Clinical and Translational Science

ARTICLE OPEN ACCESS

Safety, Tolerability, and Pharmacokinetics of Single and Multiple Topical Applications of Sodium Taurodeoxycholate, a Treatment for Atopic Dermatitis

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Received: 19 January 2025 | **Revised:** 15 April 2025 | **Accepted:** 18 April 2025

Funding: The authors received no specific funding for this work.

Keywords: pharmacokinetics | phase 1 | safety

ABSTRACT

Sodium taurodeoxycholate (TDCA) gel is a novel candidate for the treatment of atopic dermatitis and is currently under clinical development. TDCA is a taurine-conjugated bile acid derivative that acts as a G protein-coupled bile acid receptor agonist and modulates immune responses. This phase 1 study aimed to investigate the safety, tolerability, and pharmacokinetic profile of sodium TDCA after single and multiple topical administrations of sodium TDCA gel in healthy male subjects. Subjects were randomized to receive a single topical administration of sodium TDCA 5, 10, 30, and 50 mg (0.05%, 0.1%, 0.3%, and 0.5% of 10 g) gel or placebo in the single-ascending dose (SAD) study ($N = 32$), and sodium TDCA 10, 30, and 50 mg (0.1%, 0.3%, and 0.5% of 10 g) gel or placebo for 28 days ($N = 24$) in the multiple-ascending dose (MAD) study. Safety profiles were assessed based on adverse events (AEs), global irritation score (GIS), and numerical pain rating scale (NPRS). Serial blood samples were collected for 24 h at baseline and up to 168 h post-dose in the SAD study and for 72 h at baseline and up to 240 h post-dose at steady state in the MAD study. No serious AEs were reported and all AEs were mild in severity for both SAD and MAD studies. The plasma concentrations of TDCA did not increase significantly after topical administrations. Changes in the plasma concentrations of TDCA likely reflected the circadian rhythm rather than the administration of sodium TDCA gel.

1 | Introduction

Atopic dermatitis (AD) is one of the most prevalent chronic inflammatory skin disorders, characterized by pruritus, with erythematous and eczematous lesions [1]. AD significantly reduces quality of life, increases healthcare costs, and elevates the risk of developing other atopic comorbidities. Recent epidemiological studies estimate that the prevalence of AD ranges from 2.1% to 4.9% in adults and reaches up to 20.1% in children [2, 3]. Approximately one-third of these patients are estimated to have moderate to severe disease, which is associated with a higher risk of atopic comorbidities and a greater disease burden [3].

The etiology and pathophysiology of AD remain incompletely understood, as they are influenced by multiple factors, including defects in the skin barrier, dysregulation of innate immune responses, impaired adaptive immune response, and alterations in the skin microbiome [1]. Therefore, AD management primarily focuses on symptomatic relief rather than achieving a cure. Current pharmacological treatments for AD are

Summary

- What is the current knowledge on the topic?
  - Topical treatments for atopic dermatitis (AD) are associated with limitations such as adverse effects and systemic exposure risks, highlighting the need for safer and more targeted therapeutic alternatives.
  - Sodium taurodeoxycholate is a taurine-conjugated bile acid derivative that acts as a G protein-coupled bile acid receptor agonist and modulates the immune response.
- What question did this study address?
  - The study evaluated the safety, tolerability, and systemic absorption of sodium taurodeoxycholate topical gel in healthy volunteers.
- What does this study add to our knowledge?
  - Sodium taurodeoxycholate gel was safe and well-tolerated, with minimal systemic absorption, suggesting its safety as a topical AD treatment.
- How might this change clinical pharmacology or translational science?
  - Sodium taurodeoxycholate gel provides a promising novel therapeutic option for AD, potentially advancing targeted treatment approaches with limited systemic exposure.

stratified according to the disease severity. Mild AD can typically be managed with topical corticosteroids or calcineurin inhibitors, whereas moderate-to-severe AD often requires systemic therapies, including cyclosporine, systemic steroids, biologics, or other immunomodulators [4–6]. However, these treatments have significant limitations. Systemic steroids pose risks of rebound effects and long-term toxicity, while biologics (e.g., dupilumab and tralokinumab) are associated with high costs, placing a burden on patients who require long-term maintenance therapy. These challenges underscore the need for alternative therapies.

