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CLINICAL TRIAL REPORT

Safety, Tolerability and Pharmacokinetics of Intravenous Sodium Taurodeoxycholate, HY209, a GPCR19 Agonist Inhibiting Inflammasomal Activation

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Background: HY209 is a synthesized sodium taurodeoxycholate (TDCA) that is expected to serve as a novel treatment for sepsis by inhibiting the inflammasomal activation that suppresses the production of pro-inflammatory cytokines. This study aimed to assess the safety, tolerability and pharmacokinetics (PKs) of HY209 after intravenous administration in healthy subjects.

Methods: A dose-block randomized, double-blind, placebo-controlled, single ascending dose study was conducted. Eight subjects in each dose group were randomized to receive an intravenous administration of HY209 (0.1, 0.2, 0.4, 0.8 and 1.6 mg/kg) or a placebo at a 3:1 ratio. Safety and tolerability variables including adverse events (AEs) and vital signs were monitored. For the PK analysis, serial blood samples were collected for 72 hours at baseline and up to 24 hours post-dose. A power model was used to evaluate the dose-proportionality of HY209. Given that TDCA is an endogenous compound, time-matched baseline differences in plasma concentrations were analyzed.

Results: A total of 39 subjects completed the study. All AEs were mild, and no serious AEs were observed. There was no significant correlation between the frequency of AEs and the administered dose. A circadian pattern was observed in the plasma TDCA concentration at baseline. After infusion, the plasma TDCA was rapidly eliminated; the plasma TDCA concentration at one hour after the end of infusion showed no significant differences from the baseline. The baseline-adjusted maximum plasma concentration of TDCA demonstrated dose-proportionality in a HY209 range of 0.1–1.6 mg/kg.

Conclusion: A single intravenous administration of HY209 was well tolerated and its systemic exposure showed dose-proportionality in a dose range between 0.1 and 1.6 mg/kg.

Keywords: phase I clinical trial, pharmacokinetics, sepsis, bild acid

Introduction

Sepsis refers to a state of life-threatening organ dysfunction due to a dysregulated host response to infection.[1] It is one of the leading causes of sudden death in critically ill patients, usually in an intensive care unit (ICU).[2] Estimated sepsis cases in the world number approximately 50 million, and more than 10 million deaths are estimated to be related to sepsis.[3] Sepsis can cause fever, mental fog, temporary hypotension, decreased urine amounts and unexplained thrombocytopenia.[4] Previous studies have estimated that a range of sepsis mortality of about 10–20%, and even up to 50%, with a possible increase to as high as 90% with the onset of shock.[5]

Guidelines published by Surviving Sepsis Campaign (SSC) recommend the systematic management of infections and hemodynamic instability with ventilation and other measures.[6] Therefore, antimicrobial therapy, infection source control, fluid therapy and vasoactive medication strategies are conventional treatments for sepsis control.[6,7] Balancing of the immune system is also highlighted during the treatment of sepsis.[8,9] In the early phase of sepsis, a hyper-inflammatory state is triggered

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by infection, which can then cause many of the symptoms mentioned above. However, in the later phase, immunosuppression may be caused by poor nutrient intake and secondary infections.[8,9] Given this phase transformation, many clinical trials focusing on immunosuppressant-only treatments have presented disappointing results.[10] Currently, the more precise use of immunotherapy and finding a balance between immunosuppressant use and immunostimulatory therapy are emphasized during sepsis treatments.

