2. SYNOPSIS

Study Title: A First-in-Human, Double-Blind, Randomised, Vehicle Controlled Phase I/II Proof of Concept Study to Investigate the Safety, Tolerability, Pharmacokinetics and Efficacy of BEN2293 in Patients with Mild to Moderate Atopic Dermatitis

Sponsor: BenevolentAI Bio Limited

Coordinating Investigator: Dr Alex Thompson

Study Sites: Part A was a single-centre study in a Clinical Research Unit (CRU) in the United Kingdom. Part B was a multi-centre study to be conducted across sites globally.

Publication (reference): Not applicable.

Length of Study:	**Phase:** I/II
Date of first patient entered: 14 October 2020 Date of last patient completed: 26 January 2023	

Objectives:

The primary objective of the study was to assess the safety and tolerability of BEN2293, administered as multiple topical doses to increasing body surface area (BSA), in patients with mild to moderate atopic dermatitis (AD).

The secondary objectives of the study were:

Pharmacokinetics (PK)

- To investigate the plasma PK of BEN2293 and metabolite BEN6403 following multiple topical doses to mild to moderate AD patients.

Efficacy

- To investigate the effect of BEN2293 on pruritis in patients with mild to moderate AD.
- To investigate the effect of BEN2293 on AD in patients with mild to moderate AD.

Exploratory objectives may or may not have been assessed, depending on the results from primary and secondary objectives. The exploratory objectives of the study were:

Pharmacokinetics

- Evaluation of BEN2293 and metabolite BEN6403 in urine (Part A only).
- Evaluation of concentrations of BEN2293 (subset only in Part B) and metabolite BEN6403 (Part A only) in skin biopsy samples.
- Characterisation of metabolite profile in plasma and urine.

Pharmacodynamics (PD)

- Evaluation of effects of BEN2293 on exploratory biomarkers of AD and pruritis in serum and skin biopsies (Part B only).
- Visual evaluation of effects of BEN2293 on skin affected by AD (subset only in Part B).

Pharmacogenomics

- To characterise responders/non-responders and mechanism(s) of action of BEN2293.

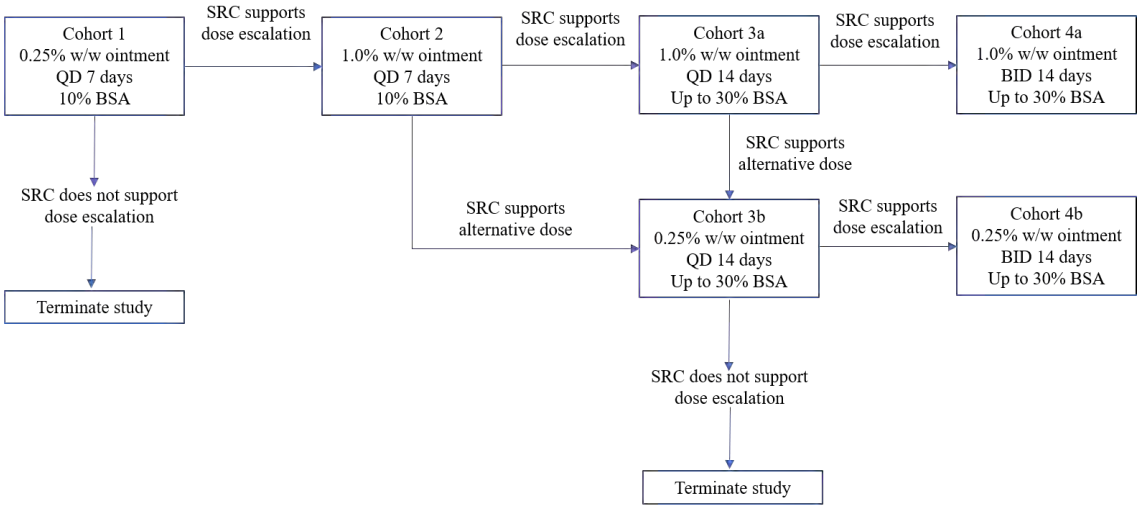
Study Design:

This was a randomised, adaptive design, double-blind, placebo-controlled, first-in-human (FIH), two-part study (Parts A and B) to investigate the safety, tolerability, PK and preliminary efficacy of multiple topical doses of BEN2293 in patients with mild to moderate AD.

The Protocol was adaptive and was designed to enable knowledge gained from the previous cohort to be applied to subsequent cohorts. Changes made were within the boundaries of the adaptive elements with clear control mechanisms and guidance for staying within those boundaries. Except for the starting dose, the doses outlined in the Protocol were preliminary, with actual subsequent dose regimens determined by the Safety Review Committee (SRC) based on ongoing evaluations. The maximum dose in Part A did not exceed 1.0% w/w BEN2293 ointment to 30% BSA three times daily for 14 days. Increasing strength levels of topically applied BEN2293 was achieved by increasing the BSA over which ointment was applied, the concentration of active ingredient in the ointment and the frequency of administration. The maximum dose administered in Part B did not exceed the maximum tolerated or safe dose, as determined in Part A of the study by the SRC.

Part A

Part A was a randomised, double-blind, placebo-controlled, sequential group study to investigate ascending multiple topical doses of BEN2293 in patients with mild to moderate AD. Patients participated in only one cohort. The planned dose levels are shown below.



Abbreviations: BID – twice daily; BSA – body surface area; QD – once daily; SRC – Safety Review Committee.

The SRC supported the planned dose escalations from Cohort 1 to Cohort 2, and from Cohort 2 to Cohort 3 (top row in the above figure). Patients in Cohort 4 were dosed at 1.0% w/w ointment, twice daily (BID) for 14 days at 30% BSA.

It was planned to enrol up to 40 patients into a maximum of 5 cohorts. Each cohort was planned to consist of 8 patients (6 BEN2293: 2 placebo). Patients commenced treatment in staggered subgroups. The first subgroup consisted of 2 sentinel patients; 1 patient was treated with BEN2293 ointment and 1 patient was treated with matching placebo ointment. Subgroup 2 (6 patients; 5 patients BEN2293 and 1 patient placebo) commenced treatment at least 48 hours after commencement of treatment in the sentinel patients after satisfactory review of safety data. For Cohort 4 only, sentinel patients were dosed for 14 days and their safety laboratory tests were reviewed out to Day 14 prior to initiation of the remainder of Cohort 4.

Patients were required to switch from their usual emollient to using the study emollient once daily (QD) in the evening for at least 7 days prior to Day 1 and throughout their participation in the study. Similarly, patients were required to use E45 emollient shower cream for at least 7 days prior to Day 1 and throughout their participation in the study. If a patient could not tolerate E45 products, Doublebase Gel and Doublebase Shower Gel may have been used, at the discretion of the Investigator and Medical Monitor. Dosing commenced on Day 1 and continued for 7 or 14 days, depending on which cohort patients were allocated to.

Dosing was individualised to each patient, based on total BSA (calculated by the Mosteller formula) and required percentage BSA for each cohort. BEN2293 was applied at 2 mg/cm^2 initially, which may have been adjusted by the SRC because of emerging data.

<u>Cohort 1 and Cohort 2:</u>

Patients participated in a Screening Visit (Day -28 to Day -8), an emollient-only washout phase from Day -7 to Day -1 and a treatment period of 7 days. Patients participated in an inpatient visit from Day -1 to Day 3. Patients then completed an outpatient visit on Day 5, returned for an inpatient visit on the morning of Day 7 and were discharged on Day 9. Patients attended an outpatient visit on Day 14 and then a Follow-up visit 14 days (±1 day) after the final BEN2293 application. The patients were contacted by telephone on Days 4, 6 and 11. Sentinel patients in Cohorts 1 and 2 were given a choice as to whether they resided in the CRU for the full duration of Day -1 to Day 9, or from Day -1 to Day 3, as per the remainder of the cohort. Further outpatient visits may have occurred in the event that additional PK samples were required to demonstrate elimination of BEN2293.

