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ORIGINAL RESEARCH

Safety, Tolerability and Pharmacokinetics of Single and Multiple Doses of Mirogabalin in Healthy Chinese Participants: A Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Introduction: Mirogabalin is a treatment option for patients with neuropathic pain; however, safety, tolerability, and pharmacokinetics (PK) data specifically for Chinese individuals are limited to a single-dose study. We aimed to assess these for both single- and multiple-dose mirogabalin in healthy Chinese participants.

Methods: In this randomized, double-blind, placebo-controlled, phase I study, 54 healthy Chinese men and women aged 18–45 years were randomly allocated to receive single- (5, 10, or 15 mg, daily) or multiple-dose (5 mg titrated to 15 mg, twice-daily, over 22 days) oral mirogabalin or placebo. In each of three single-dose groups, 10 participants received mirogabalin and 2 received placebo; in the multiple-dose group, 14 participants received mirogabalin and 4 received placebo. The primary endpoints were PK, safety, and tolerability variables, including treatment-emergent adverse events (TEAEs), laboratory tests, and vital signs. PK data were collected for both single- and multiple-dose cohorts and evaluated by non-compartmental analysis.

Results: Single- and multiple-dose mirogabalin was generally well tolerated with no deaths, serious TEAEs, or TEAEs leading to treatment discontinuation. Frequently reported TEAEs included dizziness, nystagmus, increased blood triglycerides, headache, and increased blood uric acid and creatine phosphokinase. Single-dose mirogabalin was rapidly absorbed (median time to maximum plasma concentration, 1.00 h) and eliminated (mean terminal elimination half-life, 2.57–3.08 h). The exposure was approximately dose-proportional. In the multiple-dose cohort, the trough plasma concentration increased dose-proportionally, and exposure and clearance were comparable to that following a single 15-mg dose. The mean cumulative amount excreted into urine up to

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48 h post-dose increased in a dose-proportional manner, the mean cumulative percentage excreted into urine was 61.9%–74.3%, and renal clearance remained relatively constant.
Conclusion: Consistent with previous phase I studies in other populations, mirogabalin was safe and well tolerated in healthy Chinese participants at single and multiple doses of up to 15 mg twice-daily.

Keywords: China; Neuropathic pain; Mirogabalin; Multiple-dose; Pharmacokinetics; Phase I; Post-herpetic neuralgia; Safety; Single-dose; Tolerability

Key Summary Points

Why carry out this study?
An estimated 90 million individuals in China are currently living with neuropathic pain, including post-herpetic neuralgia and diabetic peripheral neuropathic pain, and the demand for effective therapeutic agents for these difficult to treat, often debilitating conditions is expected to increase in coming years.
A new selective $\alpha_2\delta$-1 ligand, mirogabalin, is in development for the treatment of neuropathic pain, and has demonstrated sustained analgesic effects, yet despite availability as a treatment option for patients with neuropathic pain, there are limited safety, tolerability, or pharmacokinetic data in Chinese individuals.
This study assessed whether mirogabalin at single (5, 10, and 15 mg, once-daily) and multiple doses (up to 15 mg twice-daily) would have an acceptable safety and tolerability profile in healthy Chinese participants and a similar pharmacokinetic profile to those shown in other populations.
What was learned from this study?
Consistent with previous phase I studies in other populations, this phase I study showed that both single- and multiple-dose mirogabalin were safe and well tolerated in healthy Chinese participants, with comparable pharmacokinetic parameters.
No significant safety issues related to the central nervous system were identified.
The results of this study were used to inform the dosing protocol for a phase III, double-blind, placebo-controlled, randomized study investigating the efficacy and safety of mirogabalin in Chinese patients with diabetic peripheral neuropathic pain (ClinicalTrials.gov NCT04094662).

INTRODUCTION

Neuropathic pain is primarily caused by a lesion or disease that leads to an abnormal and dysfunctional somatosensory system, and may result in disability and reduced quality of life [1–3]. Depending on the pathophysiology, neuropathic pain may be classified anatomically as peripheral neuropathic pain or central neuropathic pain [4]. Peripheral neuropathic pain is associated with several conditions, including post-herpetic neuralgia (PHN) and diabetic peripheral neuropathic pain (DPNP) [5, 6].

The $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits of voltage-dependent Ca^{2+} channels play a key role in neuropathic pain [7–9]. Ligands of the $\alpha_2\delta$-1 subunit of these channels reduce Ca^{2+} influx into neurons of the central nervous system (CNS), resulting in analgesic effects [8–10]. The $\alpha_2\delta$-1 subunit is the primary therapeutic target of pregabalin and gabapentin, which are currently available in Europe, America, and Japan for treatment of neuropathic pain [11, 12].