Sodium taurodeoxycholate (TDCA) gel (NuGel) is a topical formulation of TDCA, a taurine-conjugated bile acid derivative developed by Shaperon Inc. (Seoul, Republic of Korea) as a novel therapeutic candidate for AD. TDCA, a G protein-coupled receptor 19 (GPCR19) agonist, inhibits P2X7 receptor activation and nuclear factor kappa B (NF-κB) signaling via the adenylate cyclase-protein kinase A (PKA) pathway, which plays a crucial role in the inflammatory process [7, 8]. In an AD mouse model induced by dinitrochlorobenzene (DNCB), MC903, or oxazolone, TDCA has demonstrated efficacy in improving skin lesions and reducing inflammatory cell infiltration [9]. Based on various in-house animal studies, TDCA has been shown to decrease levels of serum immunoglobulin E (IgE) and other inflammatory cytokines, including interleukin-13 (IL-13), thymic stromal lymphopoietin (TSLP), and interleukin-33 (IL-33), after multiple topical administrations. These findings suggest that it has the potential to regulate systemic IgE levels and mitigate inflammatory responses.

Conjugated secondary bile acids, such as ursodeoxycholate (UDCA), tauroursodeoxycholate (TUDCA), and TDCA, are endogenous compounds derived from the conversion of primary bile acids, known for their established safety and therapeutic potential in immune-related diseases [8, 10]. UDCA is widely recognized as a first-line treatment for biliary cholangitis, supported by its proven safety and efficacy profile [11–13]. Taurine-conjugated bile acids like TUDCA and TDCA have been reported to attenuate inflammation and protect tissues against oxidative and endoplasmic reticulum (ER) stress [14, 15]. Therefore, TDCA is being studied as a potential therapeutic agent for various inflammatory diseases via multiple administration routes [16–18]. Sodium TDCA has been developed as an injectable formulation for the treatment of sepsis. A phase 1 clinical study demonstrated that a single intravenous administration of sodium TDCA was well tolerated in a dose range of 0.1–1.6 mg/kg [19].

This phase 1 study aimed to investigate the safety, tolerability, and pharmacokinetic profile of sodium TDCA after single and multiple topical administrations in healthy male subjects.

2 | Methods

2.1 | Study Design

This was a randomized, double-blind, placebo-controlled single- and multiple-ascending dose (SAD and MAD, respectively) trial. Healthy male volunteers aged 20–50 years, weighing between 45 and 90 kg with a body mass index (BMI) between 17.0 and 27.0 kg/m^2 were eligible to participate (Appendix S1). Subjects who agreed to participate in the study voluntarily provided a written informed consent form. Subjects were excluded if they had any clinically significant medical history, hypersensitivity reactions, or allergies to the ingredients of TDCA or any other clinically significant drugs (Appendix S1). Eligibility was confirmed through medical history reviews, physical examinations, vital signs, 12-lead electrocardiograms (ECGs), and clinical laboratory tests conducted within 4 weeks prior to drug administration.

In the SAD study, subjects were randomized to receive a single topical dose of sodium TDCA 5, 10, 30, and 50 mg (0.05%, 0.1%, 0.3%, and 0.5% of 10 g) gel or placebo in a 3:1 ratio for each dose group ($N = 32$). In the MAD study, subjects received once-daily topical doses of sodium TDCA 10, 30, and 50 mg (0.1%, 0.3%, and 0.5% of 10 g) gel or placebo in a 3:1 ratio for 28 consecutive days ($N = 24$). Dose escalation was determined after a review of blinded safety data by the Safety Monitoring Committee.