Bile acids are amphipathic molecules synthesized from cholesterol.[11] Biosynthesis of bile acids occurs in the liver, and the products are classified as the primary bile acids (cholic acid (CA), chenodeoxycholic acid (CDCA)).[12] Gut microbiota in the intestine transforms the primary bile acids into the secondary bile acids (deoxycholic acid (DCA), lithocholic acid (LCA)) and tertiary bile acids (ursodeoxycholic acid (UDCA)).[12] The conjugation with amino acid, usually taurine or glycine, further diversifies types of bile acids.[12]

Bile acids the surfactant molecules that facilitate the uptake of fat-soluble nutrients, have been re-evaluated as novel therapeutic targets in drug development due to their role as signaling molecules.[13,14] Although it was already known that bile acids regulate their synthesis through feedback mechanism, the discovery of several ligand-activated transcription factors of nuclear hormone receptors in the 1990s provided new insights.[14] Following the recognition of bile acids as the endogenous ligand, pharmacological research into the role of bile acids as signaling molecules expanded significantly.[14] Further studies revealed that bile acids interact with a variety of receptors, such as farnesoid X receptors, pregnane X receptors, vitamin D receptors, GPCR19, α5β1 integrin, and sphingosine-1-phosphate receptor 2, and that different types of bile acids exhibit varying affinities for each receptor.[15]

GPCR19, also known as GPBAR1, M-BAR, or TGR5, is a G-protein-coupled receptor expressed in various tissues and mediates various actions including metabolic regulation, glucose homeostasis, digestive function, and inflammation.[16] Activation of GPCR19 expressed in monocytes and macrophages leads to the increase of cAMP production and the reduction of phagocytotic activity.[17,18] Those activities results in the inhibition of LPS-induced proinflammatory cytokine secretion.[17,18] The bile acids with the highest potency for GPCR19, in descending order, are LCA, DCA, CDCA, CA, and UDCA.[19]

HY209, the intravenous infusion of sodium taurodeoxycholic acid (TDCA), is a novel treatment aimed to inhibit inflammatory response in sepsis patients. Systemic circulation of TDCA is expected to activate GPCR19 expressed in immune cells and aid the alleviation of inflammation as the mechanism mentioned above. Among various bile acids, TDCA was selected considering both the potency and toxicity. Taurine-conjugated bile acids were more potent than both glycine-conjugated bile acids and free bile acids.[20] Despite the best potency, TLCA was deemed to be more cytotoxic than TDCA. In previous research, intravenous infusion of TDCA demonstrated the amelioration of systemic sepsis in both LPS injected sepsis mice and CLP-induced sepsis mice.[21] This study aimed to evaluate the safety, tolerability and pharmacokinetics (PKs) of HY209 after a single intravenous administration in healthy subjects.

Materials and Methods

Study Population

Healthy male subjects aged from 19 to 45 years with a body mass index (BMI) between 18.0–27.0 kg/m^2 were enrolled in this study. Subjects with a clinically significant disease or a medical history were excluded. Subjects with abnormal findings upon a physical examination, abnormal vital signs, or abnormal 12-lead electrocardiogram and clinical laboratory test (hematology, blood chemistry, serology, and urinalysis) results were also excluded. Subjects who had taken a prescription drug or an herbal medicine within two weeks or who had taken an over-the-counter drug within one week were excluded. All subjects were fully informed with regard to the study protocol, and written consent was obtained prior to any study-related procedures performed.

Study Design

A dose-block randomized, double-blind, placebo-controlled, single ascending dose study was conducted. Eight subjects in each dose group were randomized to receive an intravenous administration of HY209 (0.1, 0.2, 0.4, 0.8 and 1.6 mg/kg)

or a placebo at a 3:1 ratio over one hour in a fasting state. Subjects were admitted to SNUH CTC (Seoul National University Hospital Clinical Trial Center) four days before the study drug administration for baseline observation. Dose escalation was determined sequentially after an evaluation of the safety and tolerability of the latest dose given. The dose range was determined considering both the pharmacologically active dose (0.5 mg/kg) observed in the disease model mentioned above and NOAEL (10 mg/kg/day in both SD rats and beagle dogs) from repeat-dose toxicity studies.

This clinical study (Clinical Research Information Service identifier number: NCT04255979) was approved by the Institutional Review Board of Seoul National University Hospital, Seoul, Korea (H-1910-039-1068) and was conducted according to the principles of the Declaration of Helsinki and ICH Good Clinical Practice.

