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ORIGINAL ARTICLE

Safety, tolerability, and pharmacokinetics of single and multiple ascending Oral doses of DA-8010 in healthy subjects: First-in-human phase I study

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Abstract

This study assessed the safety, tolerability, and pharmacokinetics of single and multiple oral doses of DA-8010, a muscarinic M_3 receptor antagonist, in healthy subjects. This was a randomized, double-blind, placebo-controlled, ascending single (Part A: 1, 2.5, 5, 20, and 40 mg QD fasted and 10 mg QD fasted and fed) and multiple doses (Part B: 5, 10, and 20 mg QD from Days 1 to 7 fasted), sequential-group study. Safety data were analyzed descriptively, time to maximum plasma concentration (t_{max}) nonparametrically, and pharmacokinetic parameters using power and mixed models and ANOVA. Of 109 subjects randomized (Part A = 69 and Part B = 40; each part consisted a female group), 31 (44.9%) in Part A and 29 (72.5%) in Part B experienced treatment-emergent adverse events (TEAEs) in a dose-related manner. Common drug-related TEAEs in Part A and B were dizziness (8.7% and 15.0%), headache (5.8% and 12.5%) and blurred vision (8.7% and 20%). One male (20 mg) and one female (10 mg) from Part B discontinued the study due to a confusional state, and nausea and vomiting. Irrespective of sex, DA-8010 was steadily absorbed following single and multiple doses in the fasted state with increased systemic exposure in a dose-proportional manner with maximum plasma concentration occurring at a median t_{max} between 4.0 and 6.0 h. A high-fat meal increased systemic exposure. DA-8010 was safe, well tolerated, and well absorbed at lower doses and moderately tolerated at higher doses without any notable effects of food and sex.

KEYWORDS
drug safety, pharmacokinetics, phase I, randomized controlled trial

Abbreviations: AE, adverse events; AUC, area under the concentration-time curve; ECG, electrocardiogram; FIH, first-in-human; GI, gastrointestinal; MAD, multiple ascending doses; MRSD, maximum recommended starting dose; OAB, overactive bladder; PK, pharmacokinetics; QD, once daily; SAD, single ascending dose; SOC, system organ class; TEAE, treatment-emergent adverse events.

1 | INTRODUCTION

Overactive bladder (OAB) caused by detrusor overactivity is characterized by urinary urgency, with or without incontinence,[1] which adversely affects social, sexual, occupational, and psychological well-being.[2] The prevalence of OAB ranges from 1.8% to 30.5% in Europe, 1.7% to 36.4% in the United States, and 1.5% to 15.2% in Asia.[3] Muscarinic receptors, especially M_3 receptors, mediate the cholinergic-induced contractions of the urinary bladder. Their functions may upregulate during aging, genitourinary disease, or neurogenic lesions, leading to OAB.[4] Muscarinic receptor antagonists like oxybutynin, tolterodine, darifenacin, solifenacin, and trospium are the backbone of pharmacotherapy for OAB. However, high M_3 receptor occupation, reported with agents like darifenacin, oxybutynin, and solifenacin may cause dry mouth and/or constipation.[5,6] The involvement of M_3 receptors is also noted in visual accommodation that might lead to blurred vision which has been commonly reported with oxybutynin and solifenacin treatment.[7,8]

A novel muscarinic M_3 receptor antagonist, DA-8010 ([R]-[1-methylpyrrolidin-3-yl] methyl [3′-chloro-4′-fluoro-{1,1′-biphenyl}-2-yl]carbamate), developed by Dong-A ST Co., Ltd. (Dong-A ST) showed a high-binding affinity and great potency for human M_3 receptor. The potency of DA-8010 for bladder smooth muscle cells was 3.6-fold higher than for salivary gland cells isolated from mice. Furthermore, oral administration of DA-8010 in mice demonstrated more selective and persistent binding for muscarinic receptors in the bladder rather than in the submaxillary gland, in comparison with other antimuscarinic agents.[9] In the OAB rat model, oral administration of DA-8010 showed a significant increase in contraction interval and a decrease in contraction pressure.[10] These studies showed promise to further evaluate DA-8010 for the treatment of OAB in humans. We present the findings from a first-in-human (FIH), Phase I, single and multiple dose-escalation study to assess the safety, tolerability, pharmacokinetics (PK), food effects, effects of sex, and key metabolites of DA-8010 in healthy subjects.

What is already known about this subject

- DA-8010 is a novel M_3 receptor antagonist, developed for treating overactive bladder.
- M_3 receptors are known to mediate the cholinergic-induced contractions of the urinary bladder.
- In vivo studies, oral DA-8010 demonstrated selective and persistent binding for muscarinic receptors in the bladder, significantly increased contraction interval, and decreased contraction pressure.

What this study adds

This study generated the first-in-human data on safety, tolerability, pharmacokinetics, food effects, effects of sex, and key metabolites of DA-8010 in healthy subjects with single and multiple doses.

2 | MATERIALS AND METHODS

This randomized, double-blind, placebo-controlled, single-ascending-dose (SAD) and multiple-ascending-dose (MAD), sequential-group, single-center study was conducted in accordance with the Declaration of Helsinki, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice guidelines, other applicable legislations, and procedures after receiving clinical trial authorization by the Medicines and Healthcare products Regulatory Agency and review and approval of the study protocol, amendments, and informed consent form by the Institutional Ethics Committee. The study was registered at ClinicalTrials.gov (NCT02821312) and EudraCT (2016-001090-32).

2.1 | Study design

Overall, 110 subjects (Part A [SAD]: 70; Part B [MAD]: 40) were planned to be enrolled in the study (Tables S1 and S2). Each dose group was planned to be comprised of 8 subjects randomized to the treatment cohort and 2 subjects randomized to the placebo cohort using a randomization code generated through a computer-generated pseudorandom permutation procedure. The Investigator and study staff, except for the pharmacy and bioanalytical staff, were blinded to the randomization code.

All groups were single-period groups except for one two-period fixed sequence group, separated by a minimum of 13 days (A4), to investigate the effect of food.

Part B enrolled 4 sequential dose level groups (B1 to B4) involving once daily (QD) dosing for 7 consecutive days.

Both Parts A and B enrolled one group of females (Part A: A7, 9 females, and Part B: B4, 10 females). Doses were administered in escalating manners following a satisfactory review of safety, tolerability, and PK data (up to 48 h postdose) from the lower dose levels, with a minimum of 6 days between the dose escalations. All subjects returned for a poststudy visit 5 to 7 days following the final dose.

2.2 | Subjects

Healthy males or females of any ethnic origin, aged between 18 and 60 years at the time of informed consent, with body mass indexes between 18.0 and 32.0 kg/m^2, were included in the study. Males with partners of child-bearing potential and females not using two effective contraceptive methods (including barrier methods), pregnant women, and lactating women were excluded (Data S1).

