Name of Sponsor/Company UNION Therapeutics	**Name of Finished Product** NA	**Name of Active Ingredient:** ATx201 OINTMENT

Study Number: ATX201-207
Trial registration number: NCT04339985

Title of Study: A Randomized, Double-Blind, Parallel Group, Vehicle-Controlled Phase 2 Study to Evaluate the Safety and Efficacy of Topical ATx201 OINTMENT in Adolescents and Adults with Mild to Moderate Atopic Dermatitis

Investigators and Study Centers:
The study was conducted in 3 countries: Denmark, Bulgaria, and Poland. A total of 12 sites were open in the main study: one site in Denmark, 6 sites in Bulgaria and 5 sites in Poland. The coordinating investigator was from site in Pleven, Bulgaria.

The pharmacokinetic (PK) sub-study was conducted in only one site in Bulgaria.

Publication (reference): None at the time of report preparation

Study Period (years):	**Phase of Development:**
Date of First Subjects Enrolled: 05 November 2019 Date of Last Subject Completed: 22 October 2020	Phase 2

Objectives: To investigate the safety and efficacy of treatment with ATx201 OINTMENT 4% or 7% in subjects with mild to moderate atopic dermatitis (AD) following twice-daily application over a 6-week period.

Primary Objective:

Evaluation of clinical efficacy of ATx201 in subjects with mild to moderate AD.

Secondary Objective*:*

Confirmation of safety and tolerability of ATx201 in subjects with mild to moderate AD.

Exploratory Objectives*:*

Evaluation of PK parameters when study drug was applied to large body surface areas (BSAs) and monitoring of cardiac safety with electrocardiograms (ECGs) (in open-label sub-study)

Methodology:
This was a randomized, international, parallel group, vehicle-controlled, double blinded, multicenter Phase 2 study to evaluate the safety and efficacy of 6-week treatment with ATx201 OINTMENT 4% or 7%, or OINTMENT vehicle twice daily in adolescents and adults with mild to moderate AD.
A total of 212 trial subjects with mild to moderate AD were randomized 1:1:1 to the following treatment groups: ATx201 OINTMENT 4%, ATx201 OINTMENT 7%, or OINTMENT vehicle for 6 weeks.
A PK sub-study was included in the main study. It consisted of an open-label, single-center PK and cardiac safety study in 17 subjects all treated with ATx201 OINTMENT 7% for 2 weeks. The subjects with treatable BSA of ≥5% but ≤18% (N=8) and >18% but ≤36% (N=9) were eligible for participation in the sub-study and were stratified into 2 groups based on their treatable BSA.

Number of Subjects (planned and enrolled):
Main study: Planned 210, Enrolled 212 patients
PK sub-study: Planned 16, Enrolled 17 patients

Diagnosis and Main Criteria for Inclusion:

1. Diagnosis of AD using the Hanifin and Rajka criteria and minimum 1-year history with a current Investigator Global Assessment (IGA) score of 2 or 3 and treatable BSA ≥5% but ≤36% (treatable BSA includes all lesions present at screening except scalp)
2. Age ≥12 and <60 years
3. Male or nonpregnant and nonlactating female who was abstinent or agreed to use effective contraceptive methods throughout the course of the study. Females must have a negative urine beta-human chorionic gonadotropin hormone (hCG) pregnancy test at Day 1.

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Acceptable birth control methods were the following:

- Intrauterine device in place for at least 3 months prior to Day 1
- Use of condom or diaphragm with spermicide for at least 14 days prior to Day 1 and through study completion
- Stable hormonal contraceptive for at least 3 months prior to Day 1 and continuing through study completion

Women who were postmenopausal[1] or who had tubal ligation/hysterectomy did not need to have a urine or serum pregnancy test and did not need to agree to use contraception.

