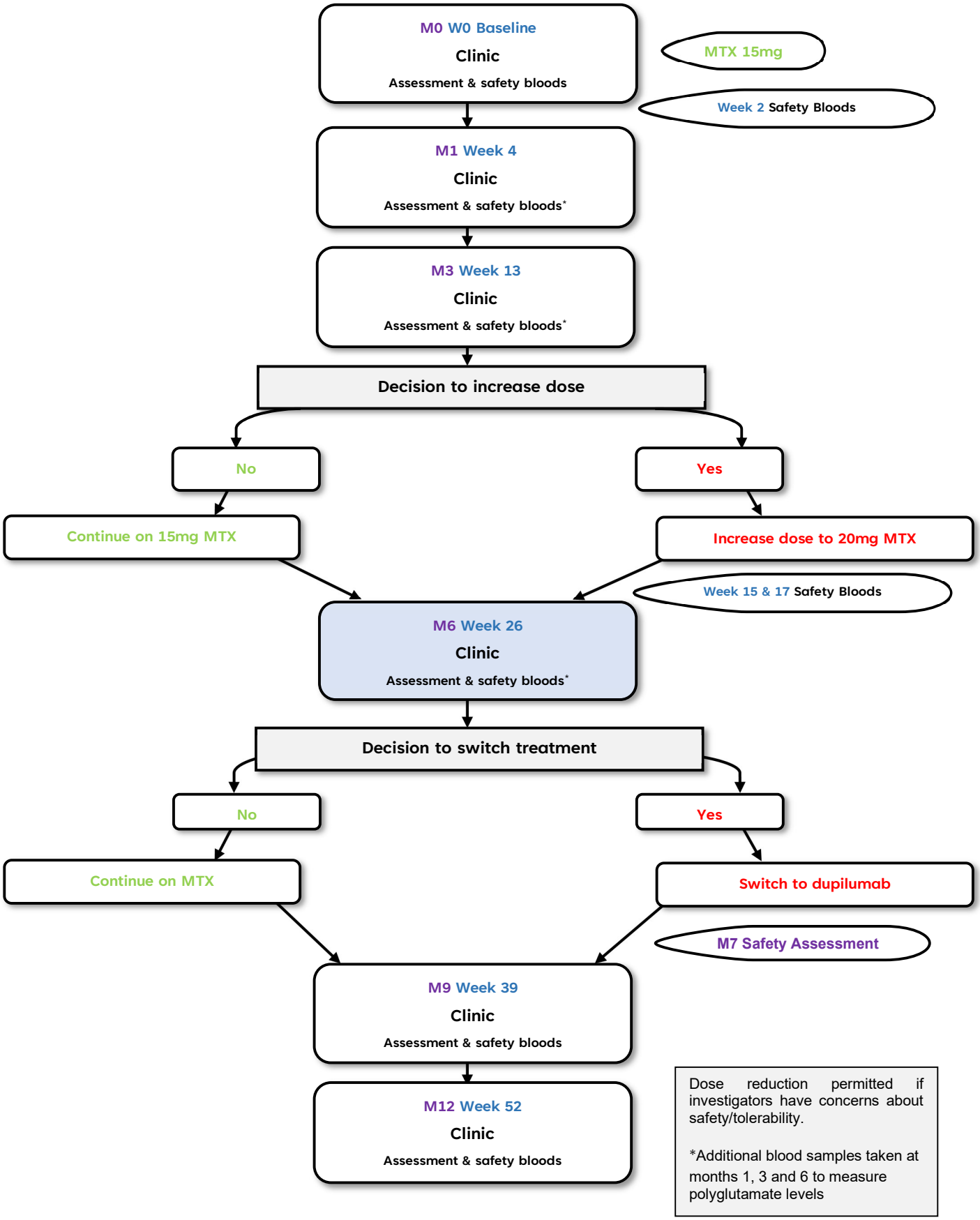
Section 4.8 of the following SmPC's form the RSI for ciclosporin for this trial: Neoral Oral Solution; Neoral Soft Gelatin Capsules. These can be found in investigator site files (SmPC & Safety Alert Updates).

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APPENDIX 2 DRUG-SPECIFIC INFORMATION: METHOTREXATE

TRIAL PARTICIPANT FLOW AND SCHEDULE OF EVENTS: METHOTREXATE



METHOTREXATE SCHEDULE OF EVENTS															
Event / form	**Screening[A]**	**Baseline[B]**	**Week 2 Safety Visit**	**Week 4 (Month 1)**	**Week 13 (Month 3)**	**Week 15 Safety Visit[C]**	**Week 17 Safety Visit[C]**	**PRIMARY OUTCOME Week 26 (Month 6)**	**Week 28 Safety Visit[D]**	**Week 30 Safety Visit[D]**	**Week 39 (Month 9)**	**Week 41 Safety Visit[E]**	**Week 43 Safety Visit[E]**	**Week 52 (Month 12) End of Study Visit**	**Ongoing**
Informed Consent	X														
Registration Form	X														
Eligibility (confirmation only at baseline)	X	X													
Medical History and demographics	X														
Skin photography (*optional*)		X						X							
Randomisation Form (after all baseline data collected)		X													
Status Form				X	X			X			X			X	
Physical examination*	X	X		X	X			X			X			X	
Blood pressure	X	X													
Urinalysis	X														
Pregnancy test[+]		X						X[++]							
Eczema Area and Severity Index (EASI) **BLINDED ASSESSOR**		X		X	X			X			X			X	
Investigator Global Assessment (vIGA-AD) **BLINDED ASSESSOR**		X		X	X			X			X			X	
Patient Orientated Eczema Measure (POEM)		X		X	X			X			X			X	
Peak pruritus numerical rating scale (NRS)		X		X	X			X			X			X	
Eczema control (RECAP)		X		X	X			X			X			X	
Patient global assessment (PtGA)		X		X	X			X			X			X	
Dermatology Life Quality Index (DLQI)		X		X	X			X			X			X	
EQ-5D-5L		X			X			X			X			X	
PHQ-9		X						X						X	
GAD-7		X						X						X	
Resource use		X			X			X			X			X	
Adherence check (VAS) & Tolerability					X			X			X			X	
Participant Online Surveys		X												X	
Dispense medication		X			X			X			X				
Screening blood tests (+DNA for filaggrin status, *optional*)	X														
Safety Blood Tests (can be remote)		X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety assessment (can be remote)**										X					
Methotrexate polyglutamate sample				X	X			X							
Study medication switch review								X							
Study medication dose increment review					X						X				
Concomitant Medications Log															X
Topical treatments		X		X	X			X							
Adverse Events Log															X
Withdrawal Form															X

* Physical examination (according to routine clinical care) required at screening and baseline, extent of physical exam during follow up as deemed appropriate by investigator

** Only for those who switched treatment to methotrexate at 6 months

+ Women of childbearing potential only. Urine test

++ Repeat pregnancy test at 6 months for patients changing treatment from dupilumab or abrocitinib to methotrexate at 6 months

A: Where there are no new risk factors, and at investigator's discretion, blood test results obtained in clinical practice within 4 months prior to randomisation can be used as screening bloods (required tests listed in section 6.7.1.1)

B: Baseline safety bloods for all treatments, at investigator discretion based upon timing of screening bloods

C: Week 15 & 17 safety bloods if methotrexate dose increased at week 13

D: Week 28 & 30 safety bloods if switched to methotrexate at 6 months

E: Week 41 & 43 safety bloods check for patients who switched to methotrexate and dose increased only

***Please note**: if IMP is switched at 6 months, the schedule of events for the second IMP must be followed for the second 6 months of the trial.*

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1 METHOTREXATE-SPECIFIC INFORMATION

1.1 BACKGROUND

1.1.1 BACKGROUND AND MECHANISM

Methotrexate is an antimetabolite (used as a chemotherapeutic agent since the early 1950s) that has immunomodulatory and anti-inflammatory effects. This is in part via the inhibition of folate-dependent enzymes which in turn suppresses transmethylation reactions and purine and pyrimidine synthesis which are required for effective lymphocyte function, for example. Further potentially relevant mechanisms include inhibiting the accumulation of polyamines (which contribute to inflammatory injury), increasing adenosine levels (affects cytokine secretion and the regulation of inflammation) and modulation of JAK/STAT and NF-κB p38MAPK intra-signalling pathways[1].