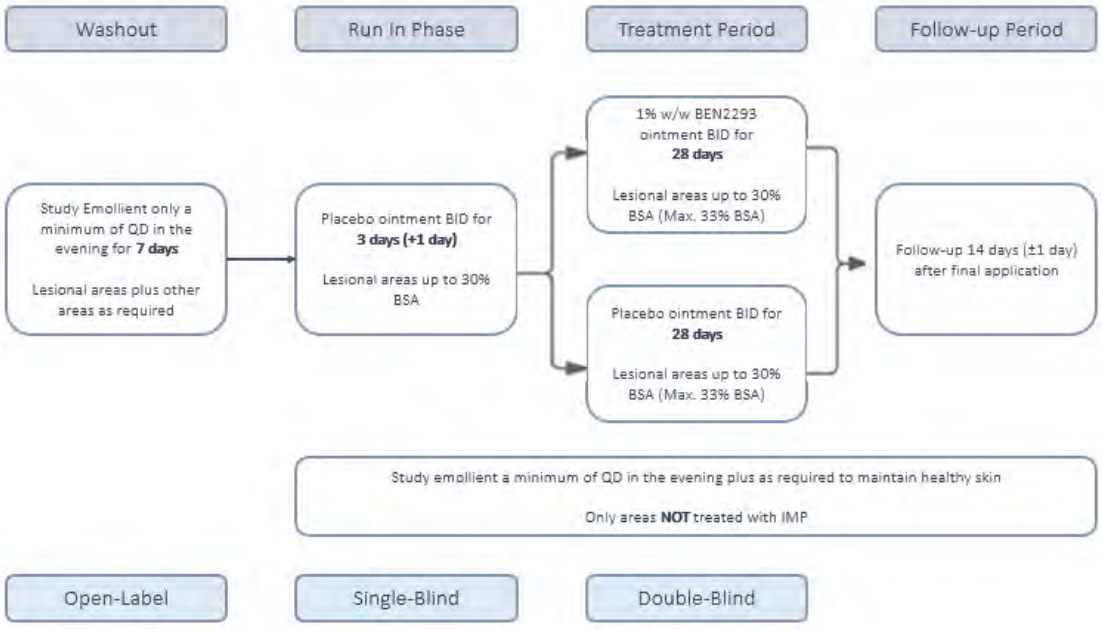
BEN2293 was administered by QD applications of 0.25% w/w (Cohort 1) ointment (6 patients) or matching placebo ointment (2 patients) to 10% BSA. In Cohort 1 and 2, the ointment was applied to 5% BSA lesional skin and 5% BSA non-lesional skin.

All topical applications of BEN2293 were administered by, or supervised by, CRU staff while resident in the CRU. The first application was applied by CRU staff and then training on self-administration was provided so patients could self-administer at all other times, i.e., the amount to apply, body area to cover and how to draw

up the correct amount of study ointment was explained. The dose for Cohort 2 was determined by the SRC based on data from Cohort 1, in line with the adaptive features of the study.
The maximum dose did not exceed 1.0% w/w BEN2293 ointment to 10% BSA QD for 7 days.
The maximum duration of participation for an individual patient in Cohorts 1 and 2 (including Screening, Washout, Treatment and Follow-up) was approximately 7 weeks.
Cohort 3 and Cohort 4:
Patients participated in a Screening Visit (Day -28 to Day -8), an emollient-only washout phase from Day -7 to Day -1 and a treatment period of 14 days. Patients participated in an inpatient visit from Day -1 to Day 3 and completed outpatient visits on Days 5, 7, 9 (Cohort 4 only) and 11. Patients returned for an inpatient visit on the morning of Day 14 and were discharged on Day 16. Patients then completed an outpatient visit on Day 21 and a Follow-up visit 14 days (±1 day) after the final BEN2293 application. The patients were contacted by telephone on Days 4, 6, 8, 9 (Cohort 3 only), 10, 12, 13 and 18. Further outpatient visits may have occurred in the event that additional PK samples were required to demonstrate elimination of BEN2293.
It was planned to administer BEN2293 by QD applications of 1.0% w/w (Cohort 3a) BEN2293 ointment (6 patients) or matching placebo ointment (2 patients) and BID applications of 1.0% (Cohort 4a) BEN2293 ointment (6 patients) or matching placebo ointment (2 patients). BEN2293 was applied up to a maximum of 30% BSA. BEN2293 was applied to all treatable lesional skin, plus a defined non-lesional skin area as required to reach the agreed BSA percentage to be treated for the cohort.
The maximum dose did not exceed 1.0% w/w BEN2293 ointment to 30% BSA three times daily for 14 days.
The maximum duration of participation for an individual patient in Cohorts 3 and 4 (including Screening, Washout, Treatment and Follow-up) was approximately 8 weeks.
All topical applications of BEN2293 were administered by, or supervised by, CRU staff while resident in the CRU. The first application was applied by CRU staff and then training on self-administration was provided so patients could self-administer at all other times, i.e., the amount to apply, body area to cover and how to draw up the correct amount of study ointment was explained.
Progression through cohorts was dependent on the demonstration of adequate safety and PK data within the Protocol defined boundaries. Data up to at least 48 hours post last dose from a minimum of 4 active patients and 1 placebo patient treated with study ointment were reviewed by the SRC in order to decide whether to proceed as planned to the next cohort.

Part B

Part B was a randomised, double-blind, placebo-controlled, parallel group study to investigate a single dose regimen of topical doses of BEN2293 versus placebo administered for 28 days in patients with mild to moderate AD. The planned study design outlined in the Protocol is shown below.



Abbreviations: BID – twice daily; BSA – body surface area; IMP – Investigational Medical Product; QD – once daily.

It was planned to enrol up to 90 patients with mild to moderate AD (two treatment arms of approximately 45 patients) to be treated with double-blind IMP. Patients were required to switch from their usual emollient to

using the study emollient a minimum of QD in the evening, plus as required during the rest of the day, for at least 10 days prior to Day 1 and throughout their participation in the study. Similarly, patients were required to use E45 emollient shower cream for at least 10 days prior to Day 1 and throughout their participation in the study. If a patient could not tolerate E45 products, Doublebase Gel and Doublebase Shower Gel may have been used, at the discretion of the Investigator and Medical Monitor. Where E45 or Doublebase were not available, the Sponsor provided a list of allowed alternatives. Dosing commenced on Day 1 and continued for 28 days.
Patients participated in a Screening Visit (Day -28 to Day -11), an emollient-only washout phase (7 days; Day -10 to Day -4), a placebo run-in phase (3 days [+1 day]; Day -3 to Day -1) and a treatment period of 28 days (Day 1 to Day 28). Following V9.0 of the Protocol (dated 16 September 2022), in mitigating circumstances the 3-day single blind placebo run-in phase could have been extended by 1 day if absolutely necessary for administrative or clinical laboratory data turn-around delays, to ensure the patient could attend the site on Day 1 of the treatment period for dosing. Patients must have received their first dose of the treatment period a minimum of 3 days and a maximum of 4 days after the start of the placebo run-in phase.
All study visits were planned to be conducted on an outpatient basis but may have been changed in line with the adaptive features of the study. Patients completed outpatient visits on Days -3, 1, 7, 14, 21 and 28 and a Follow-up visit (14 days [±1 day] after the final BEN2293 application). Patients also received a telephone call mid-way between treatment visits (Day 3 [±1 day], Day 10 [±1 day], Day 17 [±1 day] and Day 24 [±1 day]).
The recruitment of patients for Part B was enriched so as to include a planned ratio of approximately 70% of patients with a validated Investigators Global Assessment (vIGA) score of 3 (moderate AD) and approximately 30% of patients with a vIGA score of 2 (mild AD).
BEN2293 was administered as 1% w/w BEN2293 ointment or matching placebo ointment (1:1 parallel design) BID. Ointment was applied to all treatable lesioned skin (up to a maximum of 30% BSA at Day 1). Study ointment was also applied to new treatable AD lesions that arose during the study (up to a total maximum of 33% BSA) following discussion with, or assessment by, the Investigator. All treated areas must have continued to be dosed for the remaining duration of the study, even if lesions resolved.
The first application was applied by study site staff and then training on self-administration was provided so patients could self-administer at all other times, i.e., the amount to apply, body area to cover and how to remove the correct amount of study ointment was explained.
The maximum duration of participation for an individual patient in Part B (including Screening, Washout, Run-in, Treatment and Follow-up) was approximately 10.5 weeks.
In Part A, and in a subset of patients in Part B (MAC UK sites), photographs of the affected skin area(s) were taken prior to first dosing, and also after administration of the last dose.
A Sponsor-blind, non-binding futility analysis was planned in Part B. When 15 randomised patients per arm (of whom a minimum of 10 per arm had moderate AD) completed their Day 28 visit, the Numerical Rating Score (NRS) Worst Itch and Eczema Area and Severity Index **(**EASI) Total Score endpoints were assessed in terms of conditional power (CP), being the probability that, if continued to the planned total sample size of 90 patients, the trial would yield a statistically positive outcome.

Number of Patients:
Planned:
Part A – up to 40
Part B – up to 90
Randomised:
Part A – 32
Part B – 91
Treated:
Part A – 32
Part B – 91
Completed:
Part A – 31
Part B – 80

Diagnosis and Main Criteria for Inclusion:
Males and females aged between 18 to 65 years, inclusive, with a body mass index (BMI) of 18.0 to 35.0 kg/m^2, inclusive, and with mild (vIGA score of 2) to moderate (vIGA score of 3) AD affecting between ≥1% to ≤30% BSA of treatable skin (not including face, scalp, genital area, palms of hands or soles of feet). Participants must have had a history of AD (diagnosed by a dermatologist or GP) for at least 6 months, had previous or current successful treatment with topical corticosteroids, and a history of AD associated pruritis with an itch score (NRS) of ≥4.