The study drug or placebo was applied to a 25 × 40 cm area marked with a template on the subject's back while they lay prone. The subjects remained in position for at least 30 min, and the residual product was removed 1 h after drug administration. The subjects were allowed to drink water at least 2 h after drug administration. Since plasma concentrations of TDCA are influenced by food intake, the meal contents and timing were strictly controlled during the study period [20]. Environmental factors, including temperature (10°C–30°C) and humidity (10%–60%), were also managed at the study site to minimize external variability.

This study (ClinicalTrials.gov Identifier: NCT03492398) was conducted at Seoul National University Hospital, Republic of Korea, in accordance with the ethical principles of the Declaration of Helsinki, all International Conference on Harmonization Good Clinical Practice Guidelines, and local laws and regulations. This study was approved by the Ministry of Food and Drug Safety of the Republic of Korea and the Institutional Review Board of Seoul National University Hospital, Republic of Korea (IRB No. 1703–186-843).

2.2 | Safety and Tolerability Assessment

Safety and tolerability were assessed for all subjects who received either sodium TDCA gel or placebo. Safety profiles were evaluated on the basis of adverse events (AEs), physical examinations, vital signs, 12-lead ECGs, and clinical laboratory tests. Local safety and tolerability were evaluated using the global irritation score (GIS) and numerical pain rating scale (NPRS). GIS was used by the investigator to assess skin irritation at the administration site, considering irritation, erythema, edema, and papules, each scored from 0 (clear without any irritation) to 7 (severe spread beyond the administration site), according to severity. Pain intensity at the administration site was scored by subjects using the NPRS from 0 (no pain) to 10 (worst possible pain).

2.3 | Blood Sample Collection and PK Assessment

Serial blood samples were collected for PK analysis of TDCA before and after the administration. In the SAD group, blood samples were obtained at 0, 2, 4, 8, and 12 h on the day before dosing, and at 0 (pre-dose), 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 h post-dose. In the MAD group, PK blood samples were collected at 0, 2, 4, 8, and 12 h for three consecutive days just before dosing, and serial samples were taken at the same timepoints as the SAD group on day 1 (0 (pre-dose), 2, 4, 8, 12, and 24 h post-dose) and on day 28 (0 (pre-dose), 2, 4, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, and 240 h post-dose) at steady states. Sampling points were determined based on the time to reach maximum plasma concentration and half-life of TDCA. Blood samples were centrifuged at 3000 rpm (1910 g) at 4°C for 10 min. The samples were separated and stored at a −70°C freezer until analysis. The PK profiles were evaluated by quantifying plasma concentrations of sodium TDCA.

Plasma concentrations of TDCA were determined using validated liquid chromatography with tandem mass spectrometry (LC–MS/MS). The analysis was conducted using the Agilent 1260 Infinity system (Agilent Technologies, CA, USA) and the API4000 Qtrap (AB Sciex, MA, USA). Probenecid was used as an internal standard. The mobile phases were 0.1% formic acid in 10 mM ammonium acetate (mobile phase A) and a mixture of 100% acetonitrile/100% methanol (40/60, v/v; mobile phase B) at a flow rate of 0.45 mL/min. Chromatographic separations were performed using the Luna C18 analytical column (100 × 2.0 mm, 5 μm; Phenomenex, CA, USA). The analytes were detected by electrospray ionization (ESI) performed in negative ion mode, monitoring the m/z transitions of 498.25–79.9 for TDCA and 284–140 for probenecid. The lower limit of quantification (LLOQ) of TDCA was 2 ng/mL. The overall accuracy was 93.93%–106.6%, and the precision coefficient of variation was ≤ 4.34% for the plasma TDCA.