1.1.2 RATIONALE FOR USE OF METHOTREXATE

Methotrexate is a key comparator as it is the most widely prescribed systemic treatment for adult eczema in the UK[7]

1.1.3 METHOTREXATE DOSE JUSTIFICATION

Methotrexate will be initiated at 15mg weekly increasing to 20mg weekly if necessary, comparable to previous RCTs[2,3], real world practice based on published cohorts in the UK[4] and France[5], verbal consensus (feedback at UK DCTN steering group) and pre-trial UK wide clinician survey results (median starting dose 15 mg, 73% opting for the trial schedule chosen). Subcutaneous administration will optimise effectiveness (poor oral bioavailability in 20%, saturable absorption > 15mg weekly[6,7]), improve tolerability, and is increasingly adopted in routine UK practice (feedback at UK DCTN steering group).

1.1.4 RATIONALE FOR 6 MONTH SWITCH OPTION FROM METHOTREXATE (DUPILUMAB)

For those participants on methotrexate who do not meet response criteria to continue at 6 months they can switch to dupilumab. Dupilumab was chosen as the switch option to most closely mirror clinical practice (in line with NICE TA534).

1.2 METHOTREXATE TOXICITY AND SAFETY

Administration of methotrexate for this study is not anticipated to induce any potential risk other than the known potential side effects listed below (please see SmPC accessible via the official Metoject website - https://metoject.co.uk). Methotrexate should not be used in men or women planning to conceive within 6 months, in pregnant women and in breast-feeding women.

1.2.1 COMMON SIDE EFFECTS

Anaemia; appetite decreased; diarrhoea; drowsiness; fatigue; gastrointestinal discomfort; headache; increased risk of infection; leucopenia; nausea; oral disorders; respiratory disorders; skin reactions; throat ulcer; thrombocytopenia; vomiting.

1.2.2 UNCOMMON SIDE EFFECTS

Agranulocytosis; alopecia; arthralgia; bone marrow disorders; chills; confusion; cystitis; depression; diabetes mellitus; dysuria; fever; gastrointestinal disorders; haemorrhage; healing impaired; hepatic disorders; myalgia; neoplasms; nephropathy; osteoporosis; photosensitivity reaction; rheumatoid

arthritis aggravated; seizure; severe cutaneous adverse reactions (SCARs); vasculitis; vertigo; vulvovaginal disorders.

1.2.3 RARE SIDE EFFECTS

Azotaemia; brain oedema; cognitive impairment; conjunctivitis; cough; dyspnoea; eosinophilia; gynaecomastia; hypotension; immune deficiency; infertility; insomnia; lymphadenopathy; meningitis aseptic; menstrual disorder; mood altered; muscle weakness; nail discolouration; neutropenia; oligozoospermia; pain; pancreatitis; paresis; pericardial disorders; pericarditis; proteinuria; psychosis; radiation injuries; renal impairment; retinopathy; sensation abnormal; sepsis; sexual dysfunction; speech impairment; stress fracture; taste metallic; telangiectasia; tinnitus; visual impairment.

1.2.4 DRUG INTERACTIONS

Investigators should check for any relevant drug interactions in the methotrexate SmPC. Concurrent vaccination with live-vaccines is contra-indicated.

1.2.5 POST-TREATMENT CONTRACEPTION REQUIREMENTS

Both males and females need to continue effective contraception for a further 6 months after stopping methotrexate. Males cannot donate sperm whilst on methotrexate or within 6 months of stopping treatment.

1.3 SELECTION OF PARTICIPANTS

1.3.1 PARTICIPANT CORE INCLUSION AND EXCLUSION CRITERIA

To be eligible for randomisation, all participants must fulfil the core inclusion criteria and none of the exclusion criteria stated in section 5.3 of the main protocol in addition to the arm-specific criteria below.

Please note, as long as a participant is eligible to take ciclosporin (control arm) and at least one of the other trial treatments they can be randomised (i.e. they can meet exclusion criteria for one or more of the other treatments and still be randomised). If they fail to respond at 6 months, a pre-defined treatment switch (as per protocol) may or may not be possible depending on whether they still meet exclusion criteria for the relevant switch option. If the switch is not possible, they would be withdrawn from the trial at that stage.

1.3.2 METHOTREXATE-SPECIFIC EXCLUSION CRITERIA

In addition to the core inclusion and exclusion criteria documented in the main protocol, the following arm-specific exclusion criteria apply for the methotrexate arm.

1. Any contraindication to methotrexate according to standard clinical care and/or the opinion of the investigator.
2. Men and women planning conception within 6 months (cannot conceive for a minimum of 6-months after stopping methotrexate and need to continue on effective contraception through that period).

1.4 TREATMENT AND MONITORING OF PARTICIPANTS

1.4.1 PRODUCT INFORMATION

Dose: Self-administered sub-cutaneous injection, 15mg once weekly, increasing to 20mg after 3 months if required (joint patient/investigator decision, as per standard practice). A dose reduction is permitted at any point and will be documented in the participants medical notes/Source Data Worksheets and CRF.

Description of product: Metoject® 15mg and 20mg solution for injection in a pre-filled pen. Patients/carers must be trained on how to administer the product. In the unlikely event that Medac cannot supply Metoject® to sites, an alternative brand of methotrexate injection stocked at sites can be dispensed. Patients/carers must receive training on the new device, where applicable. A dose reduction is permitted at any point and will be documented in the participants medical notes/Source Data Worksheets and CRF.

Packaging: Commercial/licenced packaging.

Prescription: Trial-specific prescription. Prescription template to be provided by sponsor.

Source of product: Metoject® will be supplied free-of-charge to sites. If another brand is dispensed, hospital stock will be used, with no reimbursement from the Sponsor. Where another brand is dispensed, pharmacy staff should annotate the prescription with the brand supplied and notify the research team.

Storage: Store in accordance with the storage conditions outlined in the SmPC. Metoject® trial supplies must be stored separately to hospital stock and clearly labelled as trial stock. In the event of a temperature excursion, manage according to local pharmacy practice.

Labelling: Annex 13 (trial specific) labelling is required. Site pharmacy trial teams will be instructed to attach a dispensing label in addition to a Sponsor label which will cover the Annex 13 requirements. Refer to the pharmacy manual for further details.

Accountability:
The pharmacy clinical trials team must maintain accurate accountability records for each strength, including, but not limited to, the number of packs received, the number of packs dispensed to which participant, the number of unused packs in quarantine or destroyed, as well as a record of the batch number and expiry date. It must be clearly documented in the medical notes and CRF when a prescription is issued. There will be no patient diaries, consistent with the pragmatic trial design and real world practice. Adherence should be discussed at each trial visit. A record of study drug returns is not required for the trial. Any unused medicinal product or waste material should be disposed of in accordance with local requirements or by the participant within a sharps bin provided as per routine clinical practice. After use, place the pre-filled pen into a puncture-resistant container and discard as required by local regulations.

1.4.2 AUXILLARY MEDICINAL PRODUCT: FOLIC ACID

Participants taking methotrexate will also take 5mg folic acid once weekly as per standard guidance for the prevention of side effects related to folate deficiency. The folic acid will be labelled with a standard dispensing label in accordance with Schedule 5 to The Medicines for Human Use (SI 1994/3194) (Marketing Authorisations etc) Regulations 1994 on receipt of a valid prescription. It will be stored in accordance with the storage conditions outlined on the commercial pack/relevant SmPC. Hospital stock will be used with no reimbursement from the sponsor. It must clearly documented in the medical notes and CRF when a prescription is issued.