2.3 | Interventions

Maximum recommended starting dose (MRSD) was determined to be 0.8 mg/kg, equivalent to 48 mg for a 60-kg human subject based on a 4-week repeat oral dose toxicology study. After applying a safety factor of 20 to the human equivalent dose (oral) for the minimal effective dose in the rat, assuming the variability in oral bioavailability, protein binding, and hepatic clearance among the species in nonclinical studies, a starting dose of 0.02 mg/kg (1.2 mg for a 60 kg human) was selected; the starting dose was 1 mg to align with available tablet strengths. The planned maximum dose of 40 mg was considered supratherapeutic and was below the MRSD. For Part B, dose levels, frequency, and duration were decided on the basis of data from Part A.

To ensure subject safety, sentinel dosing was employed in Group A1 by dosing two subjects (one on active treatment and one on placebo), initially on separate days. The other subjects were treated after, ensuring the absence of safety concerns in these subjects.

In Part A, males (A1 to A3, A5, and A6) received single sequential escalating oral doses of 1, 2.5, 5, 20, or 40 mg DA-8010, or placebo for a single period and a 10-mg dose of DA-8010 or placebo for the single period was administered to females (A7). Group A4 (males) received a two-period fixed-sequence, 10-mg dose of DA-8010 or placebo.

In Part B, from Days 1 to 7, males received multiple QD sequential escalating doses of 5, 10, and 20 mg DA-8010 (B1 to B3, respectively) and females received QD doses of 10 mg DA-8010 (B4). Two subjects per group were randomly assigned to receive a placebo.

On each dosing occasion, subjects swallowed an appropriate number of tablets with approximately 240 ml of water at room temperature after an overnight fast, with an exception of treatment period 2 for Group A4 where the dose was administered 30 min after starting a high-fat breakfast, which was completed approximately 10 min prior to dosing.

Subjects were evaluated for any adverse events (AEs) from the screening visit until 5 to 7 days post-final dose. Safety was assessed based on vital signs, 12-lead electrocardiogram (ECG), telemetry, physical examinations, clinical laboratory evaluations, spirometry, and ophthalmology assessments. Blood and urine samples were collected for PK assessment and profiling of metabolites (see Data S2 study plans).

2.4 | Outcomes

The primary outcome was the incidence and severity of AEs in subjects of Parts A and B and any abnormal and clinically significant events based on safety assessments. Secondary outcomes comprised assessment of PK parameters area under the concentration-time curve (AUC) from time zero up to last quantifiable concentration ($AUC_{0\text{-}t}$), AUC from time zero to 24 h postdose ($AUC_{0\text{-}24h}$), AUC from time zero extrapolated to infinity ($AUC_{0\text{-}\infty}$) (Part A only), AUC over a dosing interval of 24 h ($AUC_{0\text{-}\tau}$) (Part B only), maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}) (both Parts A and B) to determine dose proportionality, food effects (Part A), sex effects (Parts A and B), and comparison between Day 7 and Day 1(Part B). Time of last quantifiable plasma concentration (t_{last}), apparent plasma terminal elimination half-life ($t_{1/2}$), percentage of AUC that is due to extrapolation from the last measurable concentration to infinity ($\%AUC_{extrap}$), apparent total plasma clearance (CL/F), apparent volume of distribution during the terminal elimination phase (V_z/F), accumulation ratio (AR) (Part B only), cumulative amount of dose excreted in urine (Cum A_e), cumulative percentage of dose excreted in urine (Cum F_e), renal clearance (CL_R) and key metabolites of DA-8010 and CYP2D6 were also analyzed.

2.5 | Statistical methods

Safety and tolerability data were analyzed descriptively. Dose proportionality, food, and sex effects of the single and multiple dose PK parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}\infty}$, and C_{max} and $CumA_e$ were calculated using the power model, mixed model, and ANOVA, while t_{max} was analyzed nonparametrically. An additional classification term for treatment was added to the model to assess departure from linearity. Kruskal-Wallis test was used to assess the significance of the comparison. Linearity and the power model were assumed appropriate if the treatment term was not significant at the 5% significance level. For C_{max} in Part B, the treatment term was significant at the 5% level; however, following a visual inspection of the plots the pharmacokineticist overruled the statistical test and the power model was deemed appropriate for the analysis.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[11] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[12]

3 | RESULTS

3.1 | Demographic and other baseline characteristics

A total of 109 subjects were randomized to Part A ($N = 69$) and Part B ($N = 40$) between August 2016 and April 2017. All completed the study except for two subjects in Part B who were excluded due to AEs possibly related to the study drug (Figure 1).

The mean ages of the subjects in Parts A and B were 38 ± 12.3 years and 31 ± 11.6 years; as per the study plan, ≥75% of subjects were male. Body mass indexes of subjects in Parts A and B were 25.6 ± 3.03 kg/m^2 and 25.0 ± 2.83 kg/m^2, respectively (Table 1).