Study Drug, Reference Therapy, Doses and Mode of Administration:
BEN2293 was supplied as 0.25% and 1.0% (w/w) topical ointments. Matching placebo ointment contained the same excipients as BEN2293 ointment and was manufactured in the same way except for the addition of 0.25% and 1.0% (w/w) BEN2293.
E45 lotion was supplied by the clinic/Investigator site as study emollient to all AD patients for use once a day in the evening for a minimum of 1 week (Part A) or 10 days (Part B) prior to randomisation and throughout the study. E45 emollient shower cream was supplied by the clinic/Investigator site as a study shower wash to all patients to use while on the study. If a patient could not tolerate E45 lotion, or E45 emollient shower cream, Doublebase Gel or Doublebase Shower Gel could be used, at the discretion of the Investigator and Medical Monitor. In Part B, the Sponsor provided a list of alternative allowed emollients and shower products for countries where E45 and Doublebase were not available.
Washout Period
Patients were required to apply the supplied emollient according to the regimen provided. No other AD treatment or therapy, other than E45 emollient shower cream (or Doublebase Shower Gel if E45 could not be tolerated, or allowed alternative where these were not available) could be used during this period.
Single-Blind Run-In Phase (Part B Only)
Patients applied placebo ointment twice daily. An individual patient 'body map' was used to clearly show the areas of AD lesions (and %BSA affected) on the patient's body. The body map indicated the area(s) of AD lesional skin to be treated with the run-in study ointment.
Patients must have received their first dose of the treatment period a minimum of 3 days, and a maximum of 4 days, after the start of the placebo run-in phase.
Each individual patient dose was calculated according to the required %BSA to be treated, in order to achieve the required dose per cm^2 (up to 2.2 mg/cm^2).
Double-Blind Treatment Administration
Patients had applications of either BEN2293 ointment (0.25% or 1.0% w/w) or matching placebo ointment at the determined dose and frequency. Each patient had their total BSA calculated at baseline according to the Mosteller formula. An individual patient 'body map' was used on Day 1 to clearly show the areas of AD lesions (and % BSA affected) on the patient's body.

- For Part A, the body map indicated the area(s) of AD lesional skin and non-lesional skin (if applicable in order to achieve a required %BSA for a cohort) to be treated with study ointment.
- For Part B, the body map indicated the area(s) of AD lesional skin to be treated with study ointment.

All patients had their first dose applied by study site staff and were monitored closely for 30 minutes after their first dose at run-in (Part B only) and Day 1 for signs and symptoms of local tolerability or systemic toxicity issues.
Clinic staff demonstrated the amount to apply, body area to cover using the 'body map' as a guide and how to draw up/remove the required amount of study ointment in a syringe (Part A) or using a gloved finger from a medicine spoon (Part B).
In Part A, subsequent in-unit doses were applied by the patient under supervision from clinic staff. Clinical staff ensured that the patient fully understood the application procedure prior to the commencement of any at-home administration.
In Part A Cohorts 1 and 2, the study ointment was applied to 50% AD lesion skin (i.e., 5% BSA) and 50% non-AD lesion skin (i.e., 5% BSA). For Cohorts 3 and 4, ointment was applied to all treatable lesional skin and to non-lesional skin as required to make up the defined %BSA to be treated for the cohort (up to 30% BSA). In Part B, ointment was applied to all treatable lesioned skin (up to 30% BSA on Day -3 and Day 1).

The majority of AD patients in the study needed to apply either BEN2293 ointment or placebo ointment at home. In Part A, patients were instructed to dose the same area(s) as were dosed in the clinic, using the same application method and according to their annotated 'body map' for all at-home doses.
During the double-blind treatment period in Part B (lesional dosing), patients dosed according to the most recent 'body map'. Lesional areas existing at the start of treatment should have been treated for the whole treatment period even if the lesion resolved. If new lesions developed during the treatment period, patients were to call the study site for advice.
If an evening application of ointment was required, this was done approximately 12 hours after the morning dose. Patients were supplied with a copy of their individual annotated 'body map' and dosing instructions.

Duration of Treatment:
Part A – 7 days (Cohorts 1 and 2) and 14 days (Cohorts 3 and 4)
Part B – 28 days

Criteria for Evaluation:

The primary safety endpoints of the study were:

- Adverse events (AEs), local tolerance assessments, vital signs, 12-lead electrocardiograms (ECGs), laboratory safety tests (clinical chemistry, haematology and urinalysis).

The secondary PK endpoints of the study were:

- Plasma concentration-time profiles and PK parameters for BEN2293 and BEN6403 including maximum observed plasma concentration (C_{max}), time corresponding to the maximum observed plasma concentration (t_{max}), apparent terminal half-life ($t_{1/2}$), area under the plasma concentration vs. time curve (AUC) over a dosing interval (AUC_t) (Part A only).
- Accumulation ratio (Part A only).

The secondary efficacy endpoints of the study were:

- Time to itch reduction.
- Fraction of patients achieving itch reduction.
- Change from baseline in the NRS for Pruritis (Worst Itch over 24 hours).
- Change from baseline in the NRS for Pruritis (Current Itch).
- Change from baseline in the EASI score.
- Number of patients achieving improvement in EASI score.
- Change from baseline in BSA affected by AD in treated area(s).
- Change from baseline in vIGA score.
- Change from baseline in Patient Orientated Eczema Measure (POEM).
- Change from baseline in Dermatology Life Quality Index (DLQI).
- Change from baseline in EuroQol-5 Dimension (EQ-5D).
- Change from baseline in Patient-Reported Outcomes Measurement Information System (PROMIS).
- Change from baseline in Insomnia Severity Index (ISI [for Part A, Cohorts 3 and 4 and Part B only]).

Exploratory endpoints may or may not have been assessed, depending on results from primary and secondary endpoints, and assessed outside the scope of this Clinical Study Report (CSR).

The exploratory PK endpoints of the study were:

- Urinary excretion of BEN2293 and metabolite BEN6403 (amount excreted over 24 hours [$Ae_{0\text{-}24h}$], fraction excreted over 24 hours [$fe_{0\text{-}24h}$] and renal clearance [CL_R]) (Part A only).
- Evaluation of levels of BEN2293 (subset only in Part B) and metabolite BEN6403 (Part A only) in skin biopsy samples.
- Characterisation of metabolites in plasma and urine. Since there was very low exposure of the IMP in plasma and urine, no assessment of exploratory metabolites was performed.

The exploratory PD endpoints of the study were:

- Assessment of change from baseline in exploratory biomarkers of AD and pruritis in serum (e.g., thymus and activation-regulated chemokine [TARC]) and comparison of biomarkers in end-of-treatment skin biopsies (Part B only).
- Visual changes in skin affected by AD through photographs taken pre- and postdose (subset only in Part B).

The exploratory pharmacogenomic endpoints of the study were:

- Identify genetic reasons for responders/non-responders, characterise the mechanism(s) of action of BEN2293 and to identify variations in genes related to the biological target of BEN2293.

Evaluation Methods:

Safety was assessed through AE reporting, 12-lead ECGs, vital signs, physical examinations and clinical laboratory evaluations. Pharmacokinetics was assessed by blood and urine sampling. Pharmacodynamics was assessed through the completion of questionnaires and NRS by the patient or Investigator. Assessment of the percentage of a patient's BSA affected by AD was estimated and recorded on the individual patient's body map at Screening, Day -3 (Part B only), baseline and every subsequent clinic visit.

Statistical Methods:

For Part A, there was no statistical sample size justification. A total of N = 8 per cohort randomised in a 3:1 ratio was considered appropriate for a FIH dose escalation study.

Following a review of Part A data, up to 90 treated patients were planned in Part B with an approximate split of 70%/30% with moderate/mild AD. The sample size was based on standard deviation (SD) estimates for NRS worst itch and EASI Total Score changes from baseline.

The analysis of safety was descriptively summarised by timepoint, as appropriate. Data were presented by actual treatment received and summarised separately for Parts A and B.

Actual sampling times were used for the PK analysis. Plasma, urine and skin concentration data were summarised by sampling time, dose level and dose occasion, as appropriate; PK parameters were summarised by dose level and dose occasion. An equivalence approach was used to assess dose proportionality.
The efficacy of BEN2293 in treating AD was assessed in terms of the secondary endpoints described above for Parts A and B.
Time to itch reduction was assessed in terms of current itch during 24 hours following the first dose of randomised treatment and worst itch over the full duration of the trial treatment period. A Cox regression model for time to reduction of worst itch (fitted separately for Part A and Part B) included fixed effect terms for randomised treatment and NRS worst itch rating at baseline as a covariate. The hazard ratio, 95% confidence interval (CI) and p-value were estimated for each BEN2293 dose as BEN2293:placebo. The data were also displayed using Kaplan-Meier curves. Where possible, the median time to event was estimated by randomised treatment arm along with the associated 95% CI.
Fraction of patients achieving itch reduction, fraction of patients achieving improvement in EASI score, and change from baseline in EQ-5D were analysed using generalised estimating equations (GEE) analysis separately for Parts A and B.
Other secondary efficacy endpoints were analysed via mixed model repeated measures (MMRM) analysis separately for Parts A and B.