PK parameters of TDCA were calculated by a non-compartmental method using Phoenix WinNonlin Version 8.3 (Certara, NJ, USA). The primary PK parameters included C_{max}, T_{max}, AUC_{last}, and AUC_{inf} for SAD, and $C_{max,ss}$, $T_{max,ss}$, and $AUC_{tau,ss}$ for the MAD study. The maximum plasma concentration (C_{max}) and the time to reach peak concentration (T_{max}) were directly obtained from the plasma concentration-time profiles. The area under the concentration-time curve from 0 to the last measurable time point (AUC_{last}) was determined by the linear up log down method, which is a linear trapezoidal within the absorption phase and a log-linear trapezoidal within the elimination phase. The area under the curve from 0 to infinity (AUC_{inf}) was estimated by the equation $AUC_{last} + Clast/\lambda_z$, where λ_z is the terminal elimination constant and C_{last} is the plasma concentration of the last measurable sample. After multiple administrations, the area under the concentration-time curve over a dosing interval of 24 h at steady state ($AUC_{tau,ss}$) was calculated.

Considering that TDCA is an endogenous substance, a time-matched baseline adjustment was additionally conducted for the PK analysis to account for circadian variations in plasma concentrations of TDCA. In the SAD study, plasma concentrations of TDCA during the baseline period exhibited circadian fluctuations. To address potential day-to-day variability in the MAD study, the baseline period was extended to 3 days. Time-matched baseline adjustment in the MAD study was performed using the mean plasma concentrations obtained during the extended baseline period. Negative values resulting from the baseline adjustment were set to zero for the purpose of analysis.

2.4 | Statistical Analysis

All statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc., NC, USA), and statistical significance was defined at p less than 0.05.

3 | Results

3.1 | Study Populations

A total of 56 subjects were enrolled, and eight subjects in each dose group were administered sodium TDCA gel or placebo at a ratio of 3:1 ($N = 32$ in the SAD study and $N = 24$ in the MAD study). Of these, 54 subjects completed the study as planned ($N = 32$ in the SAD study and $N = 22$ in the MAD study), with two subjects withdrawing consent after the administration in the MAD study (Figure S1).

All subjects were males, and the mean ± standard deviation values for age, height, body weight, and BMI were 27.7 ± 7.0 years, 173.4 ± 6.1 cm, 68.7 ± 8.2 kg, and 22.8 ± 2.2 kg/m^2 in the SAD study (Table S1). Corresponding values for the MAD study were 35.6 ± 8.7 years, 173.6 ± 5.8 cm, 69.6 ± 6.9 kg, and 23.1 ± 1.9 kg/m^2 (Table S2). There were no significant differences in baseline demographics among the treatment groups.

3.2 | Safety and Tolerability Assessment

The sodium TDCA gel was well tolerated after single and 28 days of multiple topical administrations at doses up to 50 mg. No serious adverse events were observed. In the SAD study, 13 AEs were reported among nine subjects, with nine of these events in six subjects assessed as adverse drug reactions (ADRs) (Table 1 and Table S3). Similarly, in the MAD study, 15 AEs were reported among nine subjects, with three ADRs reported in three subjects (Table 1 and Table S4). All AEs observed in both the SAD and MAD studies were mild in severity. The most commonly reported AEs were application site pruritus and irritation, which are considered related to the topical administration of sodium TDCA. These events recovered rapidly without any sequelae. No clinically significant changes were observed in vital signs, physical examinations, electrocardiography, and clinical laboratory evaluations.

As for the assessment of local administration site reaction, the GIS was graded 0 or 1 for most subjects who received either sodium TDCA gel or placebo, except for one placebo-treated subject in the SAD study whose GIS was graded as 2. This subject experienced mild erythema at the application site 30 min after placebo administration. The erythema resolved without sequelae and was not associated with infiltration, papules, vesiculation, or pustules. Three other subjects with GIS grade 1 also reported mild erythema, which resolved without complications. The NPRS was graded as 0 for all except three subjects: one from the sodium TDCA 10 mg dose group and two from the placebo group. Of these, one subject in the placebo group had an NPRS score of 2 and reported a slight tingling sensation and mild pruritus associated with erythematous skin lesions. These symptoms were mild and resolved without intervention.