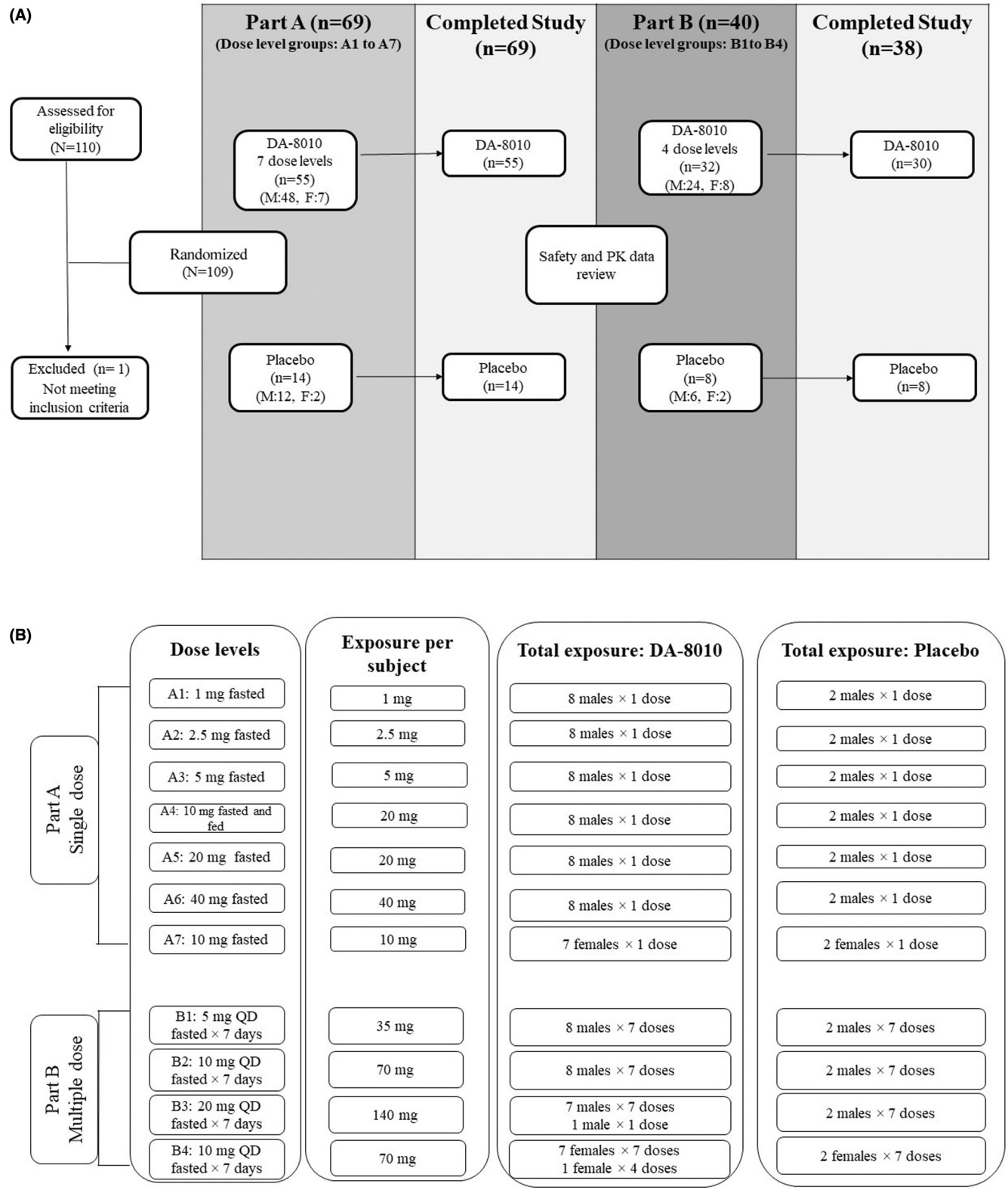

FIGURE 1 Subject disposition and drug exposure in Parts A and B. (A) Subjects disposition. (B) Drug exposure. Abbreviations: F, female; M, male; *N*, total number; *n*, number in sub category; PK, pharmacokinetics; QD, once daily. Doses were administered in an escalating manner following satisfactory review by the Sponsor and Investigator of the safety, tolerability, and PK (up to 48 h postdose) data from the lower dose levels. Part B was initiated after review of data from Part A.

TABLE 1 Demographic profile of subjects in Parts A and B

Characteristics/ Categories	Part A ($n = 69$)									Part B ($n = 40$)					
	Placebo (pooled)	1 mg (male, fasted)	2.5 mg (male, fasted)	5 mg (male, fasted)	10 mg (male, fasted/ fed)	20 mg (male, fasted)	40 mg (male, fasted)	10 mg (female, fasted)	Overall DA-8010 + placebo	Placebo (pooled)	5 mg (male)	10 mg (male)	20 mg (male)	10 mg (female)	Overall DA-8010 + placebo
	$n = 14$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 7$	$n = 69$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 8$	$n = 40$
Age, mean (SD) (years)	42 (11.2)	36 (14.2)	38 (15.0)	34 (13.2)	37 (15.2)	38 (8.9)	47 (8.6)	32 (10.2)	38 (12.3)	26 (5.2)	35 (13.7)	34 (10.7)	33 (14.2)	28 (12.2)	31 (11.6)
Gender, *n* (%)															
Male	12 (85.7)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	8 (100)	–	60 (87.0)	6 (75.0)	8 (100)	8 (100)	8 (100)	–	30 (75.0)
Female	2 (14.3)	–	–	–	–	–	–	7 (100)	9 (13)	2 (25.0)	–	–	–	8 (100)	10 (25.0)
Race, *n* (%)															
Asian	1 (7.1)	1 (12.5)	–	–	–	–	1 (12.5)	–	3 (4.3)	–	–	–	–	2 (25.0)	2 (5.0)
Black or African American	–	1 (12.5)	–	–	2 (25.0)	1 (12.5)	1 (12.5)	–	5 (7.2)	1 (12.5)	2 (25.0)	2 (25.0)	1 (12.5)	1 (12.5)	7 (17.5)
White	13 (92.9)	6 (75.0)	7 (87.5)	7 (87.5)	6 (75.0)	7 (87.5)	6 (75.0)	7 (100)	59 (85.5)	7 (87.5)	6 (75.0)	6 (75.0)	7 (87.5)	5 (62.5)	31 (77.5)
Other	–	–	1 (12.5)	1 (12.5)	–	–	–	–	2 (2.9)						
BMI, mean (SD) (kg/m^2)	25.8 (2.5)	26.4 (3.7)	25.5 (1.9)	25.3 (2.9)	26.8 (4.3)	25.1 (3.7)	26.3 (3.1)	23.5 (2.0)	25.6 (3.0)	25.9 (3.2)	26.6 (3.0)	24.8 (2.7)	23.6 (2.5)	24.1 (2.2)	25.0 (2.8)

Abbreviations: BMI, body mass index; *n*, number of subjects; SD, standard deviation.

There were no baseline signs, symptoms, or laboratory test results of clinical concern prior to the first dosing of any subjects. On all occasions, all females had negative pregnancy tests.

3.2 | Extent of exposure

Total DA-8010 exposure ranged between 1 and 40 mg in Part A and between 35 and 140 mg in males and 70 mg in females in Part B, each excluding 1 withdrawn male and female who were exposed to 20 and 40 mg of DA-8010, respectively (Figure 1B).

3.3 | Safety of single and multiple ascending doses study

All 109 subjects in Parts A and B were included in the safety data analyses.

3.3.1 | Treatment-emergent adverse events

In Part A, 31/69 (44.9%) subjects suffered 62 treatment-emergent adverse events (TEAEs), including 9 TEAEs in 3/14 (21.4%) subjects receiving a placebo. The incidence of TEAEs was marginally higher in females compared with males (8 events in 4/7 versus 5 events in 4/8) at the 10-mg dose level in a fasted state; in the fed state 2/8 (25%) males experienced TEAEs. One TEAE of dizziness with severe intensity was reported with a 1-mg dose at approximately 3 days postdose that was considered unlikely to be related to the study drug (Table 2). Commonly reported TEAEs by system organ class (SOC) were nervous system disorders (18 events; 18.8% subjects), infection and infestations (12 events; 13.0% subjects), eye disorders (11 events; 14.5% subjects) and gastrointestinal (GI) disorders (10 events; 13.0% subjects) (Table S3). Overall, 20 (29.0%) subjects experienced 31 TEAEs possibly related or related to DA-8010 (Table S4). Most frequent drug-related TEAEs by SOC were nervous system disorders (15.9%), such as dizziness (6 events in 8.7% subjects) and headache (5 events in 5.8% subjects), followed by eye disorders (11.6%), such as blurred vision (6 events in 8.7% subjects), with 3 events each reported in the highest dose level of 40 mg DA-8010 in males and the 10-mg dose level of DA-8010 in females; all were mild in severity. All events of blurred vision occurred approximately 2–6 h postdose, lasting approximately 18–20 h in males and 2–6 h in females. There were a dose-related trend in the frequency and number of subjects reporting TEAEs of dizziness and blurred vision. Drug-related TEAE of dry mouth was reported by one male (12.5%) in the 40-mg fasted cohort (Table S4).