Summary:

Results

Study Population – Part A

Thirty-two patients were enrolled, randomised evenly across treatment groups and dosed. Twenty-four patients were randomised evenly across four active treatment groups (6 patients per group) and were administered multiple topical doses of BEN2293 (0.25% w/w QD for 7 days to 10% BSA [Cohort 1], 1.0% w/w QD for 7 days to 10% BSA [Cohort 2], 1.0% w/w QD for 14 days to up to 30% BSA [Cohort 3] and 1.0% w/w BID for 14 days to up to 30% BSA [Cohort 4]). Eight patients were randomised to receive placebo ointment.
Thirty-one patients completed Part A of the study; one patient in Cohort 1 withdrew consent following two applications of BEN2293 following a treatment-emergent adverse event (TEAE) of eczema (flare up of eczema on untreated skin) on Day 2.

Study Population – Part B

Ninety-one patients were enrolled. Forty-nine patients were randomised to the active treatment group and were administered multiple topical doses of BEN2293 (1% w/w BEN2293 ointment BID for 28 days to a maximum of 33% BSA). Forty-two patients were randomised to receive placebo ointment (placebo ointment BID for 28 days to a maximum of 33% BSA).
Eighty patients completed Part B of the study and 11 patients discontinued (6 patients withdrew consent; 2 patients were discontinued due to Investigator decision; 2 patients were withdrawn due to AEs; and 1 patient for other reasons). The two patients in Part B who were withdrawn due to AEs were due to infection with COVID-19.

Safety Results

Part A

Overall, applications of BEN2293 were well tolerated when administered at dose levels of 0.25% w/w QD for 7 days up to 1.0% w/w BID for 14 days.
In Part A, 26 (81.3%) patients experienced 64 TEAEs across all treatment groups. The number of AEs reported following administration of BEN2293 in Cohorts 3 and 4 was comparable to that seen in the placebo treatment group and higher than the number of AEs reported following BEN2293 administration in Cohorts 1 and 2. In summary, TEAEs were reported most frequently following administration of placebo (7 [87.5%] patients reported 22 events), then Cohort 3 (5 [83.3%] patients reported 17 events), followed by Cohort 4 (4 [66.7%] patients reported 13 events). The incidence of TEAEs reported following administration of 0.25% and 1.0% BEN2293 over 7 days (Cohort 1 and Cohort 2) was comparable. Furthermore, the safety profile across all active treatment groups was comparable to that of placebo.
The majority of TEAEs reported were mild in severity and no serious adverse events (SAEs) occurred. Of the 64 events reported, 54 events reported by 25 (78.1%) patients were mild in severity and 10 events reported by 7 (21.9%) patients were moderate in severity. The 10 moderate events comprised of eczema (1 [16.7%] patient each in Cohorts 1 and 4, and Cohort 2 following administration of placebo), application site pain (1 [16.7%] patient in Cohort 1), post-procedural infection (2 [33.3%] patients in Cohort 4), vessel puncture site reaction (1 [16.7%] patient in Cohort 4), dry skin and COVID-19 (each reported by 1 [12.5%] patient in the placebo treatment group). Only 1 event of moderate severity was considered to be related to study treatment; an event of application site pain reported by 1 (16.7%) patient in Cohort 1.

Overall, the most commonly reported TEAEs were within the skin and subcutaneous tissue disorders and nervous system disorders system-organ classes **(**SOCs). Within these SOCs, the most common TEAEs (by preferred term [PT]) were: eczema (8 [25.0%] patients; 2 [33.3%] patients each in Cohort 3 and Cohort 4, 2 [25.0%] patients in the placebo treatment group, and 1 [16.7%] patient each in Cohort 1 and Cohort 2), dry skin (5 [15.6%] patients; 3 [37.5%] patients in the placebo treatment group and 1 [16.7%] patient each in Cohort 1 and Cohort 2), headache (4 [12.5%] patients; 2 [25.0%] patients in the placebo treatment group and 1 [16.7%] patient each in Cohort 1 and Cohort 3) and pruritis (4 [12.5%] patients; 2 [33.3%] patients in Cohort 3, 1 [16.7%] patient in Cohort 4 and 1 [12.5%] patient in the placebo treatment group). With the exception of application site pain, application site paraesthesia, medical device site rash (rash on ECG electrode area), seasonal allergy, COVID-19 and post-procedural infection (each reported by 2 [6.3%] patients), all other TEAEs were reported by a single patient.

Of the 64 events reported during Part A of the study, 7 were considered to be possibly or probably related to study treatment. There were no obvious dose-related trends in the frequency of treatment-related TEAEs; 3 of the 6 treatment-related TEAEs were reported by patients in Cohort 3, 3 were reported by patients administered placebo and 1 was reported by a patient in Cohort 1. The only treatment-related TEAEs (by PT) reported by more than 1 patient were application site pain (2 [6.3%] patients; 1 [16.7%] patient in Cohort 1 and 1 [12.5%] patient in the placebo treatment group) and application site paraesthesia (2 [6.3%] patients; 2 [33.3%] patients in Cohort 3). One event of application site pain and both events of application site paraesthesia were mild in severity and resolved without treatment. A single treatment-related event of transaminases increased was observed in Cohort 3, which was considered to be possibly related to study treatment by the Investigator. There were no treatment-related TEAEs reported in Cohort 2 or Cohort 4.

Sixteen of the 64 events reported were related to local tolerability of study treatment; the highest incidence of AEs relating to local tolerability was observed in the placebo treatment group (4 [50.0%] patients reported 7 events). Four events were reported by 4 (66.7%) patients in Cohort 3, 3 events were reported by 2 (33.3%) patients in Cohort 4 and 1 event was reported by 1 (16.7%) patient in both Cohorts 1 and 2. The only TEAEs relating to local tolerability (by PT) reported by more than 1 patient were eczema (3 [9.4%] patients; 1 [16.7%] patient each in Cohort 2 and Cohort 4 and 1 [12.5%] patient in the placebo treatment group), application site pain (2 [6.3%] patients; 1 [16.7%] patient in Cohort 1 and 1 [12.5%] patient in the placebo treatment group) and application site paraesthesia (2 [6.3%] patients; 2 [33.3%] patients in Cohort 3). One event of application site pain (reported by 1 [16.7%] patient in Cohort 1) was moderate in severity; all other TEAEs relating to local tolerability reported by more than one patient in the active treatment groups were mild in severity. Treatment-emergent AEs related to local tolerability were reported in all treatment groups.

There were no significant treatment-related trends observed for any safety laboratory parameters, vital signs, physical examinations or ECG parameters in Part A of the study. Twenty-three clinically significant findings in the physical examinations performed were reported during Part A of the study; all clinically significant findings were related to skin.

Part B

Overall, applications of BEN2293 were well tolerated when administered at a dose level of 1% w/w BEN2293 ointment BID for 28 days to a maximum of 33% BSA.

In Part B, 43 (47.3%) patients experienced 92 TEAEs across both treatment groups. The incidence of TEAEs reported following administration of BEN2293 was comparable to the placebo treatment group (21 [42.9%] patients reported 49 events in the BEN2293 treatment group and 22 [52.4%] patients reported 43 events in the placebo treatment group).

The majority of TEAEs reported were mild in severity, no treatment-emergent SAEs occurred, and 2 patients were discontinued due to TEAEs of COVID-19. Of the 92 events reported, 87 events reported by 40 (44.0%) patients were mild in severity and 5 events reported by 5 (5.5%) patients were moderate in severity. The 5 moderate events comprised of COVID-19 (1 [2.0%] patient in the BEN2293 treatment group), herpes zoster (1 [2.0%] patient in the BEN2293 treatment group), headache (1 [2.4%] patient in the placebo treatment group), syncope (1 [2.4%] patient in the placebo treatment group) and eczema (1 [2.0%] patient in the BEN2293 treatment group). None of the TEAEs of moderate severity were considered to be related to study treatment.