A new selective $\alpha_2\delta$-1 ligand, mirogabalin monobenzenesulfonate (DS-5565), is in development for the treatment of neuropathic pain

[13]. In preclinical studies, mirogabalin demonstrated sustained analgesic effects and provided pain relief with a more favorable CNS safety profile than pregabalin [7]. Specifically, a study in rats demonstrated superior CNS safety margins for mirogabalin versus pregabalin in both the rota-rod and locomotor activity tests [7]. Clinical studies of mirogabalin have demonstrated the efficacy and safety in the management of patients with DPNP [14, 15] and PHN [16], and mirogabalin was first approved in Japan for the treatment of peripheral neuropathic pain in 2019 [17, 18]. Additionally, a placebo-controlled study that investigated the efficacy and safety of mirogabalin in patients with central neuropathic pain has recently been completed (ClinicalTrials.gov: NCT03901352). Based on the results from that trial, the approved indications of mirogabalin in Japan were extended to neuropathic pain including both central and peripheral neuropathic pain [19].

There are currently an estimated 90 million individuals in China with neuropathic pain [20], and the demand for effective therapeutic agents for peripheral neuropathic pain is expected to increase in the coming years. DPNP is estimated to affect 20%–30% of patients with diabetes mellitus and results in significant morbidity and reduced quality of life [21, 22]. In 2021, China was ranked as having the highest number of adults with diabetes worldwide: 140.9 million individuals, a number projected to increase [23]. Therefore, it is expected that as the incidence of diabetes in China increases, the incidence of DPNP will also increase.

PHN is a known chronic complication of herpes zoster infection [24]. The risks of both herpes zoster infection and developing subsequent PHN increase with age [24–27]. Moreover, with the aging of the population in countries such as China, it is expected that the number of Chinese patients with PHN will increase.

Although mirogabalin may be an option for the treatment of patients with neuropathic pain in China, there are insufficient data regarding the safety, tolerability, and pharmacokinetics (PK) of mirogabalin in Chinese individuals, which are limited to an Asian study that included only five Chinese participants among the Japanese/Korean/Chinese population receiving a single dose of mirogabalin [27]. In the present study, for the first time, the safety, tolerability, and PK of single (5, 10, and 15 mg) and multiple [15-mg twice-daily (BID)] doses of mirogabalin were assessed in healthy Chinese participants.

METHODS

Study Design and Compliance with Ethics Guidelines

This was a randomized, double-blind, placebo-controlled, single- and multiple-dose, phase I study in healthy participants. The study was conducted at a single center: Huashan Hospital, Fudan University, Shanghai, China. The first participant was enrolled on 4 September 2017 and the last participant completed the study on 30 November 2017. Ethical approval for the study was obtained from the institutional review board at Huashan Hospital, Fudan University, on 24 January 2017 (approval number 2016–322). The study was conducted in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), the Chinese GCP, and all applicable regulatory requirements. This study was registered with the Japan Pharmaceutical Information Center Clinical Trials Information registry with the identifier JapicCTI-173680. All participants provided written informed consent prior to study participation.

Participants

Healthy Chinese men and women aged between 18 and 45 years at the time of informed consent were enrolled if they met the following inclusion criteria: body weight $\geq$ 45 kg (for women) or $\geq$ 50 kg (for men), body mass index 19.0–26.0 kg/m^2; able to understand the nature of the study and any potential hazards; and willing to provide written informed consent.

Key study exclusion criteria were: a clinically relevant abnormal medical history, physical findings, electrocardiography, or laboratory values at the pre-study screening assessment that could interfere with the study objectives or participant's safety; history of medical conditions such as CNS, cardiovascular, respiratory, blood/hematopoietic, muscular, gastrointestinal, hepatic, renal, or endocrine disease; history of clinically relevant dizziness or vertigo; surgery (e.g., gastric bypass) or medical condition that might affect the absorption of medicines; history of severe adverse drug reaction (ADR); presence or history of drug or alcohol abuse; pregnancy or breastfeeding; and unwillingness to use reliable contraception.

Prohibited prior therapies included prescription or non-prescription drugs known to significantly inhibit or induce liver enzymes involved in cytochrome P450 metabolism (from 28 days prior to study entry); any other prescription drug, with the exception of acetaminophen $\leq$ 2000 mg/day (from 14 days prior to study entry); and any other non-prescription drug, including herbal supplements (from 7 days prior to study entry).

During screening and the study period, all other medications were prohibited unless necessary for the treatment of an adverse event (AE). Any medications received during the study period were recorded in the electronic case report form, along with the daily dose, duration, and reasons for administration. Participants who received any prohibited concomitant medications could be withdrawn from the study at the discretion of the sponsor and the investigator.

Treatments and Blinding

The study was designed to enroll 54 healthy individuals who were ethnically Chinese: 36 participants in the single-dose cohort (Groups 1, 2, and 3) and 18 participants in the multiple-dose cohort (Group 4); placebo-treated participants were included in all groups (Fig. 1).