1.4.3 SAFETY VISITS AND MONITORING REQUIREMENTS

Timing of post-randomisation safety tests (bloods, urine, blood pressure and safety assessment) are shown in the main protocol schedule of events (Table 1, section 2 Trial Design), and in the drug-specific schedule of events at the beginning of each drug-specific appendix. Further details, including the exact laboratory tests required, are provided below.

1.4.3.1 SAFETY VISITS (IN ADDITION TO MAIN TRIAL VISITS)

All participants randomised to methotrexate will be followed up for safety at week 2. In addition, if their dose is increased at 3 months, they will be seen at weeks 15 and 17. At month 6, all patients who are switched to methotrexate will be followed for safety at weeks 28 and 30. In addition, if their dose is increased at month 9, they will be seen again at weeks 41 and 43. In the event of dose reduction, additional safety assessments should be arranged at the discretion of the investigator.

1.4.3.2 SAFETY BLOODS

The following safety bloods will be performed at weeks 2, 4, 13, 26, 39 and 52. For those who dose increment at month 3 additional safety bloods will be performed at weeks 15 and 17. For those who switch on to methotrexate at month 6 additional safety bloods will be performed at weeks 28 and 30. For those who increase dose at month 9, further saftey bloods will be performed at weeks 41 and 43.

HAEMATOLOGY
Haemoglobin
Haematocrit
Total and differential leukocyte count
Red blood cell count
Platelet count

BIOCHEMISTRY
Creatinine
Potassium
Liver function tests (LFTs)

1.4.3.3 URINE PREGNANCY TEST

A urine pregnancy test is required for those who switch on to methotrexate at the 6 month stage.

1.4.4 METHOTREXATE POLYGLUTAMATE LEVEL (MONTHS 1,3,6)

Methotrexate arm patients only, please refer to lab manual for full procedure on how to collect and send samples.

1.4.5 MANAGING TOXICITY WITH METHOTREXATE

Methotrexate is the most commonly prescribed standard systemic therapy for this study population (adults with moderate-severe eczema) in the UK, but is used off license. Investigators should refer to the relevant summary of product characteristics in the event of toxicity.

Further British Association of Dermatologists drug related guidance for the safe and effective prescribing of methotrexate can be found here:

Methotrexate: https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjd.14816

1.4.6 EVALUATING AE'S AND SAE'S – ASSESSMENT OF EXPECTEDNESS

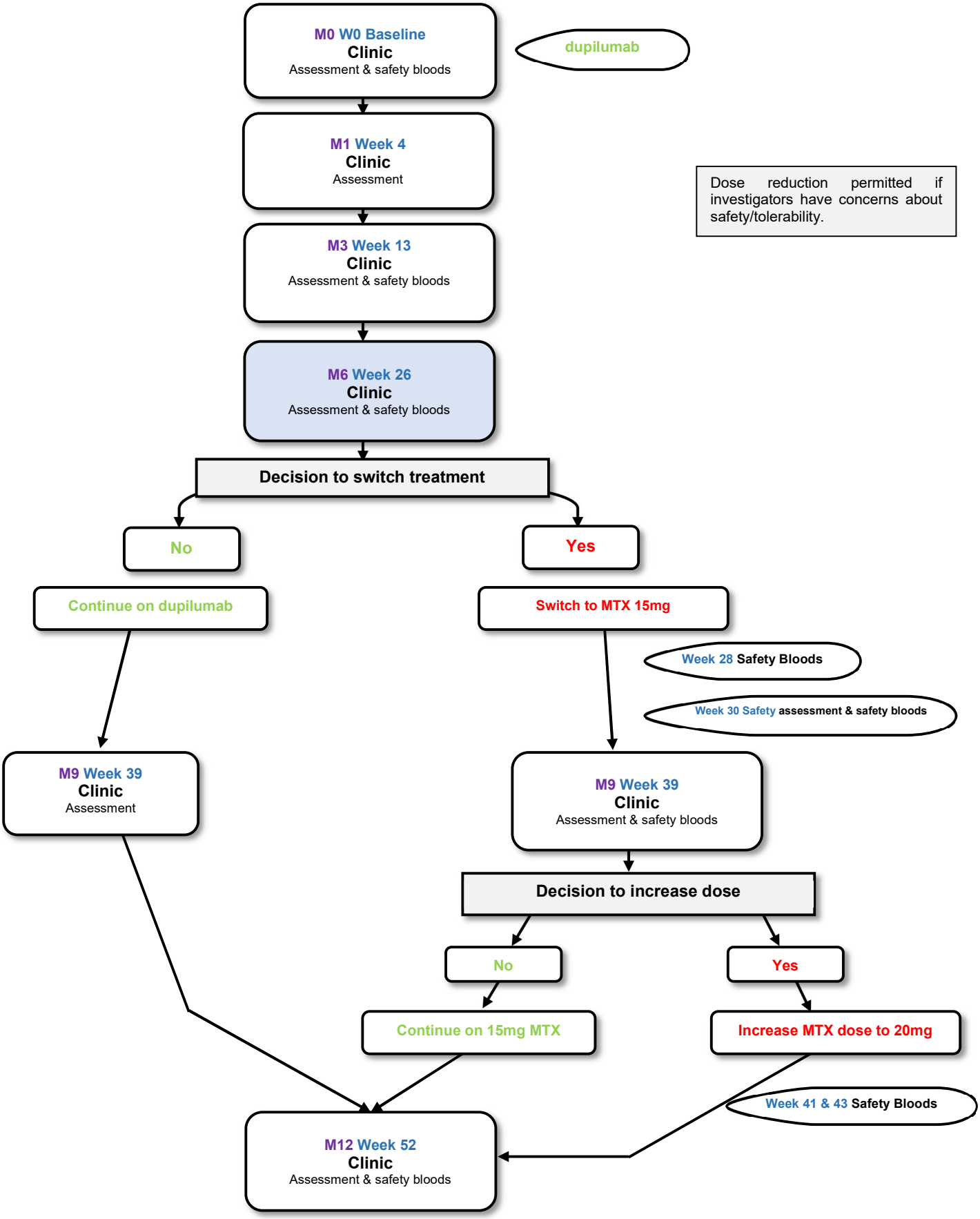
Section 4.8 of the following SmPC forms the RSI for methotrexate for this trial: Metoject PEN solution for injection pre-filled pen. This can be found in investigator site files (SmPC & Safety Alert Updates).

1.5 REFERENCES

1. Pink AE, Woolf RT, Smith CH (2024). Principles of Systemic Therapy. In Rook's Textbook of Dermatology (eds Barker J, Griffiths C, Bleiker T, Simpson R, Hussain W)
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7. Schiff MH, Jaffe JS, Freundlich B. Head-to-head, randomised, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses >/=15 mg may be overcome with subcutaneous administration. *Ann Rheum Dis* 2014;73:1549-51.