4. Subject or legally authorized representative (LAR) were able to understand and provide signed informed consent. Assent was also required of adolescents.
    - Adults signed the "Participant information and informed consent form"
    - LAR of subjects <18 years signed the "Information Leaflet and ICF for the Parent/Legal Guardian of Minor Participant"
    - Adolescents from 12-17 years signed "Adolescent Assent form"
5. Normally active and otherwise in good health by medical history and physical examination

Exclusion Criteria

Subjects who met any of the following criteria were not eligible to participate in this study:

1. Actively infected AD (i.e. requiring antimicrobial therapy as determined by the investigator)
2. Acute exacerbation or flare in the 4 weeks prior to Day 1 that necessitated treatment with a high potency corticosteroid (such as clobetasol propionate or betamethasone dipropionate), or antibiotics, or prednisolone
3. Enrollment in an ATx201 study in the previous 6 months
4. Allergy or history of significant adverse reaction to niclosamide or related compounds, or to any of the excipients used
5. Underlying skin condition that might interfere with the placement of study treatment or impede clinical evaluations (including active Herpes simplex)
6. Current acute or chronic condition unless considered clinically irrelevant and stable by the investigator
7. The presence of a condition the investigator believed would interfere with the ability to provide informed consent or assent, or comply with study instructions, or that might confound the interpretation of the study results or put the subject at undue risk
8. Unable or unwilling to comply with study procedures
9. Exposure to any investigational medicinal product (IMP) within 30 days prior to randomization

Prior or concomitant therapy

10. Systemic anti-inflammatory/immunomodulatory/immunosuppressant drugs, systemic antimycotic treatments, or topical high-potency corticosteroids 4 weeks prior to Day 1
11. Ultraviolet phototherapy or use of tanning booths within 4 weeks prior to Day 1, or was not willing to minimize natural and artificial sunlight exposure during the study
12. Topical medium-potency corticosteroids, topical calcineurin or PDE4 inhibitors, topical retinoids, topical antimycotic treatments, oral antibiotics for infected AD, or bleach baths within 2 weeks prior to Day 1
13. Topical low-potency corticosteroids or topical antibacterial medications within 1 week prior to Day 1

Use of emollients on the target lesion within 4 hours of the first application

[1] Menopause is defined as the time when there has been no menstrual periods for 12 consecutive months and no other biological or physiological cause can be identified.

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Test Product, Dose and Mode of Administration, Batch Number (main study):
Name: Placebo; 0% (vehicle) ointment; topical application, twice daily; Batch number: K902A
Name: ATx201; 4% ointment; topical application, twice daily; Batch number: K903A
Name: ATx201; 7% ointment, topical application, twice daily; Batch number: K904A
Test Product, Dose and Mode of Administration, Batch Number (PK sub-study**):**
Name: ATx201; 7% ointment; topical application, twice daily; Batch number: K904A

Duration of Treatment (main study): Up to 6 weeks, excluding the screening period
Duration of Treatment (PK sub-study**):** 2 weeks, excluding the screening period

Endpoints for Evaluation:
Primary efficacy endpoint - Week 6

- Eczema Area and Severity Index (EASI) mean change from baseline at Week 6

Secondary efficacy endpoints - Week 6

- EASI-50 and EASI-75
- IGA success defined as clear (0) or almost clear (1) with ≥2grade improvement from baseline
- Distribution of IGA scores (full scale/all categories) and of its change from baseline
- Proportion of subjects with a treatable BSA<5%
- Target lesion total sign score (TSS) mean change from baseline

PK Sub-study

Parameters such as maximum quantity of active drug molecules in blood (C_{max}), time to reach maximum level (T_{max}), and area under the curve of drug level in blood versus time (AUC) were measured.

Safety:
Safety was assessed through clinical laboratory analysis (hematology and serum chemistry), ECGs (PK sub-study), vital sign assessment, local tolerability (0 [no irritation), 1 [mild], 2 [moderate], 3 [severe], 4 [very severe]), and adverse event (AE) monitoring. AEs were collected throughout the treatment and follow-up periods.

Statistical Methods:
The primary endpoint was analyzed using analysis of covariance (ANCOVA) with treatment group as factor and baseline EASI as covariate. Each ATx201 concentration was compared to OINTMENT vehicle. No adjustment for multiplicity was made and the 0.05 level of significance was used to claim efficacy compared to OINTMENT vehicle.