In Part B, 29/40 (72.5%) subjects (including 6 receiving placebo) reported 92 TEAEs. The highest number of TEAEs (34 events) were reported in 6 (75%) males receiving 20-mg doses. Females receiving a 10-mg doses experienced a higher number (31 events; 75% subjects) of TEAEs compared with males (12 events;

TABLE 2 Summary of treatment-emergent adverse events single-ascending-dose of DA-8010

	DA-8010									
TEAEs	**Placebo (pooled) (*N* = 14)**	**1 mg (male, fasted) (*N* = 8)**	**2.5 mg (male, fasted) (*N* = 8)**	**5 mg (male, fasted) (*N* = 8)**	**10 mg (male, fasted) (*N* = 8)**	**10 mg (male, fed) (*N* = 8)**	**20 mg (male, fasted) (*N* = 8)**	**40 mg (male, fasted) (*N* = 8)**	**10 mg (female, fasted) (*N* = 7)**	**Overall (*N* = 69)**
Subjects with TEAEs, *n* (%)	3 (21.4)	2 (25.0)	3 (37.5)	2 (25.0)	4 (50.0)	2 (25.0)	5 (62.5)	7 (87.5)	4 (57.1)	31 (44.9)
Number of TEAEs	9	11	5	3	5	2	7	12	8	62
Subjects with SAEs	—	—	—	—	—	—	—	—	—	—
Subjects discontinued due to TEAEs	—	—	—	—	—	—	—	—	—	—
Severity (All TEAEs)	Number of subjects with AEs, *n* (%)/Number of AEs									
Mild	3 (21.4) [8]	2 (25.0) [9]	3 (37.5) [4]	2 (25.0) [2]	4 (50.0) [5]	2 (25.0) [2]	5 (62.5) [6]	7 (87.5) [12]	4 (57.1) [8]	31 (44.9) [56]
Moderate	1 (7.1) [1]	1 (12.5) [1]	1 (12.5) [1]	1 (12.5) [1]	—	—	1 (12.5) [1]	—	—	5 (7.2) [5]
Severe	—	1 (12.5) [1]	—	—	—	—	—	—	—	1 (1.4) [1]
Total	3 (21.4) [9]	2 (25.0) [11]	3 (37.5) [5]	2 (25.0) [3]	4 (50.0) [5]	2 (25.0) [2]	5 (62.5) [7]	7 (87.5) [12]	4 (57.1) [8]	31 (44.9) [62]
Severity (Possibly related or related)	Number of subjects with AEs, *n* (%)/Number of AEs									
Mild	3 (21.4) [4]	1 (12.5) [4]	2 (25.0) [2]	—	—	1 (12.5) [1]	4 (50.0) [5]	5 (62.5) [6]	4 (57.1) [7]	20 (29.0) [29]
Moderate	—	1 (12.5) [1]	—	—	—	—	1 (12.5) [1]	—	—	2 (2.9) [2]
Severe	—	—	—	—	—	—	—	—	—	—
Total	3 (21.4) [4]	1 (12.5) [5]	2 (25.0) [2]	—	—	1 (12.5) [1]	4 (50.0) [6]	5 (62.5) [6]	4 (57.1) [7]	20 (29.0) [31]

Note: (), percentage of subjects with adverse events; [], number of adverse events.

Abbreviations: AE, adverse event; *N*, number of subjects; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

TABLE 3 Summary of treatment-emergent adverse events: multiple-ascending-dose of DA-8010

TEAEs	Placebo OD (pooled) (*N* = 8)	DA-8010				
		5 mg DA-8010 OD (male) (*N* = 8)	10 mg DA-8010 OD (male) (*N* = 8)	20 mg DA-8010 OD (male) (*N* = 8)	10 mg DA-8010 OD (female) (*N* = 8)	Overall (*N* = 40)
Subjects with TEAEs, *n* (%)	6 (75.0)	4 (50.0)	7 (87.5)	6 (75.0)	6 (75.0)	29 (72.5)
Number of TEAEs	9	6	12	34	31	92
Subjects with SAEs	—	—	—	—	—	—
Subjects discontinued due to TEAEs	—	—	—	1 (12.5) [4]	1 (12.5) [9]	2 (5.0) [13]
Severity (All TEAEs)	Number of subjects with AEs, *n* (%)/Number of AEs					
Mild	6 (75.0) [9]	4 (50.0) [6]	7 (87.5) [12]	6 (75.0) [29]	6 (75.0) [29]	29 (72.5) [85]
Moderate	—	—	—	3 (37.5) [5]	1 (12.5) [2]	4 (10.0) [7]
Severe	—	—	—	—	—	—
Total	6 (75.0) [9]	4 (50.0) [6]	7 (87.5) [12]	6 (75.0) [34]	6 (75.0) [31]	29 (72.5) [92]
Severity (Possibly related or related)	Number of subjects with AEs, *n* (%)/Number of AEs					
Mild	2 (25.0) [3]	2 (25.0) [4]	5 (62.5) [7]	6 (75.0) [27]	6 (75.0) [21]	21 (52.5) [62]
Moderate	—	—	—	3 (37.5) [5]	1 (12.5) [2]	4 (10.0) [7]
Severe	—	—	—	—	—	—
Total	2 (25.0) [3]	2 (25.0) [4]	5 (62.5) [7]	6 (75.0) [32]	6 (75.0) [23]	21 (52.5) [69]

Note: (), percentage of subjects with adverse events; [], number of adverse events.