Overall, the most commonly reported TEAEs were within the infections and infestations, skin and subcutaneous tissue disorders and nervous system disorders SOCs. Within these SOCs, the most common TEAEs (by PT) were: headache (7 [7.7%] patients; 5 [11.9%] patients in the placebo treatment group and 2 [4.1%] patients in the BEN2293 treatment group), nasopharyngitis (4 [4.4%] patients; 1 [2.4%] patient in the placebo treatment group and 3 [6.1%] patients in the BEN2293 treatment group), dermatitis atopic (4 [4.4%] patients; 2 [4.8%] patients in the placebo treatment group and 2 [4.1%] patients in the BEN2293 treatment group), upper respiratory tract infection (3 [3.3%] patients; 2 [4.8%] patients in the placebo treatment group and 1 [2.0%] patient in the BEN2293 treatment group), urinary tract infection (3 [3.3%] patients; 2 [4.8%]

patients in the placebo treatment group and 1 [2.0%] patient in the BEN2293 treatment group), and viral upper respiratory tract infection (3 [3.3%] patients; 2 [4.8%] patients in the placebo treatment group and 1 [2.0%] patient in the BEN2293 treatment group). The following TEAEs were reported by 3 patients: alanine aminotransferase increased (3 [3.3%] patients; 1 [2.4%] patient in the placebo treatment group and 2 [4.1%] patients in the BEN2293 treatment group), oropharyngeal pain (3 [3.3%] patients; 2 [4.8%] patients in the placebo treatment group and 1 [2.0%] patient in the BEN2293 treatment group), and orthostatic hypotension (3 [3.3%] patients; all in the BEN2293 treatment group [6.1%]). All other TEAEs were reported by a maximum of 2 patients overall.

Of the 92 events reported during Part B of the study, 11 were considered to be possibly or probably related to study treatment. Nine of the 11 treatment-related TEAEs were reported by patients in the BEN2293 treatment group and 2 were reported by patients in the placebo treatment group. The only treatment-related TEAE (by PT) reported by more than 1 patient was pruritus (2 [2.2%] patients, who were both in the BEN2293 treatment group [4.1% of the patients in the treatment group]). Both of these events were considered mild.

Fourteen of the 92 events reported were related to local tolerability of study treatment and the incidence was higher in the BEN2293 treatment group compared to placebo. Twelve events were reported by 6 (12.2%) patients in the BEN2293 treatment group, and 2 events were reported by 2 (4.8%) patients in the placebo treatment group. The only TEAEs relating to local tolerability (by PT) reported by more than 1 patient were eczema (2 [2.2%] patients, who were both in the BEN2293 treatment group [4.1% of the patients in the BEN2293 treatment group]) and pruritus (2 [2.2%] patients, who were both in the BEN2293 treatment group [4.1% of the patients in the BEN2293 treatment group]). One event of eczema (reported by 1 [2.0%] patient in the BEN2293 treatment group) was moderate in severity; all other TEAEs relating to local tolerability reported in the BEN2293 treatment group were mild in severity.

There were no significant treatment-related trends observed for any safety laboratory parameters, vital signs, physical examinations or ECG parameters in Part B of the study. Eight clinically significant findings in the physical examinations performed were reported during Part B of the study; all clinically significant findings were related to skin.

Pharmacokinetic Results

Part A

Plasma concentrations of BEN2293 and BEN6403 were only measurable on limited occasions in Cohort 1, measurable in most patients (but close to or below the quantification limit in both first and final dose plasma samples) in Cohorts 2 and 3, and measurable in all patients (and were generally above the quantification limit) in Cohort 4.

BEN2293 and BEN6403 plasma concentrations at steady state for Cohorts 1, 2 and 3, following repeated daily dermal applications, were close to or below the quantification limit. For Cohort 4, following repeated BID dermal applications, steady state plasma concentrations of BEN2293 and BEN6403 were above the quantification limit at all sampling times. The mean plasma concentrations of the metabolite BEN6403 were not appreciably different to those of parent BEN2293 at each sampling time, suggesting that the elimination of BEN6403 was formation-rate limited.

Geometric mean and coefficient of variation (CV) PK parameters of BEN2293 (t_{max} is presented as median and range, and R_o [accumulation ratio of last dose/first dose] is presented as arithmetic mean and CV) in Part A following repeated QD applications of BEN2293 to patients with AD are presented in the table below (geometric mean parameters on Day 7 excluded a value of zero in one patient).

Pharmacokinetic Parameters of BEN2293 Following Topical Applications of BEN2293 Ointment in Patients (Part A)

Part/Cohort	Day	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\tau}$ (ng.h/mL)	$t_{1/2}$ (h)[a]
Part A/Cohort 1 (0.25% w/w, 10% BSA - QD)	1	5	0.0738 (118)	11.0 (2.00, 23.4)	0.130 (579)	NC	NC
	7	4	0.0511 (27.1)	3.03 (0, 12.0)	0.905 (926)	1.02 (7.31)	NC
	R_O	2	1.01 (113)	NA	NA	NC	NA

Part/Cohort	Day	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\tau}$ (ng.h/mL)	$t_{1/2}$ (h)[a]
Part A/Cohort 2 (1% w/w, 10% BSA - QD)	1	2	0.138 (111)	10.0 (6.00, 14.0)	1.00 (91.2)	NC	NC
	7	6	0.0944 (109)	2.00 (1.00, 12.0)	1.08 (612)	1.73 (76.4)	NC
	R_O	2	1.96 (29.8)	NA	NA	2.24[b]	NA
Part A/Cohort 3 (1% w/w, 30% BSA - QD)	1	5	0.0970 (177)	4.00 (1.00, 6.00)	0.485 (266)	1.76 (54.0)	NC
	14	6	0.389 (204)	9.50 (1.00, 14.0)	1.70 (541)	4.34 (29.5)	14.5[b]
	R_O	5	11.6 (129)	NA	NA	2.90 (17.1)[c]	NA
Part A/Cohort 4 (1 % w/w, 30 % BSA - BID)	1	6	0.366 (170)	5.06 (4.00, 12.0)	6.95 (119)	1.87 (214)	NC
	14	6	1.14 (105)	2.00 (1.00, 4.20)	28.8 (139)	6.40 (76.8)	63.8 (18.1)[d]
	R_O	6	5.28 (96.9)	NA	NA	5.80 (99.9)	NA

Abbreviations: AUC_{0-t} – area under the concentration versus time curve from 0 to last quantifiable sample after dosing; $AUC_{0-\tau}$ – AUC from 0 to end of the dosing period (tau = 24h for once-daily and 12h for twice-daily); BID – twice daily; BSA – body surface area; C_{max} – maximum drug concentration; n – number of patients; NA – not applicable; NC – not calculated; QD – once daily; R_o – the accumulation ratio in plasma, calculated as C_{max} (final dose/Day 1) and $AUC_{0-\tau}$ (final dose/Day 1); $t_{1/2}$ – terminal half-life; t_{max} – time of C_{max}.
Data is presented as geometric means (coefficient of variation [CV]), with the exception of R_O, which is presented as arithmetic mean (CV) and t_{max} which is presented as median (range).
a $t_{1/2}$ could not be estimated in most cases due to insufficient data at terminal phase to estimate the apparent terminal rate constant (λ_z).
b In this calculation, n = 1.
c In this calculation, n = 2.
d In this calculation, n = 4.

Geometric mean and CV PK parameters of BEN6403 (t_{max} is presented as median and range, and R_o is presented as arithmetic mean and CV) in Part A following repeated QD applications of BEN2293 to patients with AD are presented in the table below.

Pharmacokinetic Parameters of BEN6403 Following Topical Applications of BEN2293 Ointment in Patients (Part A)

Part/Cohort	Day	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\tau}$ (ng.h/mL)	$t_{1/2}$ (h)[a]
Part A/Cohort 1 (0.25% w/w, 10% BSA - QD)	1	2	0.354 (83.3)	17.7 (12.0, 23.4)	1.55 (69.3)	NC	NC
	7	1	0	0	0.425	NC	NC
	R_O	NC	NC	NA	NA	NC	NA
Part A/Cohort 2 (1% w/w, 10% BSA - QD)	1	3	0.0566 (65.4)	23.7 (6.00, 23.9)	0.631 (177)	NC	NC
	7	5	0.0994 (174)	1.00 (0, 14.0)	1.68 (299)	1.74 (113)[b]	NC

Part/Cohort	Day	n	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\tau}$ (ng.h/mL)	$t_{1/2}$ (h)[a]
	R_O	2	8.06 (125)	NA	NA	NC	NA
Part A/Cohort 3 (1 % w/w, 30 % BSA - QD)	1	3	0.0789 (112)	8.00 (2.00, 8.08)	0.308 (3360)	1.69 47.8)	10.0[c]
	14	3	0.182 (243)	6.10 (2.00, 14.0)	1.35 (571)	3.47 (26.0)[d]	NC
	R_O	2	1.39 (98.5)	NA	NA	NC	NA
Part A/Cohort 4 (1 % w/w, 30 % BSA - BID)	1	6	0.267 (158)	4.00 (2.00, 12.0)	4.47 (108)	1.77 (134)	14.8[c]
	14	6	0.768 (73.0)	4.10 (0, 12.0)	22.3 (65.2)	5.29 (71.9)	34.2 (19.5)[e]
	R_O	6	6.09 (86.4)	NA	NA	5.99 (97.5)	NA

Abbreviations: AUC_{0-t} – area under the concentration versus time curve from 0 to last quantifiable sample after dosing; $AUC_{0-\tau}$ – AUC from 0 to end of the dosing period (tau = 24h for once-daily and 12h for twice-daily); BID – twice daily; BSA – body surface area; C_{max} – maximum drug concentration; n – number of patients; NA – not applicable; NC – not calculated; QD – once daily; R_o – the accumulation ratio in plasma, calculated as C_{max} (final dose/Day 1) and $AUC_{0-\tau}$ (Final Dose/Day 1); $t_{1/2}$ – terminal half-life; t_{max} – time of C_{max}.
Data is presented as geometric means (coefficient of variation [CV]), with the exception of R_O, which is presented as arithmetic mean (CV) and t_{max} which is presented as median (range).
a $t_{1/2}$ could not be estimated in most cases due to insufficient data at terminal phase to estimate the apparent terminal rate constant (λ_z).
b In this calculation, n = 4.
c In this calculation, n =1.
d In this calculation, n = 2.
e In this calculation, n = 3.