Study Drug Preparation and Administration

The active pharmaceutical ingredient of HY209 is sodium taurodeoxycholate, conjugation of taurine and DCA extracted from the bovine bile juice. HY209 is a water-soluble, white or off-white lyophilized powder formulation. It was stored at room temperature in a light-resistant, airtight container. We added the study drug to 100 mL of normal saline and administered it using infusion pumps at a consistent rate (90 mL/h) for 55 minutes and flushed (240 mL/h) for last 5 minutes.

Pharmacokinetic Evaluation

Because TDCA is an endogenous compound, time-matched baseline-adjusted plasma concentrations were analyzed. Serial blood samples were collected for a PK analysis of TDCA before and after the study drug administration. For the baseline evaluation, blood samples were collected at 0, 1, 2, 4, 8 and 12 h for three consecutive days just before the study drug administration. For the post-dose PK evaluation, blood samples were collected at 0 h (pre-dose) and at 0.25, 0.5, 1, 2, 4, 8, 12, and 24 h after the start of infusion. Each blood sample was collected in a sodium heparinized tube and was centrifuged at 3000 rpm for ten minutes at 4 °C. Plasma was separated in three aliquots of 0.7 mL and stored at temperatures below −70 °C until the concentration analysis.

Baseline plasma concentrations were summarized by means of individual time points of 0, 1, 2, 4, 8 and 12 h. Time-matched baseline adjustment was done by subtracting those from concentrations at the same time point. Plasma concentrations obtained post-dose at 0.25 h, 0.5 h and 24 h were matched to the mean baseline concentration at 0 h. If the baseline-adjusted concentration was below 0, this value was replaced with a value of 0.

The baseline-adjusted PK parameters of TDCA, in this case the maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), and area under the time-concentration curve (AUC) were estimated by a non-compartmental method using Phoenix WinNonlin® (Version 8.0, Certara, Princeton, NJ, USA). AUC was calculated by the linear-up, log-down trapezoidal method. According to the results of a preclinical pharmacokinetic study, the terminal elimination phase was expected to be not long enough to be observed from usual sampling intervals. Thus, parameters including clearance, half-life and the volume of distribution were not estimated.

Determination of Plasma TDCA Concentrations

Since HY209 was indistinguishable from endogenous TDCA after the infusion, total plasma TDCA was measured. Plasma TDCA concentrations were determined by validated liquid chromatography tandem mass spectrometry (LC-MS /MS) method operated by APACE, Inc. To measure plasma TDCA concentrations, 500 μL of 100% acetonitrile and 100 μL of 50% methanol were sequentially added to the sample for the precipitation and the re-dissolution, respectively. A portion of the supernatant was then transferred to autosampler vials for injection into the LC-MS/MS system. Plasma TDCA was detected by multiple reaction monitoring using an UPLC (Waters Acquity system) and mass spectrometer (Xevo-TQ) in electrospray ionization in negative mode. The average regression correlation coefficients (r) of calibration curve was greater than 0.9996 and accuracy of calibration curve was ranged from 98.08% to 102.4%. The methods were validated over the assay range of 5–2000 ng/mL. Based on the validated performance of the assays, the results of the plasma concentrations reported in this study were accurate and reliable.

Safety and Tolerability Evaluation

Adverse events (AEs), physical examinations, vital signs, 12-lead electrocardiograms and clinical laboratory test results were monitored for the safety and tolerability evaluation. AEs were collected by both the self-reporting of participants and through medical interviews by the investigators. In addition, local skin AEs around the injection site were assessed up to 24 h post-dose in a special interest. They were evaluated according to the number and severity of observed erythema, edema, papules and vesicular eruptions and other skin eruptions.

Statistical Analysis

The statistical analysis was conducted using SAS software version 9.4 (SAS Institute Inc., Cary, North Carolina). The significance level for every hypothesis test was determined as 0.05. For the PK dose-proportionality assessment, a power model analysis and comparisons among dose-normalized PK parameters were conducted. The power model analysis consisted of a linear regression between log-transformed PK parameters and log-transformed dose data. Dose-normalized C_{max}, AUC_{last} and $AUC_{0\text{-}2\ h}$ outcomes were compared among every dose group using the Kruskal–Wallis test.