APPENDIX 3 DRUG-SPECIFIC INFORMATION: DUPILUMAB

TRIAL PARTICIPANT FLOW AND SCHEDULE OF EVENTS: DUPILUMAB



DUPILUMAB SCHEDULE OF EVENTS									
Event / form	**Screening[A]**	**Baseline[B]**	**Week 4 (Month 1)**	**Week 13 (Month 3)**	**PRIMARY OUTCOME Week 26 (Month 6)**	**Week 30 safety visit**	**Week 39 (Month 9)**	**Week 52 (Month 12) End of Study Visit**	**Ongoing**
Informed Consent	X								
Registration Form	X								
Eligibility (confirmation only at baseline)	X	X							
Medical History and demographics	X								
Skin photography (*optional*)		X			X				
Randomisation Form (after all baseline data collected)		X							
Status Form			X	X	X		X	X	
Physical examination*	X	X	X	X	X		X	X	
Blood pressure	X	X							
Urinalysis	X								
Pregnancy test[+]		X							
Eczema Area and Severity Index (EASI) **BLINDED ASSESSOR**		X	X	X	X		X	X	
Investigator Global Assessment (vIGA-AD) **BLINDED ASSESSOR**		X	X	X	X		X	X	
Patient Orientated Eczema Measure (POEM)		X	X	X	X		X	X	
Peak pruritus numerical rating scale (NRS)		X	X	X	X		X	X	
Eczema control (RECAP)		X	X	X	X		X	X	
Patient global assessment (PtGA)		X	X	X	X		X	X	
Dermatology Life Quality Index (DLQI)		X	X	X	X		X	X	
EQ-5D-5L		X		X	X		X	X	
PHQ-9		X			X			X	
GAD-7		X			X			X	
Resource use		X		X	X		X	X	
Adherence check (VAS) & Tolerability				X	X		X	X	
Participant Online Surveys		X						X	
Dispense medication		X		X	X		X		
Screening blood tests (+DNA for filaggrin status, *optional*)	X								
Safety Blood Tests (can be remote)		X		X	X		X[++]	X	
Safety assessment (can be remote)**						X			
Study medication switch review					X				
Study medication dose increment review				X			X		
Concomitant Medications Log									X
Topical treatments		X	X	X	X				
Adverse Events Log									X
Withdrawal Form									X

* Physical examination (according to routine clinical care) required at screening and baseline, extent of physical exam during follow up as deemed appropriate by investigator

** Only for those who switched treatment to dupilumab at 6 months

[+] Women of childbearing potential only. Urine test

[++] Not required for those on dupilumab from the start (week 39 blood tests required for those who switch to dupilumab)

A: Where there are no new risk factors, and at investigator's discretion, blood test results obtained in clinical practice within 4 months prior to randomisation can be used as screening bloods (required tests listed in section 6.7.1.1)

B: Baseline safety bloods for all treatments, at investigator discretion based upon timing of screening bloods

***Please note**: if IMP is switched at 6 months, the schedule of events for the second IMP must be followed for the second 6 months of the trial.*

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1 DUPILUMAB-SPECIFIC INFORMATION

1.1 BACKGROUND

1.1.1 BACKGROUND AND MECHANISM

Dupilumab is a fully human IgG monoclonal antibody that binds with specificity to the shared IL-4 receptor alpha subunit of the IL-4 and IL-13 cytokine receptors. By binding to that subunit, dupilumab inhibits IL-4 signaling through the Type I receptor (IL-4Ra/yc) and IL-4 and IL-13 signaling through the Type II receptor (IL4Ra/IL-13Ra). IL-4 and IL-13 are major drivers of human type 2 inflammatory disease including atopic eczema and asthma. IL-4 induces differentiation of naïve helper T-cells to Th2 cells which in turn produce further IL-4 to create a positive feedback loop. Th2 cells produce IL-13 which is a mediator of allergic inflammation affecting the skin barrier, pathogen defense, fibrosis and neuronal sensitization within the skin[1,2].

1.1.2 RATIONALE FOR USE OF DUPILUMAB

Dupilumab is a comparator as it is a widely adopted (most commonly prescribed 'novel' treatment), new, licensed, effective and targeted therapy, but has high costs, consequent NICE-defined access criteria and there is genuine clinical equipoise with the existing treatments (see section 1.1.1 and 1.4 in main protocol for further background information).

1.1.3 DUPILUMAB DOSE JUSTIFICATION

Dupilumab has one standard licensed dose for the treatment of adults with moderate to severe eczema, which has been utilised in this trial.

1.1.4 RATIONALE FOR 6 MONTH SWITCH OPTION FOR THOSE WHO FAIL TO RESPOND TO DUPILUMAB (METHOTREXATE)

For those participants on dupilumab who do not meet response criteria to continue at 6 months they can switch to methotrexate. Methotrexate was chosen because it represents the most commonly prescribed first line systemic treatment for atopic eczema in the UK, it can be safely continued beyond 12 months (unlike ciclosporin), there would be no funding issue preventing continuation post-trial and it has a more contrasting mechanism of action compared to other novel agents (e.g. JAKi). This will also provide novel information on the sequential benefit of switching from dupilumab to methotrexate and would mean that participants would be eligible to move on to a more novel agent post-trial (e.g. JAKi) if needed.

1.2 DUPILUMAB TOXICITY AND SAFETY

Administration of dupilumab for this study is not anticipated to induce any potential risk other than the known potential side effects listed below (see SmPC).

1.2.1 COMMON SIDE EFFECTS

Conjunctivitis; allergic conjunctivitis; arthralgia; eosinophilia; oral herpes; injection site reactions (including erythema, oedema, pruritis, pain, swelling, and bruising).

1.2.1.1 OCULAR REACTIONS

Dupilumab is commonly associated with cases of conjunctivitis and allergic conjunctivitis, eye pruritus, blepharitis, and dry eye and with infrequent cases of keratitis and ulcerative keratitis. In line

with MHRA drug safety update (November 2022), clinicians are advised to be alert to the risks of ocular reactions and promptly review new onset or worsening ocular symptoms, referring patients for ophthalmological examination as appropriate. Conjunctivitis or dry eye that does not resolve following initial treatment, or patients with signs and symptoms suggestive of keratitis (especially eye pain and vision changes) should undergo ophthalmological examination, as appropriate. Sudden changes in vision and significant eye pain warrant urgent ophthalmology review.

Clinicians should discuss with patients or caregivers the potential for, and symptoms of, ocular side effects at initiation of dupilumab, including symptoms of conjunctivitis and dry eye (which can also include paradoxical eye watering), keratitis and ulcerative keratitis and advise patients to promptly report new-onset or worsening eye symptoms to their healthcare professional so that appropriate treatment can be initiated.

1.2.2 UNCOMMON SIDE EFFECTS

Facial rash; keratitis; blepharitis; eye pruritis; dry eye; angioedema.

1.2.3 RARE SIDE EFFECTS

Ulcerative keratitis; anaphylactic reaction; serum sickness reaction; serum sickness-like reaction.

1.2.4 DRUG INTERACTIONS

Investigators should check for any relevant drug interactions in the dupilumab SmPC.

1.3 SELECTION OF PARTICIPANTS

1.3.1 PARTICIPANT CORE INCLUSION AND EXCLUSION CRITERIA

To be eligible for randomisation, all participants must fulfil the core inclusion criteria and none of the exclusion criteria stated in section 5.3 of the main protocol in addition to the arm-specific criteria below.

Please note, as long as a participant is eligible to take ciclosporin (control arm) and at least one of the other trial treatments they can be randomised (i.e. they can meet exclusion criteria for one or more of the other treatments and still be randomised). If they fail to respond at 6 months, a pre-defined treatment switch (as per protocol) may or may not be possible depending on whether they still meet exclusion criteria for the relevant switch option. If the switch is not possible, they would be withdrawn from the trial at that stage.

1.3.2 DUPILUMAB-SPECIFIC EXCLUSION CRITERIA

In addition to the core inclusion and exclusion criteria documented in the main protocol, the following arm-specific exclusion criteria apply for the dupilumab arm.

1. Any contraindication to dupilumab according to standard clinical care and/or the opinion of the investigator.

Please note: in relation to main exclusion criteria point 2 (main protocol section 5.3), systemic therapies in the same class as dupilumab would, for example, include tralokinumab and lebrikizumab.

1.4 TREATMENT AND MONITORING OF PARTICIPANTS: DUPILUMAB

1.4.1 PRODUCT INFORMATION

Dose: Self-administered sub-cutaneous injection, 600mg (week 0) followed by 300mg every 2 weeks. A dose reduction is permitted at any point and will be documented in the participants medical notes/Source Data Worksheets and CRF.

Description of product: Dupixent® 300 mg/2ml solution for injection in a pre-filled pen (if pen formulation unavailable/ inappropriate for any reason, syringe can be used). Patients/carers must receive training on administration for the formulation prescribed in accordance with the package leaflet.

Packaging: Commercial/licenced packaging.