Abbreviations: AE, adverse event; *N*, number of subjects; OD, once daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

87.5% subjects) who received the same dose (Table 3). Nervous system disorders (24 events; 37.5% subjects) and GI disorders (21 events; 27.5% subjects) were common types of TEAEs (Table S5). Sixty-nine events in 21 (52.5%) subjects in Part B were assessed as either possibly related or related to the study drug; the most common being nervous system disorders, such as headache (7 events; 12.5% subjects) and dizziness (6 events; 15.0% subjects). Among eye disorders, blurred vision was the most common drug-related TEAE with 16 events in 20.0% of subjects. There was an apparent dose-dependent increase in the number of drug-related events of blurred vision, dry mouth, and headache, with no events reported in placebo and 5-mg dose groups. Similarly, 4 males receiving multiple doses of 20 mg DA-8010 reported 5 events of somnolence, of which 3 were moderate in severity. Seven of the 8 events of nausea reported were by females receiving a 10-mg dose, of which one was moderate in severity and resulted in study discontinuation. One male receiving a 20-mg dose was discontinued from the study before dosing on Day 2 because of a confusional state (Table S6).

Most of the drug-related TEAEs in Part B occurred on Day 1, and none were reported after Day 10 (3 days post-final dose). There were no treatment- or dose-related changes in clinical laboratory parameters, vital signs, spirometry, cardiac telemetry, physical examinations, or ocular surface disease index (OSDI) scores in Parts A and B, except 50% of males receiving 20-mg dose experienced dose-dependent increases in OSDI scores from normal at Day −1 to mild or moderate at Day 8. There were no clinically relevant findings in 12-lead ECGs. There were no apparent differences in 12-lead ECG parameters between males receiving 10 mg DA-8010 in fasted and fed conditions in Part A, or between males and females after receiving single or multiple doses of 10 mg DA-8010. In Part A, 7 subjects had >30 milliseconds (ms) increases in QT interval corrected for heart rate using Bazett's formula (QTcB) from baseline, with one male each for placebo, 1, 2.5, 10 (fasted), and 20-mg dose levels, and 2 females at the 10-mg dose level. Two subjects (1 male receiving 5 mg; 1 female receiving 10 mg) had QTcB intervals >450 ms. In Part B, at least 1 subject at each dose level, with the exception of subjects receiving a 20-mg dose, had a > 30 ms increase in QTcB from baseline. One male receiving a placebo had a >60 ms increase in QTcB from baseline, and a > 30 ms increase in QT interval corrected for heart rate by Fridericia's formula from baseline at the poststudy visit.

3.4 | Pharmacokinetics of DA-8010

Fifty-five subjects in Part A and 32 subjects in Part B who received at least one dose of DA-8010 and had evaluable PK data were included in the PK analyses.

3.4.1 | Single-dose pharmacokinetics of DA-8010

The mean plasma concentration versus time profile after single oral dose administration of DA-8010 in the fasting state in males

TABLE 4 Summary of plasma and urine pharmacokinetic parameters for DA-8010 (Male fasted subjects)—Part A

Parameter	DA-8010						
	1 mg (male, fasted) (*N* = 8)	2.5 mg (male, fasted) (*N* = 8)	5 mg (male, fasted) (*N* = 8)	10 mg (male, fasted) (*N* = 8)	20 mg (male, fasted) (*N* = 8)	40 mg (male, fasted) (*N* = 8)	Dose proportionality estimates (95% CI)[a]
AUC_{0-t} (h*pg/ml)	1070 (66.7)	2480 (33.0)	6230 (35.7)	12400 (58.4)	21700 (50.2)	42000 (35.0)	1.01(70.904–1.11)
AUC_{0-t} (norm)	86600 (66.8)	75600 (36.7)	99500 (40.2)	103000 (80.0)	84200 (55.5)	84800 (34.9)	–
$AUC_{0-\infty}$ (h*pg/ml)	1190 (62.8)	2550 (32.6)	6330 (35.4)	12600 (57.5)	21900 (50.0)	42700 (35.2)	0.986 (0.885–1.09)
$AUC_{0-\infty}$ (norm)	96400 (63.1)	77700 (36.3)	101000 (40.1)	105000 (78.9)	85100 (55.2)	86300 (34.9)	–
$\%AUC_{extrap}$[b] (%)	10.1 (4.14)	2.65 (0.566)	1.60 (0.616)	1.50 (1.18)	0.997 (0.725)	1.68 (1.62)	–
C_{max} (pg/ml)	99.7 (65.2)	218 (49.9)	492 (38.3)	1210 (42.5)	2230 (55.3)	4390 (44.7)	1.05 (0.948–1.16)
C_{max} (norm)	8070 (66.5)	6650 (52.3)	7850 (45.5)	10000 (61.2)	8690 (64.5)	8880 (42.7)	–
t_{max}[c] (h)	6.00 (5.00–8.00)	5.00 (4.00–12.0)	5.00 (2.00–6.00)	5.50 (3.00–8.00)	6.00 (5.00–12.0)	6.00 (5.00–6.00)	
t_{last}[c] (h)	24.0 (16.0–36.0)	36.0 (24.0–36.0)	48.1 (36.0–48.1)	48.0 (24.0–48.2)	48.0 (36.0–48.1)	48.0 (48.0–48.1)	–
$t_{1/2}$ (h)	5.79 (23.5)	5.78 (18.3)	6.82 (18.0)	6.72 (28.8)	6.56 (21.8)	8.16 (22.9)	–
CL/F (ml/min)	14000 (62.8)	16300 (32.6)	13200 (35.4)	13200 (57.5)	15200 (50.0)	15600 (35.2)	–
Vz/F (L)	7020 (62.3)	8170 (45.5)	7760 (29.4)	7700 (63.0)	8650 (53.1)	11000 (38.6)	–
Cum Ae (μg)	2.16 (103)	3.57 (38.7)	6.65 (39.6)	14.0 (82.6)	23.1 (76.3)	48.4(52.8)	–
Cum Fe (%)	0.216 (103.0)	0.143 (38.7)	0.133 (39.6)	0.140 (82.6)	0.115 (76.3)	0.121 (52.8)	–
CL_R (ml/min)	30.5 (70.2)	23.5 (57.1)	17.7 (32.9)	16.5 (50.6)	17.7 (76.9)	19.2 (42.1)	–

Note: Geometric mean (CV%) data are presented.

Abbreviations: $\%AUC_{extrap}$, percentage of AUC that is due to extrapolation from the last measurable concentration on to infinity; AUC_{0-t}, area under the concentration-time curve from time zero up to last quantifiable concentration; $AUC_{0-\infty}$, area under the concentration-time curve from zero to infinity; CI, confidence interval; CL/F, apparent total plasma clearance; CL_R, renal clearance; C_{max}, maximum plasma concentration; Cum Ae, cumulative amount of dose excreted in urine; Cum Fe, cumulative percentage of dose excreted in urine; CV, coefficient of variation; *N*, number of subjects; (norm), normalized for dose and body weight (mg/kg); $t_{1/2}$, apparent plasma terminal elimination half-life; t_{last}, time of last quantifiable plasma concentration; t_{max}, time of maximum plasma concentration; Vz/F, apparent volume of distribution during terminal phase.