Randomization was performed by group and stratified by sex, with the same number of male and female participants enrolled in each group. The Clinical Supply Operation created a table that randomly assigned a study drug ID to each treatment arm. Next, an independent biostatistician used that information to create another table to randomly assign a study drug ID to each subject number, which was sent to the study site prior to study initiation. All random number generation was done by computer, and the code was kept strictly confidential until unblinding. For Groups 1–3, 36 participants (12 per group) were randomized to receive single-dose mirogabalin besylate (hereafter, mirogabalin) (5, 10, or 15 mg) or matching placebo after an overnight fast of at least 10 h. The participants were screened in the 28 days before the first dose of study drug and admitted to the study site for 4 days (Day −1 to Day 3). The follow-up visit was 7–9 days after dosing (approximately Day 9).

Eighteen participants were randomly allocated to multiple-dose oral mirogabalin or matching placebo. To maintain blinding, the placebo tablets and packaging were indistinguishable from those of mirogabalin, with both tablets having the same shape, size, color, and odor. The mirogabalin titration period was applied during the first 2 weeks (Fig. 1). Mirogabalin was administered at a dose of 5 mg BID (once every 12 h) for 7 days (Days 1–7) followed by 10 mg BID for 7 days (Days 8–14). After the titration period, the participants received 15 mg BID for 7 days (Days 15–21) during the fixed-dose period, and received a single dose of 15-mg mirogabalin on the morning of Day 22. The participants were screened in the 28 days before the first dose of study drug and admitted to the study site for 25 days (Days −1 to Day 24). The follow-up visit was 7–9 days after the last dose (approximately Day 30). Participants were required to fast prior to drug administration, with no water or food permitted within 2 h prior to and 1 h after administration, except for the water to be taken with the dose. Participants were required to fast

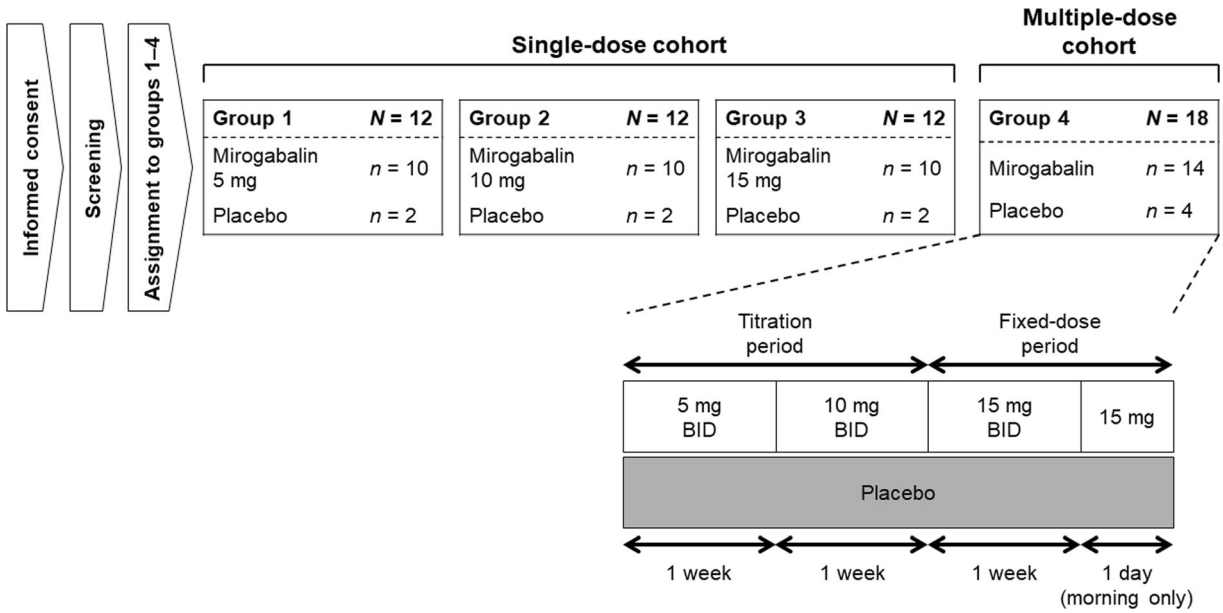

Fig. 1 Study design and dosing schedule. *BID* twice daily

for at least 10 h overnight prior to receiving the final dose on Day 22, and 4 h post-dosing.

Safety and Tolerability Assessments

Safety and tolerability endpoints were treatment-emergent AEs (TEAEs), general laboratory tests, vital signs, body weight, electrocardiography, and physical examinations. TEAEs were categorized using the Medical Dictionary for Regulatory Activities v.20.0 and described by System Organ Class and Preferred Term.