Prescription: Trial-specific prescription. Prescription template to be provided by sponsor.

Source of product: Supplies are ordered by the site pharmacy procurement team. Reimbursement of the excess treatment costs will be managed locally by site staff.

Storage: Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the original carton to protect from light.

Note: the pre-filled pens/syringes may be kept at room temperature up to 25°C for a maximum of 14 days. Do not store above 25°C. After removal from the refrigerator, Dupixent® must be used within 14 days or discarded. The trial supplies must be stored in a designated section of the fridge, which is clearly labelled and is in a separate location to the storage of hospital dupilumab supplies. In the event of a temperature excursion, manage according to local pharmacy practice.

Special precautions for handling: The solution should be clear to slightly opalescent, colourless to pale yellow. If the solution is cloudy, discoloured or contains visible particulate matter, the solution should not be used. After removing the 300 mg pre-filled pen/syringe from the refrigerator, it should be allowed to reach room temperature up to 25°C by waiting for 45 min before injecting. The pre-filled pen/syringe should not be exposed to heat or direct sunlight. Do not shake the pre-filled pens or syringes.

Labelling: Attach a dispensing label in addition to a Sponsor label. Refer to the pharmacy manual for further details.

Accountability: The pharmacy clinical trials team must maintain accurate accountability records for the formulation, including, but not limited to, the number of packs received, the number of packs dispensed to which participant, the number of unused packs in quarantine or destroyed, as well as a record of the batch number and expiry date. It must be clearly documented in the medical notes and CRF when a prescription is issued. There will be no patient diaries, consistent with the pragmatic trial design and real world practice. Adherence should be discussed at each trial visit. A record of study drug returns is not required for the trial. Any unused medicinal product or waste material should be disposed of in accordance with local requirements or by the participant within a sharps bin provided as per routine clinical practice. After use, place the pre-filled pen/ syringe into a puncture-resistant container and discard as required by local regulations.

1.4.2 SAFETY VISITS AND MONITORING REQUIREMENTS

Timing of post-randomisation safety tests (bloods, urine, blood pressure and safety assessment) are shown in the main protocol schedule of events (Table 1, section 2 Trial Design), and in the drug-specific schedule of events at the beginning of each drug-specific appendix. Further details, including the exact laboratory tests required, are provided below.

1.4.2.1 SAFETY VISITS (IN ADDITION TO MAIN TRIAL VISITS)

No additional safety visits are required for participants randomised to dupilumab at the start of the trial. For participants who switch on to dupilumab at 6 months a safety assessment (no bloods needed, can be remote) is required at week 30. Participants who switch from dupilumab to methotrexate at 6 months will require a pregnancy test. In the event of dose reduction, additional safety assessments should be arranged at the discretion of the investigator.

1.4.2.2 SAFETY BLOODS

The following safety bloods will be performed at weeks 13, 26 and 52:

HAEMATOLOGY
Haemoglobin
Haematocrit
Total and differential leukocyte count
Red blood cell count
Platelet count

BIOCHEMISTRY
Creatinine
Potassium
Liver function tests (LFTs)

1.4.3 MANAGING TOXICITY WITH DUPILUMAB

Dupilumab is licensed for use in this study population (adults with moderate to severe eczema). Investigators should refer to the relevant summary of product characteristics in the event of toxicity.

1.4.4 EVALUATING AE'S AND SAE'S – ASSESSMENT OF EXPECTEDNESS

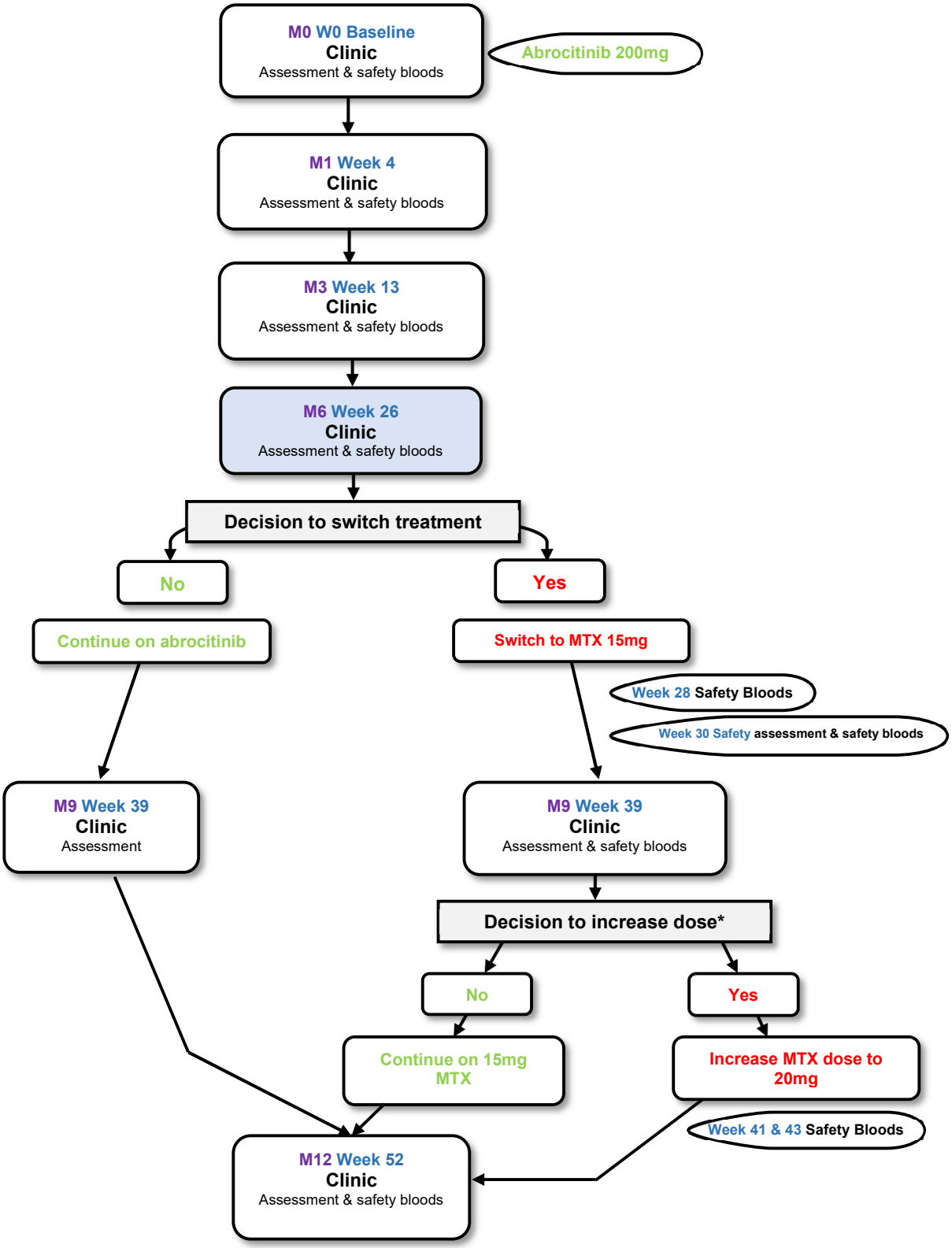
Section 4.8 of the following SmPC's form the RSI for dupilumab for this trial: Dupixent 300mg pre-filled pen SmPC; Dupixent 300mg pre-filled syringe. These can be found in investigator site files (SmPC & Safety Alert Updates).

1.5 REFERENCES

1. Pink AE, Woolf RT, Smith CH (2024). Principles of Systemic Therapy. In Rook's Textbook of Dermatology (eds Barker J, Griffiths C, Bleiker T, Simpson R, Hussain W)
2. Leung DYM, Berdyshev E, Goleva E. Cutaneous barrier dysfunction in allergic diseases. J Allergy Clin Immunol. 2020;145(6):1485-1497.