3.3 | PK Assessment

The mean baseline concentration-time profiles of sodium TDCA were consistent across all treatment groups, exhibiting a circadian rhythm characterized by an increase during daytime, followed by a decline at night (Figure 1). After the topical administration of sodium TDCA, the plasma concentration-time profiles of TDCA were similar to those observed during the baseline period (Figure 2).

While large inter-individual variability was evident, the PK parameters of TDCA did not show significant differences between the placebo and sodium TDCA-treated groups, and no dose-dependent increases in exposure were observed with escalating doses of sodium TDCA in both the SAD and MAD studies (Table S5 and Table 2). The observed fluctuations in plasma concentrations of TDCA are more likely attributable to endogenous diurnal variations rather than systemic exposure after the topical administration of sodium TDCA.

4 | Discussion

This study demonstrated that sodium TDCA was well-tolerated up to 50 mg in healthy subjects. The adverse events, including local administration site reactions, were mild and resolved without sequelae. The incidence and severity of reactions, as assessed using GIS and NPRS, were comparable among the treatment groups, indicating a favorable safety profile for sodium TDCA gel.

The observed changes in plasma concentrations of TDCA were attributed to the circadian rhythm of this bile acid rather than to the systemic absorption of sodium TDCA topical administration. Bile acids, including TDCA, play a crucial role in lipid digestion and absorption, with their plasma concentrations demonstrating well-known diurnal fluctuations influenced by intrinsic circadian rhythms and postprandial feedback mechanisms [21]. These fluctuations are regulated by the circadian clock of the liver and meal-induced hormonal signaling. Specifically, postprandial stimulation triggers the release of bile acids from the gallbladder to facilitate digestion, resulting in a transient increase in plasma concentrations of TDCA following meals [20]. This physiological process aligns with the timing of food intake, supporting the interpretation that the observed changes in TDCA levels reflect natural secretion patterns rather than any pharmacological effects of sodium TDCA gel.

Despite rigorous control of environmental and dietary conditions, considerable inter-individual variability in plasma TDCA concentrations was observed. This variability can also be attributed to the intrinsic fluctuations in endogenous bile acid levels described earlier. To address this issue, a time-matched baseline adjustment was employed to account for diurnal variation; however, this adjustment had an impact on PK parameter calculations, particularly in subjects with elevated pre-dose concentrations in the SAD study. Consequently, reduced AUC_{last} values were observed despite high unadjusted concentrations (Table S5 and Figure S2). In the MAD study, this limitation was addressed by extending the baseline period to 72 h and calculating the mean plasma concentrations for time-matched adjustments. This methodological refinement effectively minimized the influence of day-to-day variability and enhanced the interpretability of the PK parameters (Table 2).

Although the study confirmed promising safety and minimal systemic exposure of sodium TDCA gel, it is important to acknowledge the limitations regarding the study population. The trial was conducted in healthy volunteers to address the unknown safety of a new drug and minimize confounding factors. However, in patients with AD, systemic exposure of sodium TDCA could potentially increase due to compromised skin barrier integrity [22]. Nevertheless, considering the physicochemical properties of TDCA, its penetration through weakened skin barriers is expected to be minimal. An ongoing phase 2 clinical trial is collecting PK data, which will provide more definitive evidence regarding potential systemic exposure in patients with AD. This phase 2 study will further contribute to understanding the safety and efficacy of sodium TDCA gel in the target population. An additional limitation of this study is that it included only healthy males. Although these findings provide valuable insights into the safety, tolerability, and PK profile of sodium TDCA in this population, further studies are necessary to evaluate these parameters in female subjects. Future clinical trials should include both male and female subjects

TABLE 1 | Summary of adverse events after single and multiple topical administrations of sodium taurodeoxycholate or placebo.