Results

Study Population

A total of 40 Korean subjects were enrolled, and 39 subjects completed the study. These 39 subjects were included in the safety and tolerability evaluation. During the PK evaluation, as one subject with inappropriate PK data to analyze was excluded, 38 subjects were included. The arithmetic mean ± standard deviation (SD) age of the total subjects was 31.90 ± 7.37 years, and the mean ± SD height and weight was 174.10 ± 5.17 cm and 71.09 ± 8.79 kg, respectively. Demographic characteristics showed no significant differences among the dose groups.

Pharmacokinetics

The baseline TDCA concentration appeared to have a diurnal circadian pattern (Figure 1). Except for four subjects whose baseline concentrations were not quantifiable for all three days of assessment, a pattern of elevation of the concentration during the daytime with a subsequent reduction at night was commonly observed (Supplementary File 1).

The plasma concentration of TDCA increased in a biphasic manner during the infusion step. Upon the end of infusion, TDCA appeared to be rapidly eliminated to its baseline level within one hour (Figure 2). As the administered TDCA appeared to be fully eliminated within two hours post-dose, the AUCs during the additional observation times were considered possibly to be inaccurate. Thus, both AUC_{last} and $AUC_{0\text{-}2\ h}$ (AUC from 0 h to 2 h post-dose) were evaluated (Table 1). We assessed dose-proportionality in a dose range of 0.1–1.6 mg/kg. During the dose-proportionality

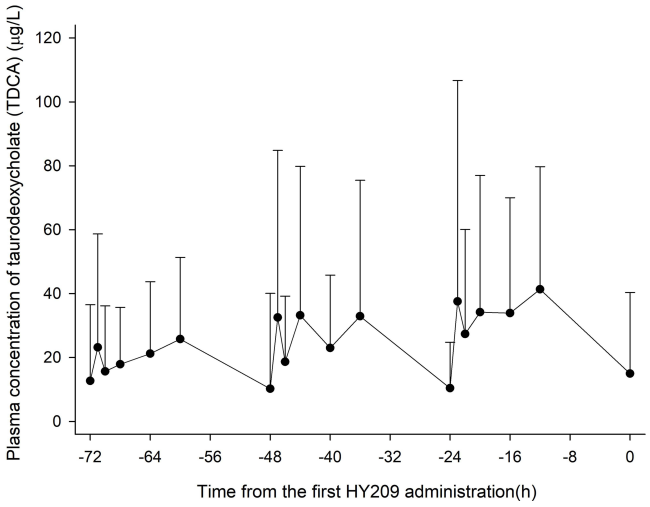

Figure 1 Mean baseline plasma TDCA concentration over three consecutive days. Error bars denote the standard deviation.