Following repeated BID dosing of BEN223 at 1% w/w for 14 days (30% BSA), systemic exposure to BEN2293 on Day 14 tended to be greater than that on Day 1, indicating that BEN2293 accumulated in plasma after repeated BID dosing. Mean C_{max} and $AUC_{0-\tau}$ values for BEN2293 and BEN6403 on Day 14 were approximately 5- to 6-fold greater than those on Day 1, indicating an effective $t_{1/2}$ in the order of 37 to 46 hours, according to linear kinetic theory.
The mean apparent $t_{1/2}$ of BEN2293 was 63.8 hours (based on the highest dose after 14 days since $t_{1/2}$ could not be calculated at lower doses), which was not appreciably longer than the predicted effective $t_{1/2}$ and was considered to be reliably estimated. The mean apparent $t_{1/2}$ of BEN6403 was 34.2 hours, which was not appreciably different to the effective $t_{1/2}$ but was considered to be unreliably estimated. Based on the predicted effective $t_{1/2}$ for BEN2293, steady-state plasma levels would be reached within approximately 6 to 8 days. The predicted time to steady state based on the effective $t_{1/2}$ was consistent with visual inspection of the predose concentrations.
Between-patient variability in the extent of systemic exposure of BEN2293 and BEN6403 was generally high with geometric CVs for C_{max} and $AUC_{0-\tau}$ of 7.31 to 243%.
After multiple daily administrations of BEN2293 (QD or BID), the increase in systemic exposure to BEN2293 was found to be less than dose proportional. With the exception of C_{max} after repeated dosing, for a doubling dose, C_{max} and $AUC_{0-\tau}$ were predicted to increase 1.3- to 1.7-fold. For C_{max} after repeated dosing, the increase in exposure was approximately proportional.
As an exploratory endpoint, the urinary excretion of BEN2293 and BEN6403 was assessed in Cohort 4 of Part A. The renal clearance of BEN2293 was less than the glomerular filtration rate (GFR), indicating net tubular reabsorption. Renal clearance of BEN6403 was variable but not markedly different to GFR in most patients, indication no net tubular reabsorption or excretion.
Evaluation of levels of BEN2293 and BEN6403 in skin biopsy samples was also assessed. Mean concentrations of BEN2293 in skin samples taken at the end of treatment in Part A Cohorts 1, 2, 3 and 4 increased with increasing dose (ranging from 5.06 to 10.7 µg/g),but were undetectable at Follow-up (with the exception of one patient in Cohort 4). Concentrations of BEN6403 were below the limit of quantification at all sampling timepoints.

Part B

Pharmacokinetic parameters were not calculated for Part B. Mean predose plasma concentrations of BEN2293 for Part A, Cohort 4 (0.548 ng/mL) and Part B (0.464 ng/mL) (both dosed using 1 mg w/w BEN2293 BID) were not appreciably different. Likewise, mean predose plasma concentrations of BEN6403 for Part A, Cohort 4 (0.501 ng/mL) were not appreciably different to those values in Part B (0.601 ng/mL).

Efficacy Results

Part A

The efficacy of BEN2293 in treating AD was assessed through numerous measures as secondary endpoints in both Parts A and B. In Part A, the time to itch reduction hazard ratio results showed that each active treatment group was more likely than the placebo treatment group to produce a current itch reduction ≥2 points and Kaplan-Meier estimates showed there was a higher probability that a patient in the placebo treatment group did not achieve a reduction in current itch by ≥2 points compared to all four active treatment groups. None of the hazard ratio results were statistically significant and the Kaplan-Meier estimates were inconclusive due to the large CIs surrounding each estimate. Cohorts 1 and 4 were more likely than placebo to achieve a reduction in current itch by ≥3 points and were superior to placebo by Kaplan-Meier estimates, but similar to reduction in current itch by ≥2 points, the results were not statistically significant. Cohort 4 was more likely than placebo to achieve a worst itch reduction ≥2 points, and Cohorts 2 and 4 were more likely to achieve a reduction in worst itch by ≥3 points, compared to placebo, although the results were not statistically significant and the Kaplan-Meier estimates were inconclusive due to large CI ranges. Therefore, these results should be interpreted with caution.

For the fraction of patients achieving itch reduction, each active treatment group was more likely than placebo to achieve a current itch reduction ≥2 points. As per the time to itch reduction findings, the results were not statistically significant with large CI ranges. Results for current itch reduction ≥3 points, worst itch reduction ≥2 points and worst itch reduction ≥3 points were inconclusive.

The NRS score for current itch decreased from baseline for all active treatment groups and placebo, and all these decreases were statistically significant with the exception of Cohort 2 at 8 hours postdose. Cohorts 1 and 4 showed the largest decreases from baseline and these were greater than the reduction in the placebo group at 2 and 4 hours postdose. At 8 hours postdose the reductions were less than those seen in the placebo group. Reductions for Cohorts 2 and 3 were either comparable to, or less than those in the placebo group. Due to the reductions observed in the placebo group, none of the changes from baseline were statistically significant compared to placebo.

The NRS score for worst itch showed decreases from baseline for placebo and Cohorts 1, 2 and 4 at all timepoints, while this was only true for Cohort 3 from Day 11 onwards. None of the changes from baseline were statistically significant though. Due to the reductions observed in the placebo group, none of the changes from baseline were statistically significant compared to placebo.

EASI scores were decreased from baseline for placebo at all timepoints, and for all active treatment groups with the exceptions of Cohort 2 at Day 5 and Cohort 4 at Day 5 and Day 7. None of the changes from baseline in EASI score were statistically significant, with the exception of a statistically significant reduction in EASI score for Cohort 2 on Day 7. Due to the reductions observed in the placebo group, none of the changes from baseline were statistically significant compared to placebo.

No evaluable results were obtained for the number of patients achieving improvement in EASI score (EASI 50 and EASI 70) and no statistical analysis was performed on vIGA score as the data did not converge.

Decreases from baseline were observed in the BSA affected by AD in treated areas for all active treatment groups at most timepoints, and for placebo at Days 2, 3, 11 and 14. The only statistically significant reduction was for Cohort 2 at Day 2 and Day 7. Compared to placebo, the decrease from baseline for Cohort 2 at Day 7 was statistically significant ($p=0.013$) and close to statistical significance ($p=0.052$) on Day 2.

With the exception of Cohort 4 at Day 14, decreases from baseline were observed in POEM score for all active treatment groups and placebo at all timepoints. The reduction was statistically significant for Cohort 1 at Day 7, Cohort 3 at Day 14, and placebo at Day 14. Due to the reductions observed in the placebo group, none of the changes from baseline were statistically significant compared to placebo.

Decreases from baseline were observed in DLQI score for all active treatment groups and placebo at all timepoints, with the exception of Cohort 2 at Day 7. The reduction was statistically significant for Cohort 1 at Day 7, Cohorts 3 and 4 at Day 14, and for placebo at Day 7 and Day 14. The largest decrease from baseline was in the placebo group at each timepoint and due to this, were no statistically significant reductions in DLQI score compared to placebo for any active treatment group.

For the responses to each of the 5 dimensions of the EQ-5D, no odds ratio was statistically significant for any active treatment groups. The 95% CI range was very wide for a number of the dimensions suggesting unreliable

results and that there was no difference compared to placebo in the responses to each of the 5 dimensions of the EQ-5D.

Cohort 2 at Day 7 and Cohort 3 at Day 14 showed improved quality of life as assessed by the EQ-5D analogue scale, however the increases from baseline were not statistically significant. The placebo treatment group showed a decrease from baseline at both Day 7 and Day 14. No differences in LS mean compared to placebo were statistically significant but the positive change in the visual analogue scale on Day 14 although it was not statistically significant (p-value of 0.099) compared to placebo.