Pharmacokinetic Analysis

For the single-dose cohort, plasma PK samples were taken pre-dose, and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, and 48 h post-dose. Urine PK samples were taken pre-dose, and 0–4, 4–8, 8–12, 12–24, 24–36, and 36–48 h post-dose. For the multiple-dose cohort, plasma PK samples were taken prior to the morning dose on Days 1–4, 8, 11, 15, 18, and 22, and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, and 48 h post-dose on Day 22.

PK analyses were conducted on A200-0700, the free form of mirogabalin [28]. The plasma and urine PK parameters were derived by non-compartmental analysis using Phoenix WinNonlin® (v.6.4; Certara USA, Princeton, NJ, USA). Missing data were not imputed and only observed data were included in the analyses. The PK parameters included area under the plasma concentration–time curve (AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), terminal elimination half-life ($t_{½}$), elimination rate constant associated with the terminal phase (K_{el}), apparent total body clearance (CL/*F*), renal clearance (CLr), apparent total body clearance at steady state (CL_{ss}/F), mean residence time up to infinity (MRT_{inf}), apparent volume of distribution based on the terminal phase (V_z/F), cumulative amount excreted into urine up to 48 h ($Ae_{0–48\ h}$), and cumulative percentage of dose excreted into urine up to 48 h ($Fe_{0–48\ h}$).

Plasma A200-0700 concentrations were analyzed at Fudan University (Shanghai, China) using a previously described, validated high-performance liquid chromatography-tandem mass spectrometry (LC–MS/MS) method [29], with the following modifications. Quality control samples for the validation assay of mirogabalin were prepared at 1.00, 3.00, 75.0, 400, and 750 ng/mL, and dilution integrity was verified up to 10,000 ng/mL. The intra- and inter-assay

precision (coefficient of variation [CV]) values in the validation were within 9.5% and 7.3%, respectively, and the ranges for intra- and inter-assay accuracy were − 4.0% to 6.9%, and − 0.9% to 3.6%, respectively.

Similarly, urine concentrations of A200-0700 were also analyzed at Fudan University using a validated LC–MS/MS method [29], with the following modifications. Quality control samples were prepared at 0.100, 0.300, 7.50, 40.0, and 75.0 μg/mL. The intra- and inter-assay precision values were within 14.5% and 9.5%, respectively, and the respective accuracy ranges were − 5.7% to 4.0% and − 2.4% to − 1.0%.

Statistical Methods

The sample size was not based on statistical considerations; the number of participants was considered sufficient based on Chinese regulatory requirements. The safety and PK analyses were performed using the safety analysis set (all participants who provided written informed consent and received at least one dose of the study drug) and the PK analysis set (all participants from the safety set with available PK data), respectively.

All analyses were performed separately for the single-dose and the multiple-dose cohorts. For the single-dose cohort, participants' baseline demographics and characteristics were summarized by each dose level of mirogabalin and placebo, and participants randomly assigned to placebo in each group were pooled for analysis. For the multiple-dose cohort, baseline demographics and characteristics were summarized according to mirogabalin or placebo treatment. All data for safety endpoints were summarized using descriptive statistics.

All quantitative PK data were tabulated with descriptive statistics: arithmetic mean, standard deviation (SD), CV, standard error of the mean, median, minimum and maximum values, and number of observations. Geometric mean and CV for geometric mean were calculated for C_{max} and AUC values. The Statistical Analysis System (SAS® v.9.2 or higher; SAS Institute, Cary, NC, USA) software package was used to produce tables, figures, and listings.

RESULTS

Participants

The single-dose cohort comprised three dose groups: 5-, 10-, and 15-mg mirogabalin. Within each single-dose group, 10 participants were allocated to receive mirogabalin and 2 participants to receive placebo (36 participants in total), as planned. The multiple-dose cohort included 14 participants allocated to mirogabalin and 4 to placebo (18 participants in total), as planned. All participants completed the study. One participant was excluded from the single-dose PK analysis set because it was determined at a follow-up visit that she was pregnant and may have been before the study drug was administered. One participant was excluded from the multiple-dose PK analysis set because of concomitant medication use.

The study had an equal number of male and female participants, and the baseline characteristics of each cohort were generally comparable (Table 1). The mean ± SD age, body weight, and body mass index of the single- and multiple-dose cohorts were 27.6 ± 5.2 and 27.8 ± 4.7 years, 63.0 ± 9.8 and 60.7 ± 7.5 kg, and 22.7 ± 2.2 and 22.5 ± 1.9 kg/m^2, respectively. Baseline characteristics were also comparable between participants in the placebo and mirogabalin groups.