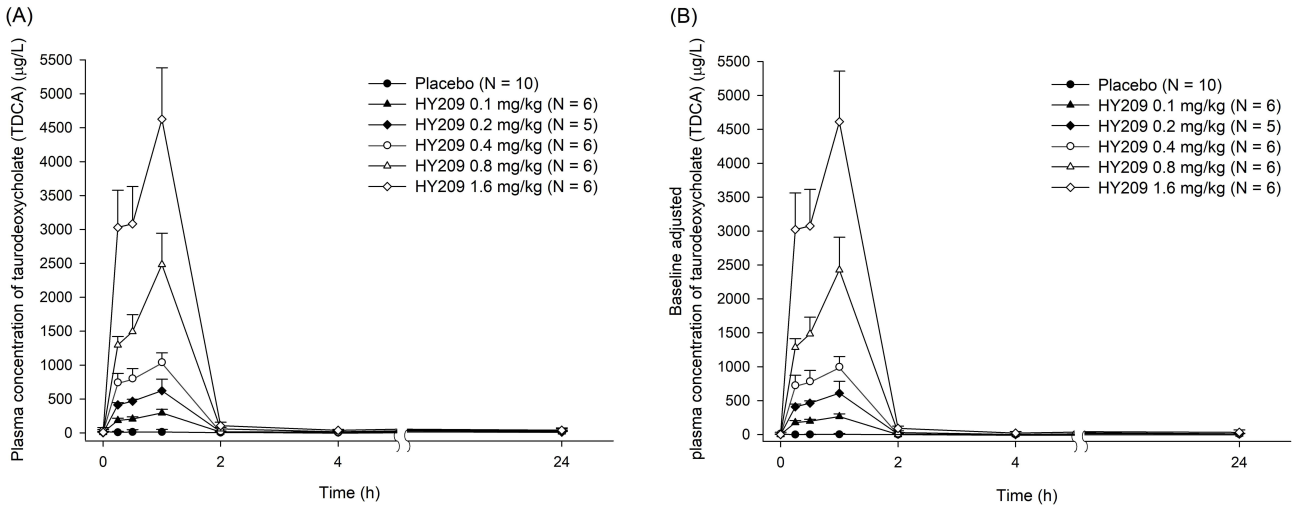

Figure 2 Mean plasma TDCA concentration-time profiles after a single intravenous administration of HY209 at 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, 0.8 mg/kg or 1.6 mg/kg or a placebo ((**A**) No baseline adjustment, (**B**) Time-matched baseline adjustment).

evaluation using AUC_{last}, an infra-proportional pattern was observed (Table 2). Nevertheless, from the evaluation of C_{max} and $AUC_{0\text{-}2\ h}$, we concluded that HY209 is dose-proportional in a dose range of 0.1–1.6 mg/kg. No significant differences were observed among the comparisons of the dose-normalized C_{max}, AUC_{last}, and $AUC_{0\text{-}2\ h}$ outcomes (Figure 3).

Safety and Tolerability

The administration of intravenous HY209 was well tolerated in the range of 0.1–1.6 mg/kg (Table 3). Six treatment-emergent adverse events (TEAEs) from two subjects in the HY209 0.4 mg/kg dose group and one TEAE from one subject in the placebo group were observed. A total of two cases (nausea and headache) in one subject (0.4 mg/kg dose group) were related to the study drug administration, whereas the others were not related. All TEAEs were mild and

Table 1 Summary of Baseline-Adjusted PK Parameters of TDCA After a Single Intravenous Administration of 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, 0.8 mg/kg and 1.6 mg/kg of HY209 or a Placebo

Parameter	Statistics	Placebo (N=10)	HY209 0.1 mg/kg (N=6)	HY209 0.2 mg/kg (N=5*)	HY209 0.4 mg/kg (N=6)	HY209 0.8 mg/kg (N=6)	HY209 1.6 mg/kg (N=6)
C_{max} (µg/L)	Mean (SD)	21.93 (17.76)	265.15 (40.16)	623.50 (159.45)	997.22 (151.99)	2425.98 (482.99)	4612.18 (746.63)
	Min	3.68	208.06	476.70	806.10	1807.45	3813.00
	Max	58.48	307.69	885.42	1162.06	2936.46	5560.12
AUC_{last} (µg h/L)	Mean (SD)	107.87 (141.41)	565.76 (230.80)	950.85 (260.93)	1202.13 (287.74)	2905.83 (864.83)	5398.53 (1026.04)
	Min	8.51	220.10	617.35	798.01	2231.49	4041.68
	Max	493.22	797.34	1329.99	1531.36	4424.45	6933.70
$AUC_{0\text{-}2\ h}$ (µg h/L)	Mean (SD)	3.99 (8.23)	196.423 (41.72)	519.1503 (141.15)	929.437 (226.91)	1902.33 (476.22)	4214.37 (685.98)
	Min	0	149.85	371.99	581.65	1177.17	3609.11
	Max	23.28	265.79	713.96	1205.91	2530.04	5339.39
T_{max} (h)	Median	8.00	1.00	1.00	1.00	1.00	1.00
	Min	0.00	1.00	0.50	1.00	1.00	1.00
	Max	24.00	1.00	1.00	1.02	1.00	1.00

Note: *Subject with inappropriate PK data was excluded.