APPENDIX 4 DRUG-SPECIFIC INFORMATION: ABROCITINIB

TRIAL PARTICIPANT FLOW AND SCHEDULE OF EVENTS: ABROCITINIB



ABROCITINIB SCHEDULE OF EVENTS								
Event / form	**Screening[A]**	**Baseline[B]**	**Week 4 (Month 1)**	**Week 13 (Month 3)**	**PRIMARY OUTCOME Week 26 (Month 6)**	**Week 39 (Month 9)**	**Week 52 (Month 12) End of Study Visit**	**Ongoing**
Informed Consent	X							
Registration Form	X							
Eligibility (confirmation only at baseline)	X	X						
Medical History and demographics	X							
Skin photography (*optional*)		X			X			
Randomisation Form (after all baseline data collected)		X						
Status Form			X	X	X	X	X	
Physical examination*	X	X	X	X	X	X	X	
Blood pressure	X	X						
Urinalysis	X							
Pregnancy test[+]		X						
Eczema Area and Severity Index (EASI) **BLINDED ASSESSOR**		X	X	X	X	X	X	
Investigator Global Assessment (vIGA-AD) **BLINDED ASSESSOR**		X	X	X	X	X	X	
Patient Orientated Eczema Measure (POEM)		X	X	X	X	X	X	
Peak pruritus numerical rating scale (NRS)		X	X	X	X	X	X	
Eczema control (RECAP)		X	X	X	X	X	X	
Patient global assessment (PtGA)		X	X	X	X	X	X	
Dermatology Life Quality Index (DLQI)		X	X	X	X	X	X	
EQ-5D-5L		X		X	X	X	X	
PHQ-9		X			X		X	
GAD-7		X			X		X	
Resource use		X		X	X	X	X	
Adherence check (VAS) & Tolerability				X	X	X	X	
Participant Online Surveys		X					X	
Dispense medication		X		X	X	X		
Screening blood tests (+DNA for filaggrin status, *optional*)	X							
Safety Blood Tests (can be remote)		X	X	X	X		X	
Study medication switch review					X			
Study medication dose increment review				X		X		
Concomitant Medications Log								X
Topical treatments		X	X	X	X			
Adverse Events Log								X
Withdrawal Form								X

* Physical examination (according to routine clinical care) required at screening and baseline, extent of physical exam during follow up as deemed appropriate by investigator

[+] Women of childbearing potential only. Urine test

A: Where there are no new risk factors, and at investigator's discretion, blood test results obtained in clinical practice within 4 months prior to randomisation can be used as screening bloods (required tests listed in section 6.7.1.1)

B: Baseline safety bloods for all treatments, at investigator discretion based upon timing of screening bloods

***Please note**: if IMP is switched at 6 months, the schedule of events for the second IMP must be followed for the second 6 months of the trial.*

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1 ABROCITINIB-SPECIFIC INFORMATION

1.1 BACKGROUND

1.1.1 BACKGROUND AND MECHANISM

Abrocitinib is a Janus kinase (JAK) inhibitor. Cytokines that are integral to the pathogenesis of atopic eczema, including IL-4, IL-13, IL-31 and IL-22, require effective janus kinase activity to exert their effects. Binding of the cytokines to their extracellular receptors induces cross-phosphorylation of JAKs, facilitating STAT binding and subsequent downstream signalling (JAK-STAT pathway). The JAK family comprises four enzymes, JAK1, JAK2, JAK3 and TYK2. The key cytokines relevant to atopic eczema all require JAK1 function. Abrocitinib is significantly more selective for JAK1 than JAK2, JAK3 or TYK2 and has proven effective in treating atopic eczema[1].

1.1.2 RATIONALE FOR USE OF ABROCITINIB

Janus kinase inhibitors are a new class of treatment for atopic eczema offering a different mechanism of action to the previously available options. They have demonstrated effectiveness in trials[2,3] and are increasingly used in practice. The aim of BEACON is to integrate such novel and efficacious treatments into the platform to get head-to-head comparative data against existing therapies. Like dupilumab, no JAKi have been compared against the existing 'standard' treatments including methotrexate and ciclosporin. The more JAK1 specific agents (e.g. abrocitinib and upadacitinib) have proven most effective in trials (more effective than baricitinib), with the top dose of abrocitinib and upadacitinib showing similar levels of effect (measured by absolute change in EASI) in a current living network meta-analysis (effect sizes compared with dupilumab: 2.2, 95% CI 0.2-0.4 and 2.7, 95% CI 0.6-4.7, respectively)[4]. Abrocitinib has been chosen as a JAK class exemplar to enter BEACON (unless clear reason we would not aim to integrate more than one treatment from the same mechanistic class). See main protocol sections 1.1.1 and 1.4 for further background information.

1.1.3 ABROCITINIB DOSE JUSTIFICATION

Abrocitinib is licensed for the treatment of moderate to severe eczema in adults and comes in two available doses, 100mg or 200mg daily. As per license, the lower dose is recommended for people in whom there are risk factors (e.g. those at higher risk of venous thrombo-emobolism (VTE), major adverse cardio-vascular events (MACE) or malignancy) whereas the higher dose may be more appropriate for those without risk factors and with a high disease burden (see abrocitinib SmPC). Given the population entering this study (moderate-severe eczema requiring systemic treatment, i.e. high burden), that people with relative contraindications to the treatment would unlikely be put forward for randomisation to this arm, and the superior effect of higher dose treatment over lower dose treatment in trials we have elected to start participants on 200mg of abrocitinib[2]. This is in line with current clinical practice and the dose can be reduced at any stage in the trial at the discretion of the investigator.

1.1.4 RATIONALE FOR 6 MONTH SWITCH OPTION FOR THOSE WHO DO NOT RESPOND TO ABROCITINIB (METHOTREXATE)

For those participants on abrocitinib who do not meet response criteria to continue at 6 months they can switch to methotrexate. Methotrexate was chosen because it represents the most commonly prescribed first line systemic treatment for atopic eczema in the UK, it can be safely continued beyond 12 months (unlike ciclosporin), there would be no funding issue preventing continuation post-trial and it has a more contrasting mechanism of action compared to other novel agents. This will

also provide novel information on the sequential benefit of switching from abrocitinib to methotrexate and would mean that participants would be eligible to move on to a more novel agent post-trial (e.g. dupilumab) if needed.

1.2 ABROCITINIB TOXICITY AND SAFETY

Administration of abrocitinib for this study is not anticipated to induce any potential risk other than the known potential side effects listed below (see SmPC).

1.2.1 COMMON SIDE EFFECTS

Nausea; abdominal pain; vomiting; herpes simplex (including oral, ophthalmic, genital and eczema herpeticum); herpes zoster (including ophthalmic); headache; dizziness; acne; creatinine phosphokinase increase.

1.2.2 UNCOMMON SIDE EFFECTS

Pneumonia; thrombocytopaenia; lymphopenia; hyperlipidaemia (including dyslipidaemia and hypercholesterolaemia); venous thromboembolism (including pulmonary embolism and deep vein thrombosis).

1.2.3 DRUG INTERACTIONS

Investigators should check for any relevant drug interactions in the abrocitinib SmPC.

1.2.4 POST-TREATMENT CONTRACEPTION REQUIREMENTS

Females need to continue effective contraception for 1 month after stopping abrocitinib.

1.3 SELECTION OF PARTICIPANTS

1.3.1 PARTICIPANT CORE INCLUSION AND EXCLUSION CRITERIA

To be eligible for randomisation, all participants must fulfil the core inclusion criteria and none of the exclusion criteria stated in section 5.3 of the main protocol in addition to the arm-specific criteria below.

Please note, as long as a participant is eligible to take ciclosporin (control arm) and at least one of the other trial treatments they can be randomised (i.e. they can meet exclusion criteria for one or more of the other treatments and still be randomised). If they fail to respond at 6 months, a pre-defined treatment switch (as per protocol) may or may not be possible depending on whether they still meet exclusion criteria for the relevant switch option. If the switch is not possible, they would be withdrawn from the trial at that stage.