	Single-ascending dose study					Multiple-ascending dose study			
Adverse event	**Placebo (*N* = 8)**	**Sodium TDCA 5 mg (*N* = 6)**	**Sodium TDCA 10 mg (*N* = 6)**	**Sodium TDCA 30 mg (*N* = 6)**	**Sodium TDCA 50 mg (*N* = 6)**	**Placebo (*N* = 6)**	**Sodium TDCA 10 mg (*N* = 6)**	**Sodium TDCA 30 mg (*N* = 6)**	**Sodium TDCA 50 mg (*N* = 6)**
Subjects with TEAE, *N* (%)	4 (50.0)	2 (33.3)	2 (33.3)	1 (16.7)		2 (33.3)	2 (33.3)	2 (33.3)	3 (50.0)
Gastrointestinal disorders	1 (12.5)								1 (16.7)
Dyspepsia	1 (12.5)								
Epigastric discomfort	1 (12.5)								
Lip swelling									1 (16.7)
General disorders and administration site conditions	2 (25.0)	1 (16.7)	1 (16.7)	1 (16.7)		1 (16.7)	1 (16.7)	1 (16.7)	1 (16.7)
Application site erythema	1 (12.5)								
Application site irritation	1 (12.5)			1 (16.7)		1 (16.7)			
Application site pruritus		1 (16.7)	1 (16.7)					1 (16.7)	1 (16.7)
Feeling hot	1 (12.5)								
Pyrexia							1 (16.7)		
Infections and infestations		1 (16.7)	1 (16.7)			1 (16.7)			2 (33.3)
Nasopharyngitis									1 (16.7)
Oral herpes									1 (16.7)
Upper respiratory tract infection		1 (16.7)	1 (16.7)			1 (16.7)			
Injury, poisoning and procedural complications									
Contusion									1 (4.2)

(Continues)

TABLE 1 | (Continued)

	Single-ascending dose study					Multiple-ascending dose study			
Adverse event	**Placebo (*N* = 8)**	**Sodium TDCA 5 mg (*N* = 6)**	**Sodium TDCA 10 mg (*N* = 6)**	**Sodium TDCA 30 mg (*N* = 6)**	**Sodium TDCA 50 mg (*N* = 6)**	**Placebo (*N* = 6)**	**Sodium TDCA 10 mg (*N* = 6)**	**Sodium TDCA 30 mg (*N* = 6)**	**Sodium TDCA 50 mg (*N* = 6)**
Laceration									1 (4.2)
Skin abrasion									1 (4.2)
Musculoskeletal and connective tissue disorders	1 (12.5)						1 (16.7)		
Musculoskeletal discomfort	1 (12.5)								
Myalgia	1 (12.5)						1 (16.7)		
Nervous system disorders							1 (16.7)		
Headache							1 (16.7)		
Respiratory, thoracic and mediastinal disorders								1 (16.7)	1 (16.7)
Nasal congestion								1 (16.7)	
Rhinorrhea									1 (16.7)

Note: Data are shown as the number of subjects (percentage of subjects).
Abbreviations: TDCA, taurodeoxycholate; TEAE, treatment-emergent adverse event.