Abbreviations: TDCA, Taurodeoxycholate; SD, Standard deviation; C_{max}, Maximum plasma concentration after administration; AUC_{last}, Area under the (plasma) concentration-time curve from zero up to the last quantifiable concentration time point; $AUC_{0\text{-}2\ h}$, Area under the (plasma) concentration-time curve from zero up to post-dose 2 hour; T_{max}, Time to reach maximum plasma concentration.

Table 2 Point Estimation and Corresponding 95% Confidence Interval of the Regression Slope After a Power Model Analysis of the PK Parameters

Parameter	Point Estimation	95% Confidence Interval
C_{max}	0.8848	0.5783–1.1913
AUC_{last}	0.6773	0.4062–0.9488
$AUC_{0\text{-}2\ h}$	1.0769	0.9821–1.1717

resolved without intervention. No serious TEAEs arose in this study. There were also no significant correlations between the frequency of AEs and the administered dose. There were no clinically significant changes from baseline in other safety and tolerability assessments, including the physical examinations, vital sign assessment, electrocardiogram results, and the clinical laboratory tests results.

Discussion

In this trial, adverse events after the administration of HY209 were observed only from two subjects in 0.4 mg/kg dose group. Among those events, four cases (musculoskeletal discomfort, headache, nasal congestion, and pruritus) from one subject were evaluated to be not related to the HY209 administration because there were other clear causes for these events, whereas the causal relationship with HY209 administration could not be denied in two cases (nausea and