1.3.2 ABROCITINIB-SPECIFIC EXCLUSION CRITERIA

In addition to the core inclusion and exclusion criteria documented in the main protocol, the following arm-specific exclusion criteria apply for the abrocitinib arm.

1. Any contraindication to abrocitinib according to standard clinical care and/or the opinion of the investigator.

Note, as per license, abrocitinib should only be used if no suitable treatment alternatives are available in patients:

- 65 years of age and older
- patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers);
- patients with malignancy risk factors (e.g. current malignancy or history of malignancy)

Note, the need for a shingles vaccination (Shingrix) should be considered based on any specific risk factors relevant to the individual participant and up to date formal Green Book guidance: Immunisation against infectious disease - GOV.UK (www.gov.uk).

Please note: in relation to main exclusion criteria point 2 (main protocol section 5.3), systemic therapies in the same class as abrocitinib would, for example, include baricitinib and upadacitinib.

1.4 TREATMENT AND MONITORING OF PARTICIPANTS

1.4.1 PRODUCT INFORMATION

Dose: 200mg orally daily

Description of product:
Abrocitinib 100mg: Film-coated tablet (tablet). Pink, approximately 9 mm in diameter round tablet debossed with “PFE” on one side and “ABR 100” on the other.

Abrocitinib 200mg: Film-coated tablet (tablet). Pink, approximately 18 mm long and 8 mm wide oval tablet debossed with “PFE” on one side and “ABR 200” on the other.

Packaging: blister pack containing 28 tablets

Prescription: Trial-specific prescription.

Source of product: Abrocitinib (Cibinqo®) to be supplied free-of-charge to sites.

Storage conditions: Store in accordance with the storage conditions outlined in the SmPC. In the event of a temperature excursion, manage according to local pharmacy practice.

Labelling: Attach a dispensing label in addition to the Sponsor label. Refer to the pharmacy manual for further details.

Accountability: The pharmacy clinical trials team must maintain accurate accountability records including, but not limited to, the number of packs/tablets received, the number of packs/tablets dispensed to which participant, the number of unused packs/tablets in quarantine or destroyed, as well as a record of the batch number and expiry date. It must be clearly documented in the medical notes and CRF when a prescription is issued. There will be no patient diaries, consistent with the pragmatic trial design and real world practice. Adherence should be discussed at each trial visit. A record of study drug returns is not required. Patients should be advised to bring unused medicine back to pharmacy or the research team.

1.4.2 SAFETY VISITS AND MONITORING REQUIREMENTS

Timing of post-randomisation safety tests (bloods, urine, blood pressure and safety assessment) are shown in the main protocol schedule of events (Table 1, section 2 Trial Design), and in the drug-specific schedule of events at the beginning of each drug-specific appendix. Further details, including the exact laboratory tests required, are provided below.

1.4.2.1 SAFETY VISITS (IN ADDITION TO MAIN TRIAL VISITS)

No additional safety visits (over and above standard study visit schedule) are required for participants randomised to abrocitinib at the start of the trial. In the event of dose reduction, additional safety assessments should be arranged at the discretion of the investigator.

1.4.2.2 SAFETY BLOODS

The following safety bloods will be performed at weeks 4, 13, 26, 39 and 52:

HAEMATOLOGY
Haemoglobin
Haematocrit
Total and differential leukocyte count
Red blood cell count
Platelet count

BIOCHEMISTRY

Creatinine
Potassium
Liver function tests (LFTs)
Lipids

Note: specific thresholds at which drug interruption is suggested can be found in the SmPC.

1.4.3 MANAGING TOXICITY WITH ABROCITINIB

Abrocitinib is licensed for use in this study population (adults with moderate to severe eczema). Investigators should refer to the relevant summary of product characteristics in the event of toxicity.

1.4.4 EVALUATING AE'S AND SAE'S – ASSESSMENT OF EXPECTEDNESS

Section 4.8 of the following SmPC forms the RSI for abrocitinib for this trial: Cibinqo SmPC. This can be found in investigator site files (SmPC & Safety Alert Updates).

1.5 REFERENCES

1. Pink AE, Woolf RT, Smith CH (2024). Principles of Systemic Therapy. In Rook's Textbook of Dermatology (eds Barker J, Griffiths C, Bleiker T, Simpson R, Hussain W)
2. Simpson EL, Sinclair R, Forman S, Wollenberg A, Aschoff R, Cork M, Bieber T, Thyssen JP, Yosipovitch G, Flohr C, Magnolo N, Maari C, Feeney C, Biswas P, Tatulych S, Valdez H, Rojo R. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet. 2020;396:255-266.

3. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, Thaçi D, Chu CY, Hong HC, Katoh N, Paller AS, Calimlim B, Gu Y, Hu X, Liu M, Yang Y, Liu J, Tenorio AR, Chu AD, Irvine AD. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet. 2021;397(10290):2151-2168.
4. Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochwerg B, Di Giorgio S, Arents BWM, Burton T, Spuls PI, Schmitt J, Flohr C. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. JAMA Dermatol. 2022;158(5):523-532.

APPENDIX 5 UK WORKING PARTY DIAGNOSTIC CRITERIA FOR ATOPIC ECZEMA

Must have:

An itchy skin condition (or parental report of scratching or rubbing in a child)