Binary endpoints (IGA success, EASI-50, EASI-75, BSA<5%) were analyzed using the Cochran-Mantel-Haenszel (CMH) test, comparing each active treatment group to OINTMENT vehicle in the Intent-to-Treat (ITT) analysis set with the last observation carried forward (LOCF) approach.

Categorical endpoints (distribution of IGA scores/full scale and of its change from baseline) were analyzed using the CMH test and the row mean score statistics and the ridit transformation with the ITT-LOCF approach.

AE data was presented and tabulated according to Medical Dictionary for Regulatory Activities (MedDRA) classification. Reported AEs were summarized by the number of subjects reporting the events and by System Organ Class (SOC) and Preferred Term (PT); SOC, PT, and severity; and SOC, PT, and relationship to IMP.

The local tolerability scores were presented using frequency distribution over time, and also for the worst response over time (maximum score observed from baseline to Week 6 per subject).

Laboratory (chemistry and hematology) parameters and vital signs were tabulated by visit using descriptive statistics. The value at each visit as well as the change from baseline were presented.

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General Statistical Considerations: All data was summarized using observed cases at each visit per treatment group in the main double-blind study and the PK sub-study.

Interim Analysis
Due to the COVID-19 pandemic, it became difficult to ensure inclusion of study subjects and attendance to the scheduled visits Therefore, an interim analysis was conducted to assess if an early stop of the trial was justified. A total of 98 randomized subjects who completed the Week 6 visit or discontinued before this visit were included in the interim analysis. Data was evaluated by an independent monitoring committee.

Summary of Results:
Trial population: A total of 212 subjects (79 men and 133 women, all Caucasians) were enrolled in the trial (72 subjects randomized to OINTMENT vehicle [68 completed the trial], 70 to ATx201 OINTMENT 4% [66 completed], and 70 to ATx201 OINTMENT 7% [62 completed]). Compliance with administration of trial medications was high in all treatment groups with over 90% of subjects having received 6 weeks of treatment, as planned. The mean (standard deviation [SD]) age was 37.02 years (13.23), and among them 20 (9.43%) subjects were <18 years. At baseline, mean BSA ranged from 12.26 m^2 to 14.10 m^2, mean EASI ranged from 5.41 to 5.79, and IGA ranged from 2.30 to 2.38.

Efficacy
Primary endpoint: EASI mean (SD) change from baseline at Week 6 was -2.95 (4.67) for Vehicle, -3.38 (3.55) for ATx201 OINTMENT 4%, and -2.86 (3.22) for ATx201 OINTMENT 7%.
The difference between each treatment group and OINTMENT vehicle was not statistically significant (estimated difference of least squares means and 95% CI, ITT population):

- ATx201 OINTMENT 4% vs OINTMENT vehicle: -0.541 (-1.62; 0.54, p= 0.325)
- ATx201 OINTMENT 7% vs OINTMENT vehicle: 0.181 (-0.90; 1.26, p= 0.742)

Secondary endpoints:
The frequency of subjects achieving EASI-50 and EASI-75 at Week 6 is tabulated below. The difference between each treatment group and OINTMENT vehicle was not statistically significant.

	% Subjects Achieving EASI-50 at Week 6	**% Subjects Achieving EASI-75 at Week 6**
OINTMENT vehicle	62.50	45.83
ATx201 OINTMENT 4%	64.29	44.29
ATx201 OINTMENT 7%	57.14	30.00
ATx201 OINTMENT 4% vs OINTMENT vehicle, CMH statistics	0.0341; p= 0.8535	
ATx201 OINTMENT 7% vs OINTMENT vehicle, CMH statistics	3.7490; p= 0.0528	

For IGA success at Week 6 (defined as clear (0) or almost clear (1) with ≥2 grade improvement from baseline), in the ITT population, there were 23 subjects (31.94%) in the OINTMENT vehicle treatment group, 20 subjects (28.57%) subjects in the ATx201 OINTMENT 4% treatment group and 16 subjects (22.86%) in the ATx201 OINTMENT 7% treatment group. The treatment difference of ATx201 OINTMENT 4% vs OINTMENT vehicle at Week 6 was 0.1899 (p=0.6630) and 1.4609 (p=0.2268) for ATx201 OINTMENT 7% vs OINTMENT vehicle. Distribution of IGA scores (full scale/all categories) at Week 6 did not show any difference between the treatment groups.