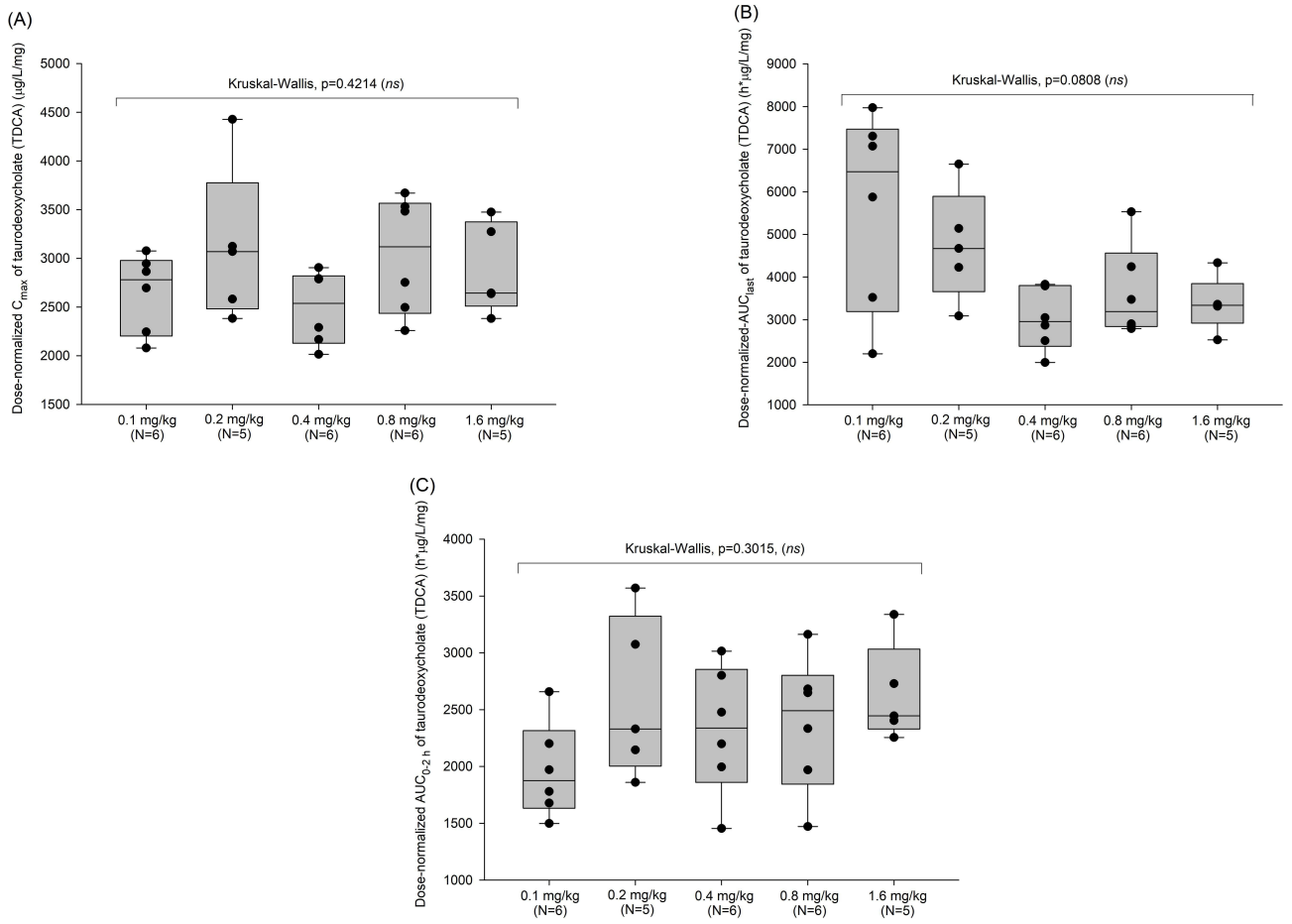

Figure 3 Dose-normalized (**A**) C_{max} and (**B**) AUC_{last} and (**C**) $AUC_{0\text{-}2\ h}$ outcomes of TDCA after a single intravenous administration of HY209 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, 0.8 mg/kg or 1.6 mg/kg or a placebo (upper bar: 95th percentile, lower bar: 5th percentile, upper quartile: 75th percentile, lower quartile: 25th percentile).

Table 3 Summary of Treatment-Emergent Adverse Events (TEAEs) After the Administration of HY209 or a Placebo

Systems Organ Class Preferred Term	Placebo (N=10)	HY209 0.1 mg/kg (N=6)	HY209 0.2 mg/kg (N=6)	HY209 0.4 mg/kg (N=6)	HY209 0.8 mg/kg (N=6)	HY209 1.6 mg/kg (N=5)
Total events	1 (10.0) [1]	–	–	2 (33.3) [6]	–	–
Gastrointestinal disorders	–	–	–	**1 (16.7) [1]**	–	–
Nausea	–	–	–	1 (16.7) [1]	–	–
Musculoskeletal and connective tissue disorders	–	–	–	**1 (16.7) [1]**	–	–
Musculoskeletal discomfort	–	–	–	1 (16.7) [1]	–	–
Nervous system disorders	**1 (10.0) [1]**	–	–	**2 (33.3) [2]**	–	–
Headache	1 (10.0) [1]	–	–	2 (33.3) [2]	–	–
Respiratory, thoracic and mediastinal disorders	–	–	–	**1 (16.7) [1]**	–	–
Nasal congestion	–	–	–	1 (16.7) [1]	–	–
Skin and subcutaneous tissue disorders	–	–	–	**1 (16.7) [1]**	–	–
Pruritus	–	–	–	1 (16.7) [1]	–	–

Notes: The Systems Organ Class term is written in bold, and the Preferred Term is indicated below it. Subject number (%) [number of cases]. Percentages are based on the subjects within each dose group.