Reductions from baseline for the PROMIS domains (mood and sleep, scratching behaviour and itch interference) were observed for all active treatment groups and placebo at all timepoints, with the exception of mood and sleep, and itch interference at Day 7 for Cohort 2. There were no statistically significant reductions in PROMIS domains compared to placebo for any active treatment group.

Cohort 3 and the placebo group showed a reduction from baseline in the ISI score at Day 14 while it was increased for Cohort 4. The reduction in the placebo group was greater than that observed in Cohort 3 but there were no statistically significant differences in the change from baseline in ISI score for Cohorts 3 and 4 when compared to placebo.

In summary for Part A, most efficacy assessments showed positive results which tended to show improvements following active treatment, but not statistically significantly so due to the results obtained following placebo treatment.

Part B

In Part B, the time to itch reduction hazard ratio results showed that the active treatment group was more likely than the placebo treatment group to produce a current itch reduction of ≥2 points, ≥3 points and ≥4 points and was less likely to produce a worst itch reduction ≥2, ≥3 and ≥4 points. None of the hazard ratio results were statistically significant though. Using Kaplan-Meier estimates where calculable, the probability that a patient has not had a current itch reduction or worst itch reduction of ≥2 points, ≥3 points and ≥4 points tended to be similar for active treatment and placebo with overlapping CIs, clearly indication that there is no statistically significant difference between the groups.

The median time to worst itch reduction ≥2 points was 14 days, but the median time to worst itch reduction ≥3 and ≥4 points and quartile estimates could not be reliably calculated, due to the small sample size and low number of events.

For the fraction of patients achieving itch reduction, the active treatment group was more likely than placebo to achieve a current itch reduction ≥2 and ≥4 points and was less likely to have a current itch reduction ≥3 points compared to placebo. The active treatment group was also more likely to have a worst itch reduction ≥2 and ≥3 points and was less likely to have a worst itch reduction ≥4 points compared to placebo. As per the time to itch reduction findings, the results were not statistically significant.

The NRS score for current itch statistically significantly decreased from baseline for both the active treatment group and placebo. The largest reductions were observed in the active treatment group but the decreases from baseline compared to placebo were not statistically significant.

The NRS score for worst itch also statistically significantly decreased from baseline for both the active treatment group and placebo. The largest reductions tended to be observed in the placebo treatment group so the decreases from baseline compared to placebo were not statistically significant.

EASI scores were decreased from baseline for both the active treatment group and placebo at all timepoints although most were not statistically significant. The largest reductions tended to be observed in the placebo treatment group, leading to decreases from baseline compared to placebo were not statistically significant. For the EASI 50 assessment, a decreased chance of an improvement from baseline compared to placebo was observed overall, although the result was not statistically significant and had a wide CI. No evaluable results were produced for EASI 70 and EASI 75.

The BSA affected by AD in treated areas, POEM score and DLQI score statistically significantly decreased for both the active treatment group and placebo at all timepoints. The largest reductions were observed in the placebo treatment group for these three parameters, so the decreases from baseline for active treatment compared to placebo were not statistically significant.

The vIGA score and ISI decreased statistically significantly for the active treatment group at most timepoints and for placebo at all timepoints. The largest reductions were observed in the placebo treatment group so the decreases from baseline for active treatment compared to placebo were not statistically significant.

For the responses to each of the 5 dimensions of the EQ-5D, the overall odds ratios were <1 compared to placebo, which would suggest that the active treatment group was likely to have a lower response value than placebo. No odds ratio was statistically significant though, indicating that there was no difference in the responses between treatment groups.

Both the placebo and active treatment groups showed improved quality of life as assessed by the EQ-5D analogue scale which were statistically significant at most timepoints. The increases from baseline were greater in the placebo group so the increases from baseline for active treatment compared to placebo were not statistically significant.

From the PROMIS questionnaires, improvements in mood and sleep, scratching behaviour and itch interference were observed for the active treatment group and placebo at all timepoints. The majority of these decreases in PROMIS scores were statistically significant for both active and placebo, although there were no statistically significant reductions in PROMIS domains for the active treatment compared to placebo.

In summary for Part B, the efficacy results showed a similar trend to Part A, with most efficacy assessments showing positive results which tended to show improvements following active treatment, but not statistically significantly compared to placebo treatment. The efficacy parameters were also assessed using the per-protocol (PP) Analysis Set in Part B and these results were consistent with those of the full analysis set (FAS). Multiple imputation (MI) to assess the impact of missing results was also carried out for change from baseline in the NRS for pruritus (worst itch over 24 hours), change from baseline in the NRS for pruritus (current itch), change from baseline in the EASI score, and change from baseline in BSA affected by AD in treated area(s) using the two MI methods. The results of these analyses illustrated that the missing data mechanisms had no impact on the results. The futility analysis was conducted as per the Protocol.

Conclusions

Safety Conclusions

Part A

- No deaths or SAEs were reported during Part A of the study and no patients were discontinued due to a TEAE.
- Applications of BEN2293 were well tolerated when administered at dose levels of 0.25% w/w and 1.0% w/w QD for 7 days to 10% BSA (Cohort 1 and Cohort 2, respectively), 1.0% w/w QD for 14 days to up to 30% BSA (Cohort 3) and 1.0% w/w BID for 14 days to up to 30% BSA (Cohort 4).
- Overall, 26 (81.3%) patients experienced 64 TEAEs across all treatment groups. The most commonly reported TEAEs were within the skin and subcutaneous tissue disorders and nervous system disorders SOCs.
- Within these SOCs, the most common TEAEs (by PT) were eczema, dry skin, headache and pruritis. With the exception of application site pain, application site paraesthesia, medical device site rash, seasonal allergy, COVID-19 and post-procedural infection (each reported by 2 [6.3%] patients), all other TEAEs were reported by a single patient.
- The incidence of AEs reported following administration of BEN2293 for 14 days was higher than the incidence of AEs reported following BEN2293 administration over 7 days and comparable to that of the placebo treatment group.
- Of the 64 events reported, 54 reported by 25 (78.1%) patients were mild in severity and 10 events reported by 7 (21.9%) patients were moderate in severity during Part A.
- One moderate severity event was considered to be related to study treatment (application site pain was reported by 1 [16.7%] patient following administration of 0.25% w/w BEN2293 QD for 7 days to 10% BSA [Cohort 1]). All other moderate severity events were not considered to be related to study treatment.
- Sixteen of the 64 reported TEAEs were related to local tolerability of study treatment. Of these 16 events, 7 were experienced by patients in the placebo treatment group, 4 were experienced following application for 14 days QD (Cohort 3), 3 were experienced following application for 14 days BID (Cohort 4) and 1 was experienced following application of both 0.25% and 1.0% BEN2293 for 7 days QD (Cohorts 1 and 2).
- Seven of the 64 reported TEAEs were considered to be possibly or probably related to treatment.
- None of the TEAEs reported following administration of 1.0% w/w BEN2293 for 7 days QD or following administration for 14 days BID were considered to be related to treatment.
- There were no significant treatment-related trends observed for any safety laboratory parameters, vital signs, physical examinations or ECG parameters in Part A of the study.
- One patient experienced clinically significant high levels of liver transaminases that were considered to be possibly related to study treatment; the event was mild in severity and resolved without treatment.
- Twenty-three clinically significant findings in the physical examinations performed were reported during Part A of the study; all clinically significant findings were related to skin.

Part B

- No deaths or treatment-emergent SAEs were reported during Part B of the study and two patients were discontinued due to TEAEs of COVID-19.
- Applications of BEN2293 were well tolerated when administered at the dose level of 1% w/w BEN2293 ointment BID for 28 days to a maximum of 33% BSA.
- Overall, 43 (47.3%) patients experienced 92 TEAEs across both treatment groups. The most commonly reported TEAEs were within the infections and infestations, skin and subcutaneous tissue disorders and nervous system disorders SOCs.
- Within these SOCs, the most common TEAEs (by PT) were headache, nasopharyngitis, dermatitis atopic, upper respiratory tract infection, urinary tract infection and viral upper respiratory tract infection. With the exception of alanine aminotransferase increased, oropharyngeal pain and orthostatic hypotension, all other TEAEs were reported by a maximum of 2 patients.
- The incidence of TEAEs reported following administration of 1% w/w BEN2293 ointment BID for 28 days to a maximum of 33% BSA was comparable to that of the placebo group.
- Of the 92 events reported, 87 reported by 40 (44.0%) patients were mild in severity and 5 events reported by 5 (5.5%) patients were moderate in severity.
- Fourteen of the 92 reported TEAEs were related to local tolerability of study treatment. Of these 14 events, 2 were experienced by 2 (4.8%) patients in the placebo treatment group and 12 were experienced by 6 (12.2%) patients in the BEN2293 treatment group.
- Eleven of the 92 reported TEAEs were considered to be possibly or probably related to treatment.
- Nine of the 11 treatment-related TEAEs were reported by patients in the BEN2293 treatment group and 2 were reported by patients in the placebo treatment group. The only treatment-related TEAE (by PT) reported by more than 1 patient was pruritus (2 [2.2%] patients, who were both in the BEN2293 treatment group [4.1% of the patients in the BEN2293 treatment group]). Both of these events were considered mild.
- There were no significant treatment-related trends observed for any safety laboratory parameters, vital signs, physical examinations or ECG parameters in Part B of the study.
- Three patients experienced clinically significant out of range clinical laboratory evaluations at various points throughout the study. None of these evaluations were considered to be related to the study treatment.
- Eight clinically significant findings in the physical examinations performed were reported during Part B of the study; all clinically significant findings were related to skin.