Safety

Single- and multiple-dose mirogabalin was generally well tolerated. No deaths, serious TEAEs, or TEAEs leading to treatment discontinuation were reported in either the single- or multiple-dose cohorts. Two hepatic-related TEAEs of special interest were reported in one participant each in the mirogabalin 15-mg single-dose and 15-mg BID multiple-dose groups. In the single-dose group, the participant experienced a transient increase in blood bilirubin on Day 7, which was mild and resolved without treatment. The event was considered unlikely to be related to mirogabalin because the temporal occurrence of the event was not consistent with the administration of the study drug, and the

Table 1 Baseline demographics and characteristics of healthy Chinese participants (safety analysis set)

	Single-dose cohort					Multiple-dose cohort		
	Mirogabalin			Placebo	Total	Mirogabalin	Placebo	Total
	5 mg $n = 10$	10 mg $n = 10$	15 mg $n = 10$	$n = 6$	$n = 36$	BID[a] $n = 14$	$n = 4$	$n = 18$
Age, years	28.3 ± 6.6	28.5 ± 4.1	27.4 ± 3.9	25.3 ± 6.5	27.6 ± 5.2	28.1 ± 4.8	27.0 ± 5.1	27.8 ± 4.7
Male sex, *n* (%)	5 (50.0)	5 (50.0)	5 (50.0)	3 (50.0)	18 (50.0)	7 (50.0)	2 (50.0)	9 (50.0)
Body weight, kg	65.7 ± 6.3	64.7 ± 11.5	62.8 ± 12.4	56.0 ± 2.6	63.0 ± 9.8	61.9 ± 7.3	56.6 ± 7.5	60.7 ± 7.5
Body mass index, kg/m^2	23.4 ± 1.5	23.3 ± 2.2	22.5 ± 2.4	21.0 ± 2.2	22.7 ± 2.2	22.8 ± 2.1	21.5 ± 0.9	22.5 ± 1.9

Data are presented as mean ± SD unless otherwise specified

BID twice daily; *SD* standard deviation

[a]During the titration period, mirogabalin was administered as 5 mg orally BID for the first 7 days, and then 10 mg orally BID for the next 7 days. During the fixed-dose period, mirogabalin was administered at a dose of 15 mg orally BID for 7 days, and then as a single dose of 15 mg orally on the morning of Day 22

investigator judged that the event was likely caused by the effect of the participant's diet following discharge. In the multiple-dose group, the participant experienced a transient mild increase in blood bilirubin on Day 24. Although the event resolved without treatment, the TEAE was considered possibly related to mirogabalin based on the temporal relationship between the occurrence of the event and administration of the study drug.

In the single-dose cohort, the incidences of TEAEs in the mirogabalin 5-,10-, and 15-mg groups were 50% (5/10), 50% (5/10), and 100% (10/10), respectively; 33.3% (2/6) of participants in the placebo group experienced a TEAE (Table 2). The most frequently reported TEAEs with single-dose mirogabalin included dizziness, nystagmus, and increased blood triglycerides. All TEAEs were mild and resolved without treatment. The incidences ADRs in the single-dose cohort were 16.7% (1/6) in the placebo group, 0.0% (0/10) in the 5-mg group, 0.0% (0/10) in the 10-mg group, and 60.0% (6/10) in the 15-mg group. These included dizziness (one participant in the placebo group and four in the 15-mg group), nystagmus (five participants in the 15-mg group), and somnolence, hot flush, nausea, and fatigue (one participant each in the 15-mg group). All ADRs were mild and resolved without any treatment.

In the multiple-dose cohort, the incidences of TEAEs in the mirogabalin and placebo groups were 85.7% (12/14) and 100% (4/4), respectively (Table 3). The frequently reported TEAEs with multiple-dose mirogabalin included headache, increased blood uric acid, increased blood creatine phosphokinase, positive bacterial test, and positive urinary white blood cell test. All TEAEs were mild, except for one TEAE of moderate abdominal pain reported in one participant. There were no ADRs in the placebo group of the multiple-dose cohort; 57.1% (8/14) of participants who received multiple-dose mirogabalin experienced an ADR. These included headache, palpitations, and diarrhea in two participants each, and abdominal pain, increased blood bilirubin, and increased blood creatine phosphokinase in one participant each. All ADRs were mild and resolved without treatment. No notable between-group trends or differences were observed in any other safety assessments.

Table 2 TEAEs in the single-dose cohort (safety analysis set)

	Mirogabalin			Placebo	Total
System Organ Class Preferred Term, *n* (%)	**5 mg *n* = 10**	**10 mg *n* = 10**	**15 mg *n* = 10**	***n* = 6**	***n* = 36**
Participants with at least one TEAE	5 (50.0)	5 (50.0)	10 (100.0)	2 (33.3)	22 (61.1)
Nervous system disorders	0 (0.0)	0 (0.0)	6 (60.0)	1 (16.7)	7 (19.4)
Dizziness	0 (0.0)	0 (0.0)	4 (40.0)	1 (16.7)	5 (13.9)
Nystagmus	0 (0.0)	0 (0.0)	5 (50.0)	0 (0.0)	5 (13.9)
Somnolence	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (2.8)
Vascular disorders	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (2.8)
Hot flush	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (2.8)
Gastrointestinal disorders	1 (10.0)	0 (0.0)	2 (20.0)	0 (0.0)	3 (8.3)
Abdominal pain	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.8)
Mouth ulceration	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (2.8)
Nausea	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (2.8)
Musculoskeletal and connective tissue disorders	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.8)
Arthralgia	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.8)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (2.8)
Fatigue	0 (0.0)	0 (0.0)	1 (10.0)	0 (0.0)	1 (2.8)