[a]The Kruskal-Wallis test.

[b]Arithmetic mean (standard deviation).

[c]Median (minimum–maximum).

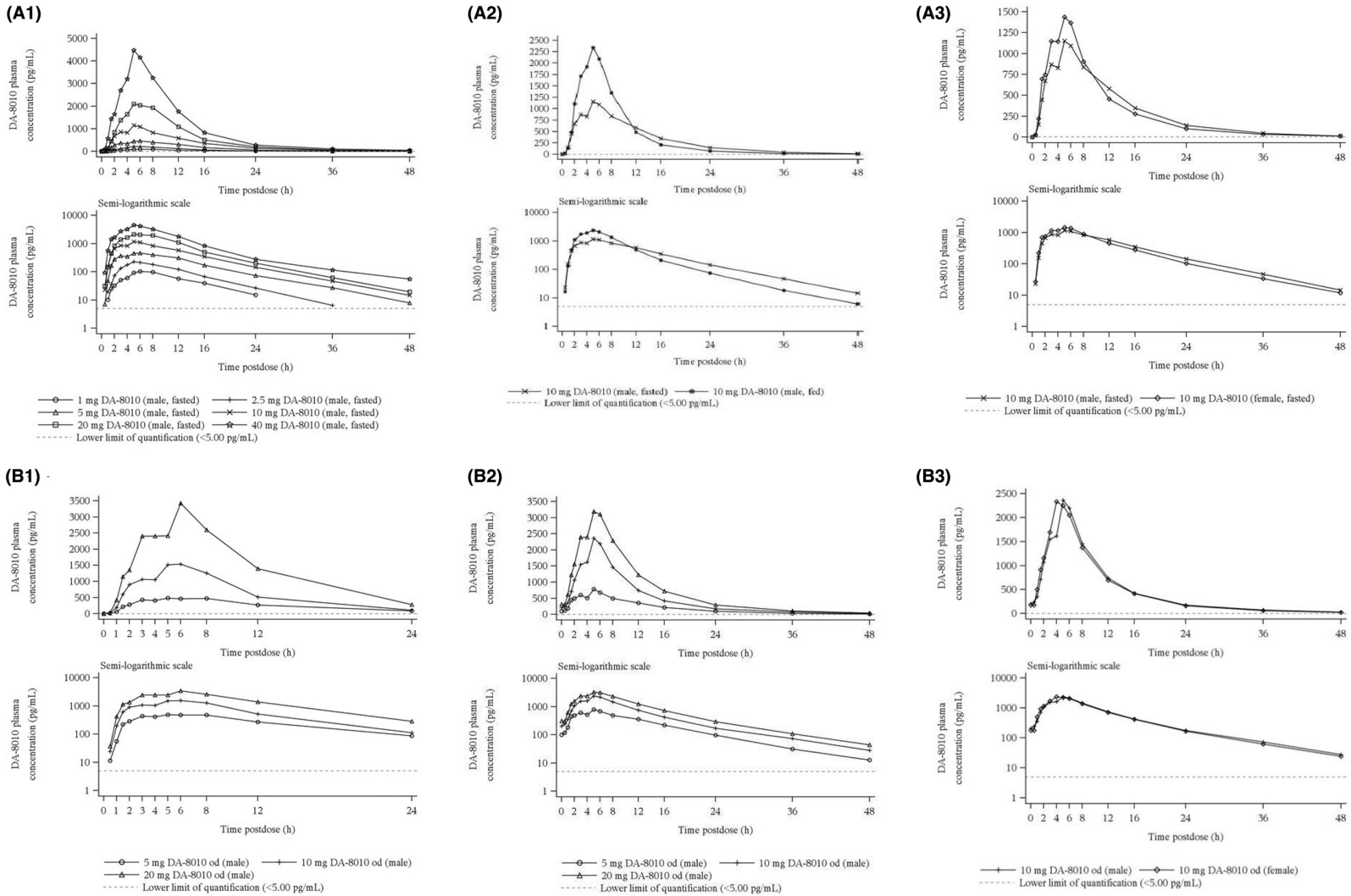

FIGURE 2 Arithmetic mean plasma concentration profiles of DA-8010. (A1) Arithmetic mean plasma concentration profiles of DA-8010—Part A (Male Fasted Subjects) (Linear and Semi-logarithmic Scales). (A2) Arithmetic Mean Plasma Concentration Profiles of DA-8010—Part A (Fed and Fasted Male Subjects) (Linear and Semi-logarithmic Scales). (A3) Arithmetic Mean Plasma Concentration Profiles of DA-8010—Part A (Male and Female Subjects) (Linear and Semi-logarithmic Scales). (B1) Arithmetic Mean Plasma Concentration Profiles of DA-8010—Part B—Day 1 (Male Subjects) (Linear and Semi-logarithmic Scales). (B2) Arithmetic Mean Plasma Concentration Profiles of DA-8010—Part B—Day 7 (Male Subjects) (Linear and Semi-logarithmic Scales). (B3) Arithmetic Mean Plasma Concentration Profiles of DA 8010—Part B—Day 7 (Male versus Female Subjects) (Linear and Semi-logarithmic Scales).

TABLE 5 Summary of plasma and urine pharmacokinetic parameters for DA-8010 on day 1—Part B

Study Day: 1				
	DA-8010			
Parameter	5 mg OD (male) (*N* = 8)	10 mg OD (male) (*N* = 8)	20 mg OD (male) (*N* = 8)	10 mg OD (female) (*N* = 8)
$AUC_{0-\tau}$ (h*pg/ml)	5720 (47.4)	14 200 (29.0)	29 700 (46.1)	18 000 (54.1)
$AUC_{0-\tau}$ (norm)	98 000 (52.9)	113 000 (23.5)	109 000 (46.7)	116 000 (58.3)
C_{max} (pg/ml)	526 (54.4)	1630 (34.6)	3420 (35.3)	2060 (64.9)
C_{max} (norm)	9000 (58.6)	13 000 (29.3)	12 500 (35.5)	13 300 (67.1)
t_{max} [a] (h)	5.00 (3.00–8.00)	6.00 (5.00–8.03)	6.00 (3.00–6.02)	6.00 (3.00–6.07)
Cum A_e (ug)	2.88 (53.3)	7.99 (47.0)	12.1 (66.5)	7.79 (81.0)
Cum Fe (%)	0.0576 (53.3)	0.0799 (47.0)	0.0603 (66.5)	0.0779 (81.0)
CL_R (ml/min)	12.2 (66.6)	11.9 (49.1)	8.83 (54.1)	9.50 (67.7)

Note: Geometric mean (CV%) data are presented.