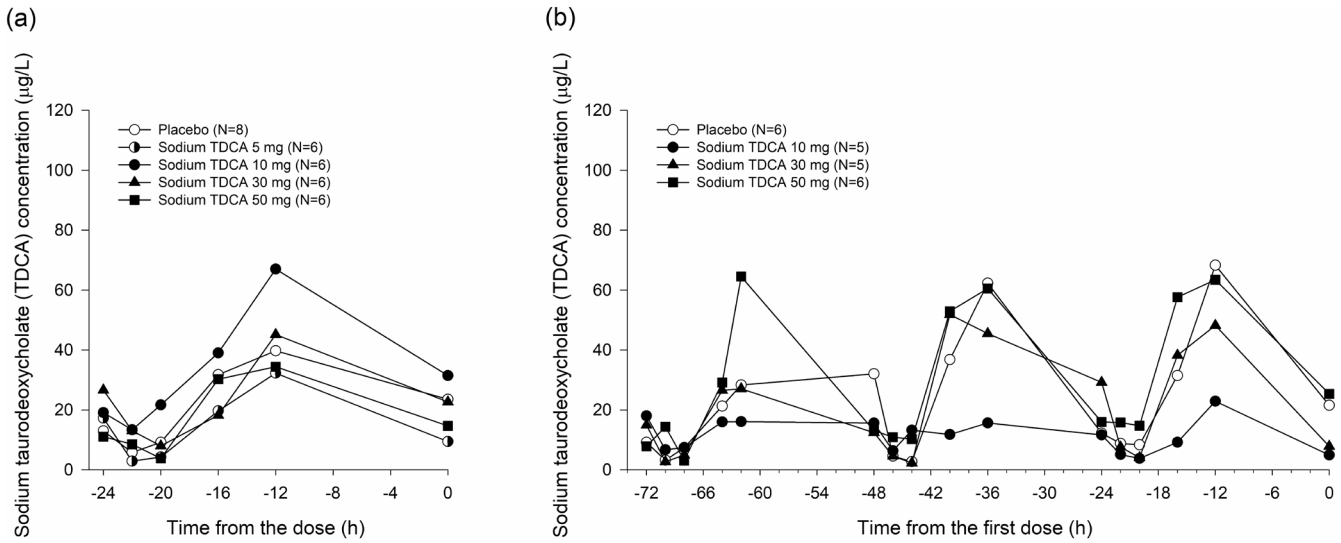

FIGURE 1 | Mean baseline plasma concentration-time profiles of sodium taurodeoxycholate (TDCA) by treatment groups before the sodium TDCA administration at (a) single-ascending dose and (b) multiple-ascending dose study.