TEAEs were categorized according to the Medical Dictionary for Regulatory Activities v20.0. If the same TEAE occurred multiple times in the same participant, the participant was counted only once in the summary table. TEAEs included investigations that were not listed in this table

TEAE treatment-emergent adverse event

Pharmacokinetic Analysis

The mean plasma A200-0700 concentration versus time profiles of mirogabalin 5, 10, or 15 mg are shown in Fig. 2. Following a single 5-, 10-, or 15-mg oral dose, mirogabalin was rapidly absorbed (median t_{max}, 1.00 h) and eliminated (mean $t_{½}$, 2.57–3.08 h) (Table 4). The exposure (C_{max} and AUC) increased in an approximately dose-proportional manner. The mean CL/*F* and V_z/F remained nearly constant regardless of the mirogabalin dose levels.

In multiple oral dosing with mirogabalin up to 15 mg BID, the mean trough plasma concentration of A200-0700 increased in an approximately dose-proportional manner: 5.99 ng/mL on Day 8, 13.5 ng/mL on Day 15, and 18.6 ng/mL on Day 22. Additionally, the mean ± SD C_{max} and AUC during a dosing interval (AUC_{tau}) of A200-0700 following multiple oral dosing (Fig. 3) were comparable to the C_{max} and AUC from time 0 to infinity (AUC_{inf}), respectively, following a single oral dose of 15 mg: C_{max} 290 ± 55.6 ng/mL versus 340 ± 75.2 ng/mL; and AUC_{tau} 938 ± 139 ng h/mL versus AUC_{inf} 970 ± 164 ng h/mL. The CL/*F* and t_{max} of A200-0700 in both regimens were also comparable. Following the final 15-mg oral dose of mirogabalin on Day 22, the median t_{max} of A200-0700 was 1.00 h, and the mean $t_{½}$ was 3.86 h. The mean C_{max} of A200-0700 was 290 ng/mL, and the mean AUC_{tau} was 938 ng h/mL.

Table 3 TEAEs in the multiple-dose cohort (safety analysis set)

System Organ Class Preferred Term, *n* (%)	Mirogabalin BID[a] *n* = 14	Placebo *n* = 4	Total *n* = 18
Participants with at least one TEAE	12 (85.7)	4 (100.0)	16 (88.9)
Infections and infestations	2 (14.3)	0 (0.0)	2 (11.1)
Appendicitis	1 (7.1)	0 (0.0)	1 (5.6)
Folliculitis	1 (7.1)	0 (0.0)	1 (5.6)
Nervous system disorders	3 (21.4)	0 (0.0)	3 (16.7)
Headache	3 (21.4)	0 (0.0)	3 (16.7)
Cardiac disorders	2 (14.3)	0 (0.0)	2 (11.1)
Palpitations	2 (14.3)	0 (0.0)	2 (11.1)
Respiratory, thoracic and mediastinal disorders	1 (7.1)	0 (0.0)	1 (5.6)
Nasal obstruction	1 (7.1)	0 (0.0)	1 (5.6)
Gastrointestinal disorders	4 (28.6)	0 (0.0)	4 (22.2)
Abdominal pain	2 (14.3)	0 (0.0)	2 (11.1)
Diarrhea	2 (14.3)	0 (0.0)	2 (11.1)
Toothache	1 (7.1)	0 (0.0)	1 (5.6)
Musculoskeletal and connective tissue disorders	3 (21.4)	0 (0.0)	3 (16.7)
Pain in extremity	2 (14.3)	0 (0.0)	2 (11.1)
Musculoskeletal pain	1 (7.1)	0 (0.0)	1 (5.6)

TEAEs were categorized according to the Medical Dictionary for Regulatory Activities v.20.0. If the same TEAE occurred multiple times in the same participant, the participant was counted only once in the summary table. TEAEs included investigations that were not listed in this table

BID twice daily; *TEAE* treatment-emergent adverse event

[a]During the titration period, mirogabalin was administered at a dose of 5 mg orally BID for the first 7 days, and then at a dose of 10 mg orally BID for the next 7 days. During the fixed-dose period, mirogabalin was administered at a dose of 15 mg orally BID for 7 days, and then a single dose of 15 mg was administered orally on the morning of Day 22

The time courses of the cumulative percentages of A200-0700 excreted into the urine following single oral doses of 5-, 10-, and 15-mg mirogabalin are shown in Fig. 4, and urinary PK parameters are described in Table 5. The mean $Ae_{0–48\ h}$ of A200-0700 increased in a dose-proportional manner, the mean $Fe_{0–48\ h}$ of A200-0700 was 61.9%–74.3%, and CLr remained relatively constant.