Abbreviations: $AUC_{0-\tau}$, area under the concentration-time curve over a dosing interval; CL_R, renal clearance; C_{max}, maximum plasma concentration; Cum Ae, cumulative amount of dose excreted in urine; Cum Fe, cumulative percentage of dose excreted in urine; CV, coefficient of variation; N, number of subjects; (norm), normalized for dose and body weight (mg/kg); OD, once daily; t_{max}, time of maximum plasma concentration.

[a]Median (minimum–maximum).

TABLE 6 Summary of plasma and urine pharmacokinetic parameters for DA-8010 on Day 7 – Part B

Study Day: 7					
	DA-8010				
Parameter	5 mg OD (male) (*N* = 8)	10 mg OD (male) (*N* = 8)	20 mg OD (male) (*N* = 8)	10 mg OD (female) (*N* = 8)	Dose proportionality estimates (95% CI)[a]
$AUC_{0-\tau}$ (h*pg/ml)	7300 (50.7)	19 900 (25.3)	29 600 (37.1)	18 800 (45.2)	1.02 (0.714–1.33)
$AUC_{0-\tau}$ (norm)	125 000 (57.2)	159 000 (22.8)	107 000 (33.9)	122 000 (52.3)	-
C_{max} (pg/ml)	692 (62.1)	2470 (39.8)	3270 (32.8)	2160 (58.3)	1.14 (0.751, 1.52)
C_{max} (norm)	11 800 (63.5)	19 700 (36.4)	11 900 (29.2)	14 000 (64.8)	-
t_{max} [b] (h)	5.00 (4.00–6.00)	5.00 (3.00–6.00)	5.00 (3.00–6.05)	4.00 (3.00–6.00)	
$t_{1/2}$ (h)	7.40 (24.0)	8.44 (17.8)	7.89 (15.4)	7.96 (15.0)	-
CL/F (ml/min)	11 400 (50.7)	8390 (25.3)	11 300 (37.1)	8850 (45.2)	-
Vz/F (L)	7310 (34.0)	6130 (29.8)	7680 (45.4)	6100 (54.8)	-
AR	1.28 (25.1)	1.40 (26.2)	1.13 (14.4)	1.17 (16.3)	-
Cum A_e (μg)	3.65 (78.4)	6.60 (43.5)	14.6 (53.6)	7.25 (96.5)	-
Cum Fe (%)	0.0730 (78.4)	0.0660 (43.5)	0.0731 (53.6)	0.0725 (96.5)	-
CL_R (ml/min)	11.9 (43.7)	7.17 (68.1)	10.7 (41.7)	8.22 (60.2)	-

Note: Geometric mean (CV%) data are presented.

Abbreviations: $AUC_{0-\tau}$, area under the concentration-time curve over a dosing interval; CI, confidence interval; CL/F, apparent total plasma clearance; CL_R, renal clearance; C_{max}, maximum plasma concentration; Cum Ae, cumulative amount of dose excreted in urine; Cum Fe, cumulative percentage of dose excreted in urine; CV, coefficient of variation N, number of subjects; (norm), normalized for dose and body weight (mg/kg); OD, once daily; $t_{1/2}$, apparent plasma terminal elimination half-life; t_{max}, time of maximum plasma concentration; Vz/F, apparent volume of distribution during terminal phase.

[a]The Kruskal-Wallis test.

[b]Median (minimum–maximum).

demonstrated a steady absorption phase with median t_{max} ranging from 5.0 to 6.0 h postdose for 1 to 40-mg dose range. Exposure (C_{max}, $AUC_{0-\infty}$, and AUC_{0-t}) increased in an approximately dose-proportional manner (Table 4). This was confirmed by statistical analysis, with the estimates of the slopes (95% confidence interval [CI]) from the regression analysis for AUC0-∞, AUC0-t, and C_{max} being 0.986 (0.885 to 1.09), 1.01 (0.904 to 1.11), and 1.05 (0.948 to 1.16), respectively. The t_{last} increased in a dose-proportional manner

for 1 to 5-mg doses and was similar for 10, 20, and 40-mg doses; however, $t_{1/2}$ and CL/F were similar across dose levels. The Cum F_e as an unchanged drug was very low for all dose levels (approximately 0.115% to 0. 216%) (Table 4), preventing reliable CL_R estimates from being calculated.

The median t_{max} of 10-mg dose in the fed and fasted states in males was not significantly different. The ratios (95% CI) for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were 1.37 (1.03, 1.83) fold, 1.39 (1.04, 1.86) fold, and 2.18 (1.62, 2.94) fold higher for the fed state, respectively, compared to the fasted state. The mean $t_{1/2}$ was similar for both dietary states, being approximately 6–7 h (Figure 2A). The AUC_{0-t} and $AUC_{0-\infty}$ were higher in the fed state. In the fasted state, between-subject variability was high for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} (58% for $AUC_{0-\infty}$ and AUC_{0-t}, and 43% for C_{max}) (Table S7). There were no significant differences in PK parameters and the between-subject variability; the geometric coefficient of variation percentages for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were similar for males and females (Table S8).

3.4.2 | Multiple dose pharmacokinetics of DA-8010

DA-8010 was steadily absorbed in all dose levels, following single (Day 1) and multiple doses (Day 7) with C_{max} achieved at a median t_{max} between 5.0 and 6.0 h postdose on Day 1, and between 4.0 and 5.0 h postdose on Day 7. For all subjects on these days, t_{max} was within the range of 3.00 to 8.03 h postdose. The geometric mean $t_{1/2}$ was approximately 8 h on Day 7 with individual values across all doses ranging from 4.9 to 10.5 h (Figure 2B). Visual inspection of trough (predose) concentrations indicated that a steady state was attained within 2 to 3 days of QD dosing. Minimal accumulation of DA-8010 was observed in plasma by Day 7. DA-8010 concentrations were increased on Day 7 compared to Day 1 at the 5 and 10-mg dose levels in males (Tables 5 and 6). On Day 7, $AUC_{0-\tau}$ and C_{max} generally appeared to increase in approximately dose-proportional manners, with 4 and 5-fold increases, respectively; for the 4-fold increase in dose from 5 to 20 mg. This was confirmed by statistical analysis, with respective estimates of the slopes (95% CI) from the regression analysis for $AUC_{0-\tau}$ and C_{max} being 1.02 (0.714, 1.33) and 1.14 (0.751, 1.52), respectively. Statistical analysis of C_{max} showed a departure from the linearity of the regression; however, this was considered to be due to higher-than-expected exposure at the 10-mg dose level. The CL/F and V_z/F remained stable across the doses. The Cum F_e postdose was very low and similar at all dose levels (0.0576% to 0.0799% on Day 1, and 0.0660% to 0.0731% on Day 7) (Tables 5 and 6). No statistical analysis was conducted on Cum A_e for the assessment of dose proportionality, the effect of sex or food, or for the comparison between days due to low levels of urinary excretion of DA-8010.