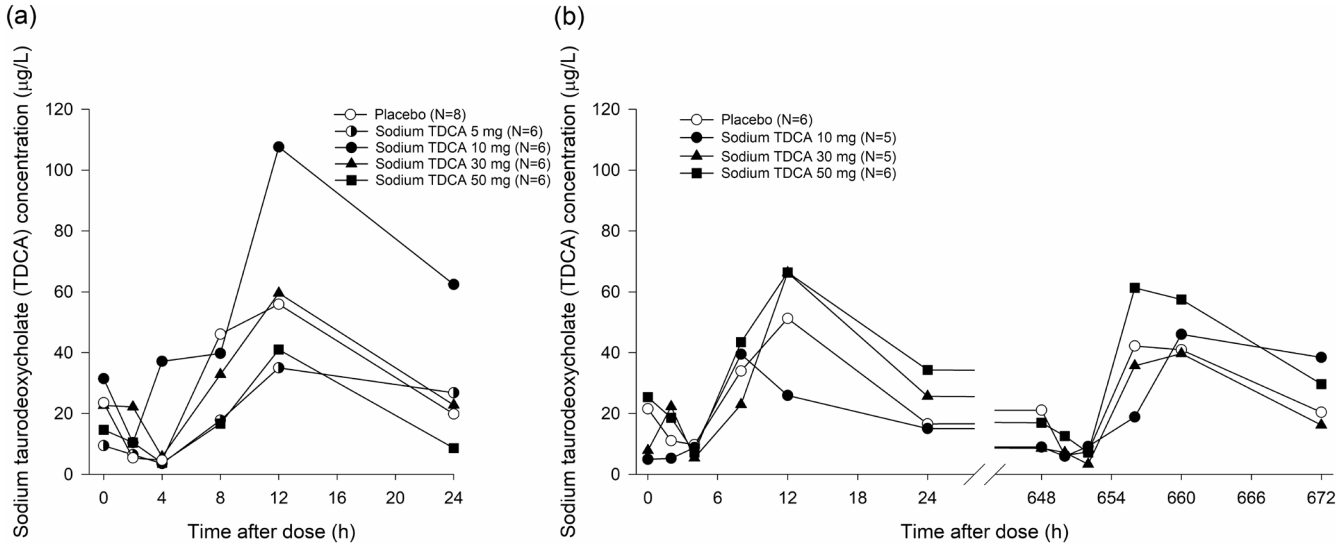

FIGURE 2 | Mean plasma concentration-time profiles of sodium taurodeoxycholate (TDCA) over 24 h by treatment groups at (a) single-ascending dose and (b) multiple-ascending dose study.

TABLE 2 | Pharmacokinetic parameters after multiple topical administrations of sodium taurodeoxycholate 10–50 mg or placebo.

Parameters	Placebo ($N=6$)	Sodium TDCA 10 mg ($N=5$)	Sodium TDCA 30 mg ($N=5$)	Sodium TDCA 50 mg ($N=6$)
Without time-matched baseline adjustment				
$T_{max,ss}$ (h)	12.03 [8.03–12.03]	12.03 [8.03–24.00]	10.03 [2.05–12.03]	12.03 [8.03–12.03]
$C_{max,ss}$ (μg/L)	44.37 ± 18.44	47.88 ± 49.07	46.21 ± 35.73	69.03 ± 34.58
$AUC_{tau,ss}$ (h•μg/L)	608.66 ± 302.79	710.80 ± 815.77	533.37 ± 319.04	882.13 ± 376.70
With time-matched baseline adjustment which replaced negative value with 0				
$T_{max,ss}$ (h)	8.03 [4.03–12.03]	12.03 [12.03–24.00]	3.06 [2.05–4.07]	4.03 [8.03–12.03]
$C_{max,ss}$ (μg/L)	15.87 ± 15.44	32.78 ± 42.37	6.91 ± 9.26	17.11 ± 6.60
$AUC_{tau,ss}$ (h•μg/L)	148.20 ± 151.54	472.11 ± 691.00	111.49 ± 215.67	212.70 ± 84.56

Note: Data are presented as mean ± standard deviation, except for $T_{max,ss}$, which is presented as median [minimum–maximum].
Abbreviations: $AUC_{tau,ss}$, area under the concentration-time curve over the dosing interval at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; TDCA, taurodeoxycholate; $T_{max,ss}$, time to reach $C_{max,ss}$.

to enhance the generalizability of the results and ensure broader applicability across diverse populations.

5 | Conclusion

Sodium TDCA gel was well tolerated after single and 28 days of multiple topical administrations up to 50 mg. No systemic absorption was observed, indicating the potential of sodium TDCA gel as a safe topical treatment option for AD.

Author Contributions

Inseung Jeon and Kyung-Sang Yu designed the research. Inseung Jeon, Joo-Youn Cho, and Kyung-Sang Yu performed the research. Heejae Won, Inseung Jeon, and Kyung-Sang Yu analyzed the data. Heejae Won and Kyung-Sang Yu wrote the manuscript.

Acknowledgments

This clinical study was sponsored by Shaperon Inc., Seoul, Republic of Korea. The clinical study was conducted at the Clinical Trials Center, Seoul National University Hospital. Heejae Won received a scholarship from the BK21 FOUR educational program.

Conflicts of Interest

Prof. Dr. Seung-Yong Seong reports personal fees from Shaperon, during the conduct of the study; personal fees from Shaperon, outside the submitted work; In addition, Prof. Dr. Seung-Yong Seong has a patent various inflammation issued to Seong et al.; and Seong SY is a CEO of Shaperon Inc., and Shaperon sponsored this project. All authors declared no other competing interests for this work.

Data Availability Statement

The data that support the findings of this study are available upon request from the corresponding author. The data is not publicly available due to confidentiality restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.