headache) from the other subject. However, we believe that those two events are unlikely to be related to HY209 administration for the following reasons. First, the onset and resolution times of the two events are completely different from each other. Nausea started at 24 hours post-dose and resolved after 6 hours, while headache started at 72 hours post-dose and resolved after 40 hours. Second, the onset time and the duration of both events does not correlate with the PK profile. Thus, we concluded that there were no significant safety issues in this trial. In addition, based on the result of preclinical toxicity studies, the primary adverse effects anticipated before the trial were elevated liver enzyme levels and inflammatory reactions at the injection site. Those concerned events were not observed even in the highest dose groups in this trial. Nevertheless, since the sample size were small and only single dose were treated, the occurrence of both observed and anticipated events will still need to be closely monitored in further trials.

In previous studies, bile acid synthesis was found to be affected by both the intrinsic circadian clock and by postprandial feedback.[22] Such findings may also explain the diurnal pattern and fluctuation of TDCA observed in this study. In addition, considerable inter-individual variation of the baseline plasma concentration of TDCA was observed, with its extent from nearly zero to about 400 μg/L (Supplementary File 1). This may have resulted from genetic differences related to individual variations in the genes linked to the homeostasis of the regulation of cholesterol and bile acid, such as CYP7A1.[22,23] In addition, since taurine is mostly obtained through diet in human, the variability in baseline taurine levels may have contributed to the inter-individual variation.[24] However, regardless of the considerable variation of the baseline level of TDCA, the level of systemic exposure of administered exogenous TDCA generally overwhelmed the endogenous baseline TDCA level. Figure 2 illustrates that no significant changes in time-concentration profile of TDCA were observed between before (A) and after (B) the baseline adjustment. The maximum baseline concentration of TDCA from the subject who demonstrated the highest baseline level was comparable to the average concentration after the administration of the minimum dose (0.1 mg/kg) used in this study. Therefore, despite the diurnal changes and considerable inter-individual variability, endogenous TDCA may not affect the overall HY209 pharmacokinetics at a dose level exceeding 0.2 mg/kg.

From the PK evaluation, a biphasic increase of TDCA during the infusion was featured. Theoretically, because the infusion pump maintained a constant flow of infusion, the increase in the plasma concentration during infusion should be monophasic and linear. We assumed that this may be related to the distribution phase of HY209. From the result of a preclinical distribution assay, HY209 was expected to be highly distributed in the proximal small intestine and liver. Rapid distribution to those organs may be considered as a reason for the biphasic increase. An additional evaluation of $AUC_{0\text{-}2\ h}$ is another featured point in the PK analysis. We determined that $AUC_{0\text{-}2\ h}$ better represents the systemic exposure of HY209 than AUC_{last} in this study. As serial blood sample results 2 h post-dose did not appear to reflect the administration of HY209, AUC_{last} is deemed to be biased by the product of the remnant time and endogenous

concentration. One limitation of the study is the lack of PK sampling points during the terminal elimination phase. Since the elimination of exogenous TDCA was much faster than we expected before the study, we could hardly observe the pattern of the pharmacokinetic disposition.

Systemic exposure and corresponding dose-proportionality were well observed. A multiple-dose study should be conducted to determine whether the PK characteristics will be maintained in the same manner and to assess safety and tolerance. In further studies, denser PK samples during and after the end of infusion can be considered to illustrate the pattern of distribution and elimination. In addition, another limitation of the study is that the participants were all males. Both male and female subjects should be included in further clinical trials.

Conclusion

A single intravenous administration of HY209 was well tolerated and demonstrated a dose-proportional PK profile in the dose range of 0.1 mg/kg to 1.6 mg/kg.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are subject to the sponsor's approval for sharing. While de-identified individual participant data, study protocols, and statistical analysis plans may be available, data sharing is dependent on the sponsor's permission. Requests for data sharing will be reviewed by the sponsor, and data will only be provided to researchers with methodologically sound proposals approved by the sponsor. Access to data will be available upon reasonable request for a period of five years following publication. All requests should be directed to the corresponding author, who will facilitate communication with the sponsor.

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Disclosure

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.

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