At Week 6, in the ITT population, there were 25 subjects (34.72%) with BSA <5% in OINTMENT vehicle treatment group. In the ATx201 OINTMENT 4% treatment group, there were 27 subjects (38.57%) and in ATx201 OINTMENT 7% treatment group there were 21 (30%). The treatment difference of ATx201

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OINTMENT 4% vs OINTMENT vehicle at Week 6 was 0.2250 (p=0.6353) and for ATx201 OINTMENT 7% vs OINTMENT vehicle it was 0.3589 (p=0.5491).

The target lesion TSS mean (SD) change from baseline at Week 6 was -3.17 (2.37) for OINTMENT vehicle, -3.16 (1.95) for ATx201 OINTMENT 4%, and -2.97 (2.2) for ATx201 OINTMENT 7%.

PK sub-study
Application of ATx201 OINTMENT 7% to 2 groups of adult AD subjects with a treated BSA of 18% and 36% for up to 2 weeks, resulted in a maximum plasma concentration of niclosamide in the range of 28.0 ng/mL (18% BSA) to 44.4 ng/mL (36% BSA) on Week 2, Day 7. The data suggest that steady state is reached by Week 1, Day 7 (C_{trough} concentrations were similar at Week 2, Day 7 compared with Week 1, Day 7).

Safety results
AEs in the main study: During the main study there were 73 AEs reported in 52 subjects (24.53%). Of these, 13 subjects (18.06%) were in the OINTMENT vehicle treatment group, 22 subjects (30.99%) in the ATx201 4% treatment group, and 17 (24.64%) in the ATx201 7% treatment group. None were serious. Five AEs led to subject withdrawal as follows: AD worsening (3 events), skin irritation (one event), and contact dermatitis (one event).
A total of 9 subjects reported events of severe intensity – 3 were reported in each treatment group as follows: localized skin disorders (8 subjects; skin irritation in 6 subjects [2 in each treatment group]), dry skin (one subject), and worsening of AD (one subject), and eyelid irritation (one subject).

Of the 73 AEs reported, 29 were considered related to the study drug by the investigator as follows: 9 events in the OINTMENT vehicle treatment group, 8 in the OINTMENT 4% treatment group, and 12 in the OINTMENT 7% treatment group.

The most frequent AEs were skin irritation, 12 events in 12 (5.66%) subjects; followed by dry skin, 8 events in 7 subjects (3.3%); infections and infestation, 9 events in 7 subjects (3.3%); and headache, 6 events in 6 subjects (2.83%).

Adverse events in the PK sub-study: There were 9 AEs reported in 5 subjects (29.41%) and 7 were considered related to the study drug by the investigator. None of these AEs led to subject withdrawal. Among the reported AEs, the most frequent was pruritus in 3 subjects (17.6%).

Laboratory parameters: In the main study, there was no clinically significant change in any of the blood chemistry and hematology parameters assessed over the time between Screening and End of treatment. In the PK sub-study, there was no clinically significant change in any of the blood chemistry and hematology parameters assessed over the time between Screening and End of treatment, except in 1 subject who developed leukopenia and lymphopenia that were assessed by the investigator as not related to study drug and that spontaneously resolved in a few days.

Interim analysis
The trial was completed as planned.

Conclusions: In this trial ATx201 OINTMENT 4%, ATx201 OINTMENT 7% or OINTMENT vehicle was administered twice daily for 6 weeks on lesioned skin of adults and adolescents with mild to moderate AD. There were no statistically significant differences between any of the groups receiving ATx201 versus OINTMENT vehicle for any of the primary or secondary efficacy endpoints. The treatment was well tolerated with no overall difference in the safety profile between the treatment groups. There was no signal indicating a systemic concern with the use of topically applied ATx201 OINTMENT. Local irritation was reported in a low number of subjects with no difference between the treatment groups. Systemic exposures following topical

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application to large BSAs (36% BSA) of ATx201 OINTMENT 7% remained low with steady state reached by Week 1, Day 7.		
Date of the Report: 06 October 2021		