Efficacy Conclusions

Part A

- For time to itch reduction, each active treatment group was more likely to have a current itch reduction ≥2 points, and Cohorts 1 and 4 were more likely to achieve a reduction in current itch by ≥3 points, compared to placebo, although the results were not statistically significant. The median time to current itch reduction and quartile estimates could not be reliably calculated, due to the small sample size and low number of events.
- Cohort 4 was more likely to have a worst itch reduction ≥2 points, and Cohorts 2 and 4 were more likely to achieve a reduction in worst itch by ≥3 points, compared to placebo, although the results were not statistically significant. The median time to worst itch reduction and quartile estimates could not be reliably calculated, due to the small sample size and low number of events.
- For the fraction of patients achieving itch reduction, each active treatment group was more likely to have a current itch reduction ≥2 points, compared to placebo, although the results were not statistically significant. Results for current itch reduction ≥3 points, worst itch reduction ≥2 points and worst itch reduction ≥3 points were inconclusive.
- There was a statistically significant reduction from baseline in the NRS score for current itch for all active treatment groups at most timepoints. However, the decreases from baseline compared to placebo were not statistically significant.
- Decreases from baseline were observed in the NRS score for worst itch for all active treatment groups at most timepoints although none were statistically significant. Changes from baseline compared to placebo were not statistically significant.
- Changes from baseline in EASI score were not statistically significant, with the exception of a statistically significant reduction in EASI score for Cohort 2 on Day 7. There were no statistically significant reductions in EASI score compared to placebo for any active treatment group.

- No evaluable results were produced for the number of patients achieving improvement in EASI score (EASI 50 and EASI 70).
- Decreases from baseline were observed in the BSA affected by AD in treated areas for all active treatment groups at most timepoints, and the reduction was statistically significant for Cohort 2 at Day 2 and Day 7. The decrease from baseline on Day 7 was statistically significant compared to placebo and close to statistical significance on Day 2.
- No statistical analysis was performed on vIGA score as the data did not converge.
- Decreases from baseline were observed in POEM score for all active treatment groups at most timepoints, and the reduction was statistically significant for Cohort 1 at Day 7 and Cohort 3 at Day 14. There were no statistically significant changes from baseline in POEM score compared to placebo for any active treatment group.
- Decreases from baseline were observed in DLQI score for all active treatment groups at most timepoints, and the reduction was statistically significant for Cohort 1 at Day 7 and Cohorts 3 and 4 at Day 14. There were no statistically significant reductions in DLQI score compared to placebo for any active treatment group.
- No odds ratio was statistically significant for any active treatment groups, suggesting that there was no difference compared to placebo in the responses to each of the 5 dimensions of the EQ-5D.
- For the EQ-5D analogue scale, no differences in LS mean compared to placebo were statistically significant. Cohort 3 had a positive change in the visual analogue score on Day 14 compared to placebo although it was not statistically significant (p-value of 0.099).
- Reductions from baseline for the PROMIS domains (mood and sleep, scratching behaviour and itch interference) were observed for all active treatment groups at all timepoints, with the exception of mood and sleep, and itch interference at Day 7 for Cohort 2. There were no statistically significant reductions in PROMIS domains compared to placebo for any active treatment group.
- Of the active treatment groups, only Cohort 3 had a reduction from baseline in the ISI score. There were no statistically significant differences in the change from baseline in ISI score for Cohorts 3 and 4 when compared to placebo.

Part B

- For time to itch reduction, the active treatment group was numerically more likely to have a current itch reduction ≥2 points, ≥3 points and ≥4 points, compared to placebo, although the differences versus placebo were not statistically significant. The median time to current itch reduction and quartile estimates could not be reliably calculated, due to the low number of events.
- The active treatment group was numerically less likely to have a worst itch reduction ≥2, ≥3 and ≥4 points, compared to placebo, although the differences versus placebo were not statistically significant. The median time to worst itch reduction and quartile estimates either could not be calculated or had wide CI ranges due to the low number of events.
- There were no clear differences between treatment arms for the fraction of patients achieving current itch reduction, and all comparative p-values were not statistically significant.
- There were no clear differences between treatment arms for the fraction of patients achieving worst itch reduction, and all comparative p-values were not statistically significant.
- There were statistically significant reductions from baseline observed for the NRS score for current itch for both the active treatment group and placebo at most timepoints. However, all comparative p-values for reductions were not statistically significant.
- There were statistically significant reductions from baseline observed for the NRS score for worst itch for both the active treatment group and placebo at most timepoints. However, all comparative p-values for reductions were not statistically significant.
- Reductions from baseline in EASI score were observed for the active treatment group and placebo at all timepoints, however all comparative p-values were not statistically significant.
- The analysis of EASI 50, EASI 70 and EASI 75 suffered from a lack of events, preventing meaningful analyses.
- There was a statistically significant reduction from baseline in BSA affected by AD in treated areas for the active treatment group and placebo at all timepoints. However, all comparative p-values were not statistically significant.
- There was a statistically significant reduction from baseline in vIGA score for the active treatment group and placebo at most timepoints. However, all comparative p-values were not statistically significant.

- There was a statistically significant reduction from baseline in POEM score for the active treatment group and placebo at all timepoints. However, all comparative p-values were not statistically significant.
- There was a statistically significant reduction from baseline in DLQI score for the active treatment group and placebo at all timepoints. However, all comparative p-values were not statistically significant.
- Overall odds ratios for each of the five dimensions of the EQ-5D were not statistically significant.
- For the EQ-5D analogue scale, statistically significant increases from baseline for the active treatment group and placebo were observed at most timepoints. However, all comparative p-values were not statistically significant.
- Statistically significant reductions from baseline for the PROMIS domains (mood and sleep, scratching behaviour and itch interference) were observed for the active treatment group and placebo at all timepoints. However, all comparative p-values were not statistically significant.
- Statistically significant decreases from baseline in ISI were observed for the active treatment group and placebo at most timepoints. However, all comparative p-values were not statistically significant.
- Efficacy endpoints for itch and reduction in EASI scores did not favour BEN2293.

Pharmacokinetic Conclusions

- Following repeated BID dosing of BEN2293 at 1% w/w for 14 days (30% BSA), systemic exposure to BEN2293 and BEN6403 on Day 14 tended to be greater than that on Day 1, indicating that BEN2293 and BEN6403 accumulated in plasma after repeated BID dosing (as predicted for a drug with a long $t_{1/2}$). However, there appeared to be no enzyme induction or inhibition.
- Mean C_{max} and $AUC_{0-\tau}$ values BEN2293 and BEN6403 on Day 14 were approximately 5- to 6-fold greater than those on Day 1, indicating an effective $t_{1/2}$ in the order of 37 to 46 hours, according to linear kinetic theory.
- The mean apparent terminal $t_{1/2}$ of BEN2293 was 63.8 hours, not appreciably longer than the predicted effective $t_{1/2}$ and was considered to be reliably estimated.
- Based on the predicted effective $t_{1/2}$, steady-state plasma levels of BEN2293 would be reached within approximately 6 to 8 days.
- The mean apparent terminal $t_{1/2}$ of BEN6403 was 34.2 hours, not appreciably different to the effective $t_{1/2}$ but was considered to be unreliably estimated.
- Between-patient variability in the extent of systemic exposure to BEN2293 and BEN6403 was generally high with geometric CVs for C_{max} and AUC_{0-24h} of 7.31 to 243%.
- Renal clearance of BEN2293 was low compared to GFR, indicating net tubular reabsorption.
- Renal clearance of BEN6403 not markedly different to GFR in most patients, indicating no net tubular reabsorption or excretion.
- The amount of BEN2293 excreted in urine was very low (<0.002%).
- Following repeated BID dosing of BEN2293 at 1% w/w, mean predose plasma concentrations of BEN2293 for Part A were not appreciably different to those values in Part B.

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