DISCUSSION

Single-dose (5-, 10- or 15-mg) and multiple-dose (up to 15-mg BID) mirogabalin was safe and well tolerated in healthy Chinese participants and showed PK parameters consistent with those seen in other phase I study populations [27, 29]. Although the PK parameters of mirogabalin are unlikely to be strongly affected by race, both genetic (e.g., polymorphisms) and environmental (e.g., diet, body composition, socioeconomic background, culture) factors

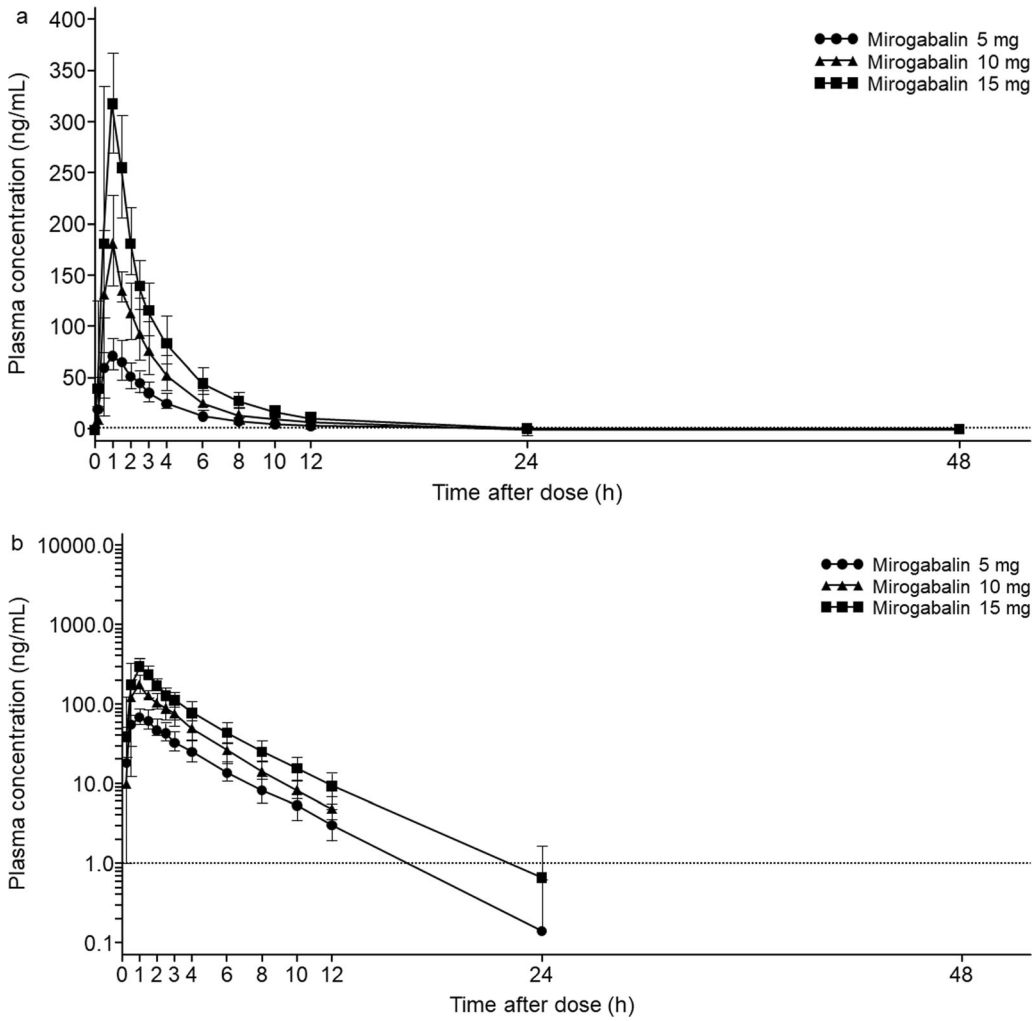

Fig. 2 Arithmetic mean plasma A200-0700 concentration versus time profiles following single oral administration of mirogabalin 5, 10, or 15 mg on linear (**a**) and semi-logarithmic (**b**) scales (PK analysis set); error bars represent SD; *SD* standard deviation; *PK* pharmacokinetic

have been suggested to indirectly influence drug metabolism [30]. Our study provides the first evidence of safety for mirogabalin in an exclusively Chinese population.

The CNS-related TEAEs reported in this study, such as dizziness and somnolence, are consistent with those reported for other $\alpha_2\delta$ ligand drugs [31]. All were mild and resolved without treatment, as was the case in previous phase I studies [29]. In this study, a dose titration regimen was selected for the multiple-dose cohort in the expectation that this would reduce the risk of CNS-related TEAEs; indeed, no TEAEs of dizziness or somnolence were reported in the multiple-dose cohort. This result may support the utility of using a dose-titration regimen to reduce the risk of CNS-related TEAEs [32; congress poster].