In females, the C_{max} was obtained at a median t_{max} of between 4.0 and 6.0 h postdose on Days 1 and 7. Correcting for body weight, the exposure to DA-8010 as measured by $AUC_{0-\tau}$ and C_{max} was 23% to 29% lower, respectively, for females compared to males. However, these differences were not statistically significant.

3.4.3 | Metabolite identification and characterization

Parent drug (DA-8010) and 21 metabolites were observed in analyzed plasma and urine samples. Four metabolites (M1, M17, M13, and H10) along with DA-8010 accounted for >85% of the total chromatographic peak area in plasma sample profiles; predominant metabolite excreted in the urine was H10 (Table S9).

4 | DISCUSSION

This FIH SAD and MAD study of DA-8010 was conducted in predominantly healthy males to assess the safety, tolerability, PK, food effects, effect of gender on PK parameters, and key metabolites of DA-8010. In Part A, subjects were exposed to a dose of 1 to 40 mg, and in Part B exposure ranged between 5 and 20 mg in males and 10 mg in females. The single doses of the drug were observed to be safe and well tolerated at doses up to 40 mg. Multiple oral doses were well tolerated by males at doses of 5 and 10 mg with only 6 and 12 events of total of 92 events in each dose cohort. The 10 mg doses administered to females were well tolerated in Part A and moderately well tolerated in Part B. The incidence of TEAEs was comparatively higher at multiple doses of 20 mg QD in males and multiple doses of 10 mg QD in females (75% subjects each) along with the incidence of one severe AE in each dose cohort, suggesting moderate tolerability to these doses and need for further evaluation.

Overall, 44.9% of subjects in Part A and 72.5% of subjects in Part B reported mostly mild TEAEs, which resolved without treatment. Consistent with nonclinical findings, there was a dose-related trend in the incidence of AEs associated with DA-8010 in both parts of the study. The TEAEs reported in Part B at the 5 mg dose level were comparable to the placebo but increased at higher dose levels. Dizziness and blurred vision were the most common TEAEs. Blurred vision was deemed a drug-related TEAE in both parts, with dose-dependent increases in incidence.

The safety profile of DA-8010 was consistent with other antimuscarinics as reported in a network meta-analysis evaluating the safety of various available antimuscarinics.[13] The incidence of dry mouth observed possibly related or related DA-8010 (1.4% with SAD and 15% with MAD) was less than that observed with other M_3 receptor antagonists, darifenacin 15 mg QD (13%), darifenacin 30 mg QD (34.4%), and oxybutynin 5 mg three times daily (36.1%) in a comparative study.[14] In another placebo-controlled study, the overall incidence of AEs was 45.3%, 52.4%, and 53.0% with the darifenacin at 3.75, 7.5, and 15 mg, respectively; the most common AE was dry mouth (3.75 mg: 13.2%, 7.5 mg: 18.8%, 15 mg: 31.3%).[15] The low frequency of dry mouth corroborates the findings from the nonclinical study in mice and rats showing good selectivity of DA-8010 for muscarinic receptors in the bladder rather than in the submaxillary gland, in comparison with other antimuscarinics agents and the ability to inhibit distension-induced rhythmic bladder contraction in rats.[9] Subjects receiving ≥10 mg DA-8010 experienced

blurred vision (8.7% in Part A and 20% in Part B); it was not observed with a 5 mg dose. Other antimuscarinics when given in similar doses caused blurred vision (solifenacin 5 mg [6.2%] and tolterodine 4 mg [3.8%]).[16] Although less prevalent, the most common drug-related TEAEs with both single and multiple doses were dizziness and headache (15.9% in Part A and 32.5% in Part B), which are similar to other anti-muscarinics.[17,18] One subject in Part B withdrew due to a confusional state and one subject withdrew in Part B due to nausea and vomiting. Further clinical evaluations in Phase II and III studies may provide further assessment of the effects of DA-8010 on the nervous system.

No evidence of treatment- or dose-related trends and no clinically important findings in 12-lead ECGs at any dose level indicate no clinically significant effects on heart muscles which may indicate the selective nature of DA-8010 for bladder muscles. Further late-phase studies may provide conclusive results. Food did not have a notable effect on the safety and tolerability of DA-8010 in males at the 10 mg dose level based on the similar incidence of TEAEs reported by subjects in both the fed and fasted states; however, females in the fasted state experienced a higher number of TEAEs compared to the males in Parts A and B.

DA-8010 was steadily absorbed following SAD and MAD in the fasted state, with systemic exposure increasing in a dose-proportional manner. Steady state was attained at 2 to 3 days with a minimal extent of accumulation (1.1- to 1.4-fold). Urinary excretion of the unchanged drug was very low (<1% of dose administered) following both single and multiple doses of DA-8010. The CL/F and V_z/F were similar across the doses.

There were no marked sex-related differences in the PK of DA-8010. A high-fat meal increased systemic exposure to DA-8010, with $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ increasing 1.4-fold and C_{max} increasing 2.2-fold. The marked increase in C_{max} without any significant effect on t_{max} in the fed state suggests that the delayed GI transit time of the modified release DA-8010 tablet by a high-fat meal increased the intraluminal drug amount and subsequently led to increased bioavailability.

5 | CONCLUSION

In this FIH Phase I study, DA-8010 was found to be safe and tolerable without any notable effect of food and sex. Headache, dizziness, and blurred vision were the most common TEAEs, and nausea and dry mouth were the less common TEAEs compared to other antimuscarinic agents (darifenacin, oxybutynin, solifenacin, and tolterodine) widely used for the treatment of OAB. Following both single and multiple oral doses, DA-8010 was steadily absorbed with median t_{max} values ranging from 4.0 to 6.0 h postdose. Plasma concentrations of DA-8010 decreased in an apparent biphasic manner with a geometric mean $t_{1/2}$ of 6.0 to 8.0 h. Systemic exposure to DA-8010 increased in an approximately dose-proportional manner across the 1 to 40-mg single oral dose range, and across the 5 to 20-mg QD multiple oral dose range. Sex and food intake did not significantly affect the PK of DA-8010. Further clinical evaluations in randomized controlled trials will generate robust evidence on the safety of DA-8010.

AUTHOR CONTRIBUTIONS

All authors contributed to the design and implementation of the study, conceptualizing the manuscript, writing, and reviewing the manuscript. All authors agree to and approve the contents of the manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

DISCLOSURE

Dae Young Lee, Min Jung Lee, Chaelim Ryu, and Heewon Lee are the full-time employees at Dong-A ST which funded the study. Dr. Ashley Brooks is a full-time employee of Labcorp Drug Development, Labcorp Clinical Research Unit Limited, the Clinical Research organization that conducted the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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