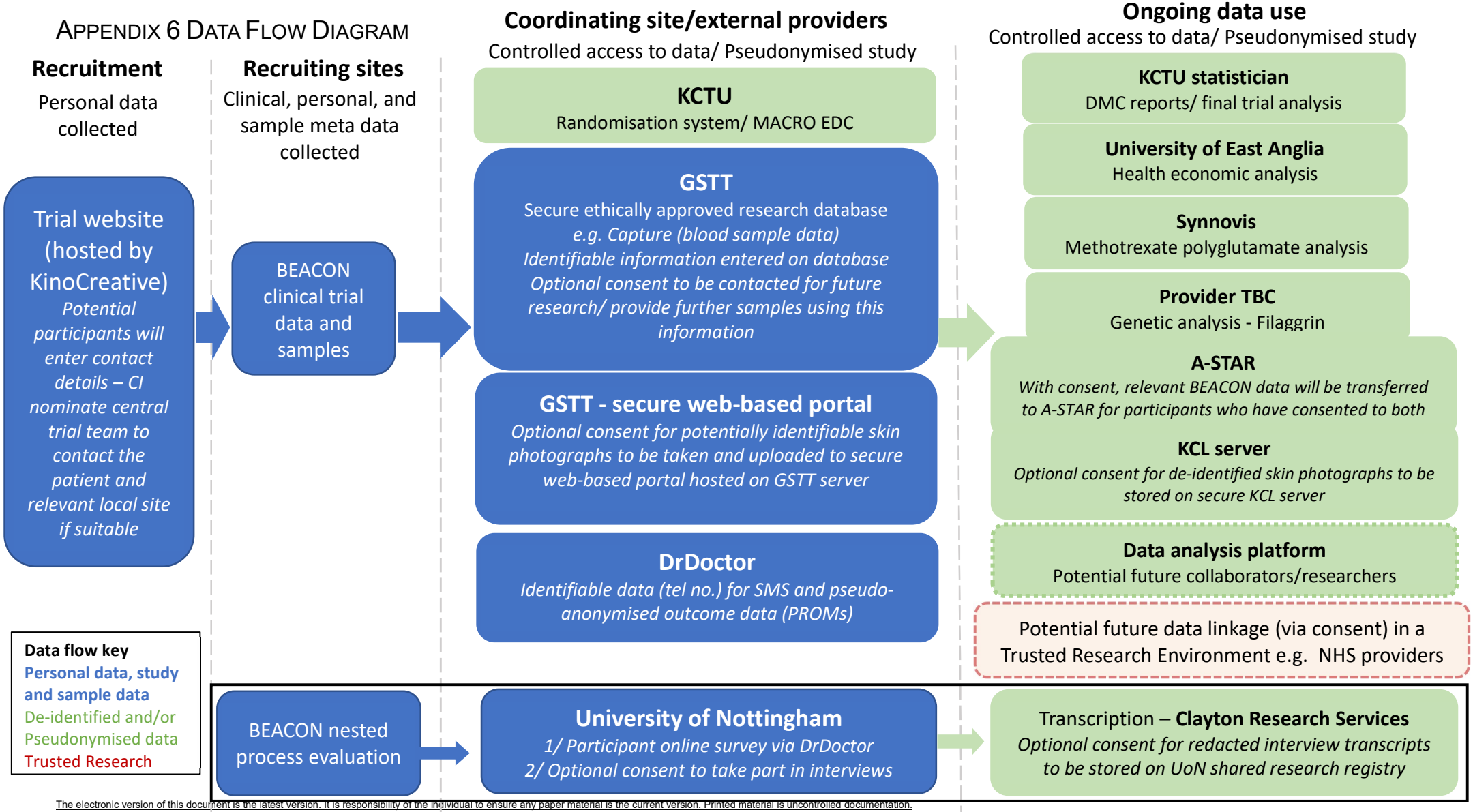
Plus 3 or more of the following

1. History or involvement of the skin creases such as folds of elbows, behind the knees, fronts of ankles or around the neck (including in children under 10)
2. A personal history of asthma or hay fever (or history of atopic disease in a first-degree relative in children under 4)
3. A history of general dry skin in the last year
4. Visible flexural eczema (or eczema involving the cheeks/forehead and outer limbs in children under 4)
5. Onset under the age of 2 (not used if child is under 4)

REFERENCE

Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. Br J Dermatol. 1994;131(3):406-416.

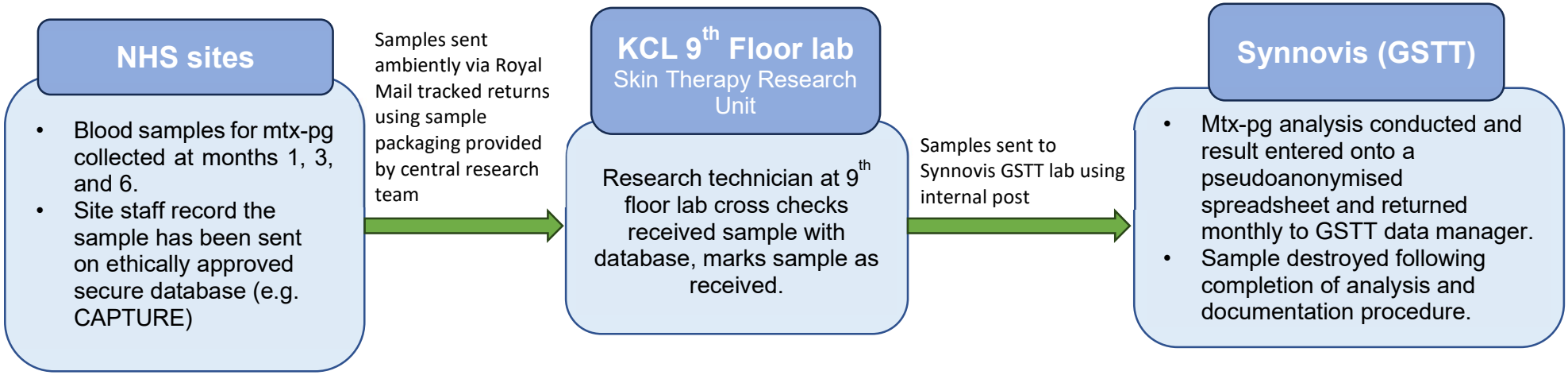
APPENDIX 6 DATA FLOW DIAGRAM



APPENDIX 7 SAMPLE FLOW DIAGRAMS

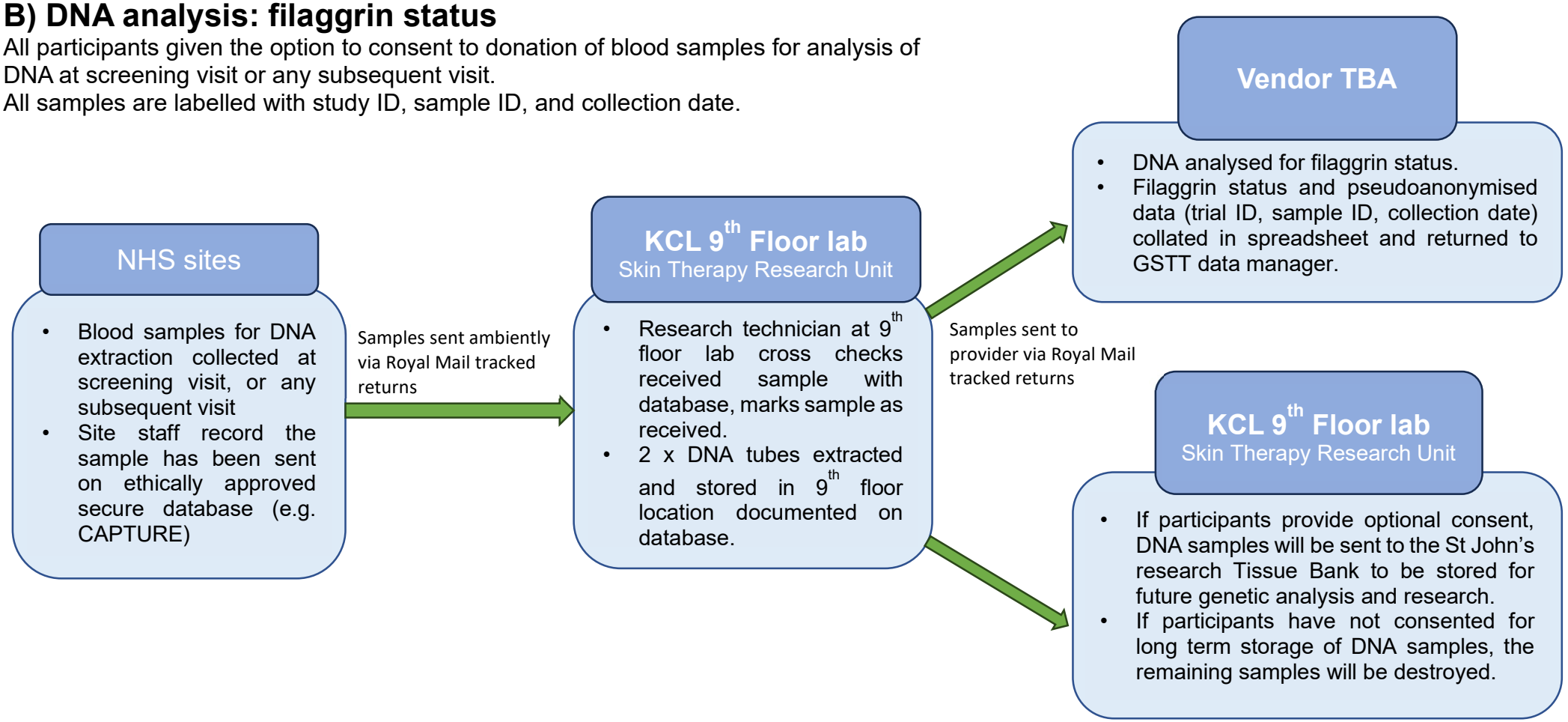
A) Methotrexate-polyglutamate analysis

Participants randomised to methotrexate consent to analysis of blood samples for methotrexate polyglutamate (mtx-pg) levels.
All samples are labelled with study ID, sample ID, and collection date.



B) DNA analysis: filaggrin status

All participants given the option to consent to donation of blood samples for analysis of DNA at screening visit or any subsequent visit.
All samples are labelled with study ID, sample ID, and collection date.



APPENDIX 8 NESTED INTERVIEW STUDY PRE-CONSENT DATA FLOW