The PK parameters (C_{max}, t_{max}, $t_{½}$ and AUC_{inf}) observed in healthy Chinese participants given single-dose mirogabalin (5 or 10 mg) in the present study are consistent with data reported in a previous study that mainly evaluated healthy Caucasian adults (C_{max} values of 89.8 ng/mL in the present study vs. 78 ng/mL reported previously at the 5-mg dose, and 194 ng/mL vs. 205 ng/mL previously at the 10-mg dose; t_{max} at 1 h in both studies; $t_{½}$ of

Table 4 Pharmacokinetic parameters of A200-0700 following single and multiple oral doses of mirogabalin (PK analysis set)

	Single-dose mirogabalin			Multiple-dose mirogabalin
	5 mg $n = 9$[a]	10 mg $n = 10$	15 mg $n = 10$	15 mg BID[b] $n = 13$[c]
AUC_{last} (ng h/mL)	277 ± 35.1	560 ± 96.2	949 ± 156	–
AUC_{inf} (ng h/mL)	289 ± 38.9	581 ± 98.5	970 ± 164	
AUC_{tau} (ng h/mL)	–	–	–	938 ± 139
C_{max} (ng/mL)	89.8 ± 31.8	194 ± 33.4	340 ± 75.2	290 ± 55.6
t_{max} (h)	1.00 (0.50, 1.52)	1.00 (0.50, 2.00)	1.00 (0.50, 1.50)	1.00 (0.50, 1.00)
$t_{½}$ (h)	2.95 ± 0.952	2.57 ± 0.461	3.08 ± 0.932	3.86 ± 1.11
CL/*F* (L/h)	17.6 ± 2.15	17.7 ± 2.81	15.9 ± 2.68	–
CL_{ss}/F (L/h)	–	–	–	16.3 ± 2.29
Vz/*F* (L)	73.4 ± 18.6	66.0 ± 18.9	69.2 ± 20.0	91.0 ± 32.8

Data are presented as mean ± SD for all parameters, with the exception of t_{max} for which median (range) values are presented

AUC_{inf} area under the plasma concentration–time curve up to infinity; *AUC_{last}* AUC up to the last quantifiable time; *AUC_{tau}* AUC during the dosing interval; *BID* twice daily; *CL/F* apparent total body clearance; *CL_{ss}/F* apparent total body clearance at steady state; *C_{max}* maximum plasma concentration; *PK* pharmacokinetic; *SD* standard deviation; *$t_{½}$* terminal elimination half-life; *TEAE* treatment-emergent adverse event; *t_{max}* time to maximum plasma concentration; *Vz/F* apparent volume of distribution based on the terminal phase

[a]One participant was excluded from the PK analysis due to a positive pregnancy test

[b]During the titration period, mirogabalin was administered as 5 mg orally BID for the first 7 days, and then 10 mg orally BID for the next 7 days. During the fixed-dose period, mirogabalin was administered at a dose of 15 mg orally BID for 7 days, and then as a single dose of 15 mg orally on the morning of Day 22

[c]Plasma A200-0700 concentration data for Day 22 for one participant were excluded from the PK analysis due to the use of concomitant medications to treat TEAEs and the resulting inability to calculate the PK parameters

2.57–2.95 h in the present study vs. 2.96–3.32 h reported previously; and AUC_{inf} of 289–581 ng h/mL in the present study vs. 276–614 ng h/mL reported previously) [29]. Following a single oral dose, mirogabalin was rapidly absorbed and mainly eliminated in urine. Exposure appeared to be dose-proportional, and clearance was unchanged regardless of dose. Moreover, urinary PK parameters (Ae, Fe, and CLr) of participants who received a single dose of mirogabalin (5 or 10 mg) were consistent [29]. Collectively, the PK parameters observed after administration of single-dose mirogabalin in healthy Chinese participants were generally similar to those observed in healthy non-Chinese adults.

In the multiple-dose cohort, PK parameters (C_{max} and AUC_{tau}) of participants receiving 15-mg mirogabalin BID were 290 ng/mL and 938 ng h/mL, respectively. No large differences were observed in these parameters compared with those observed in the elderly multiple-dose cohort of the study that enrolled healthy White participants (C_{max} of 296 ng/mL and AUC_{tau} of 1033 ng h/mL) [29]. Following multiple dosing, trough plasma A200-0700 levels appeared to be dose-proportional. Exposure and clearance rates after multiple doses of up to 15 mg BID were similar to those following a single dose of 15-mg mirogabalin. Although the plasma $t_{½}$ of mirogabalin is 3 h, the dissociation $t_{½}$ from the target $\alpha_2\delta$-1 subunit is estimated to be 11.1 h

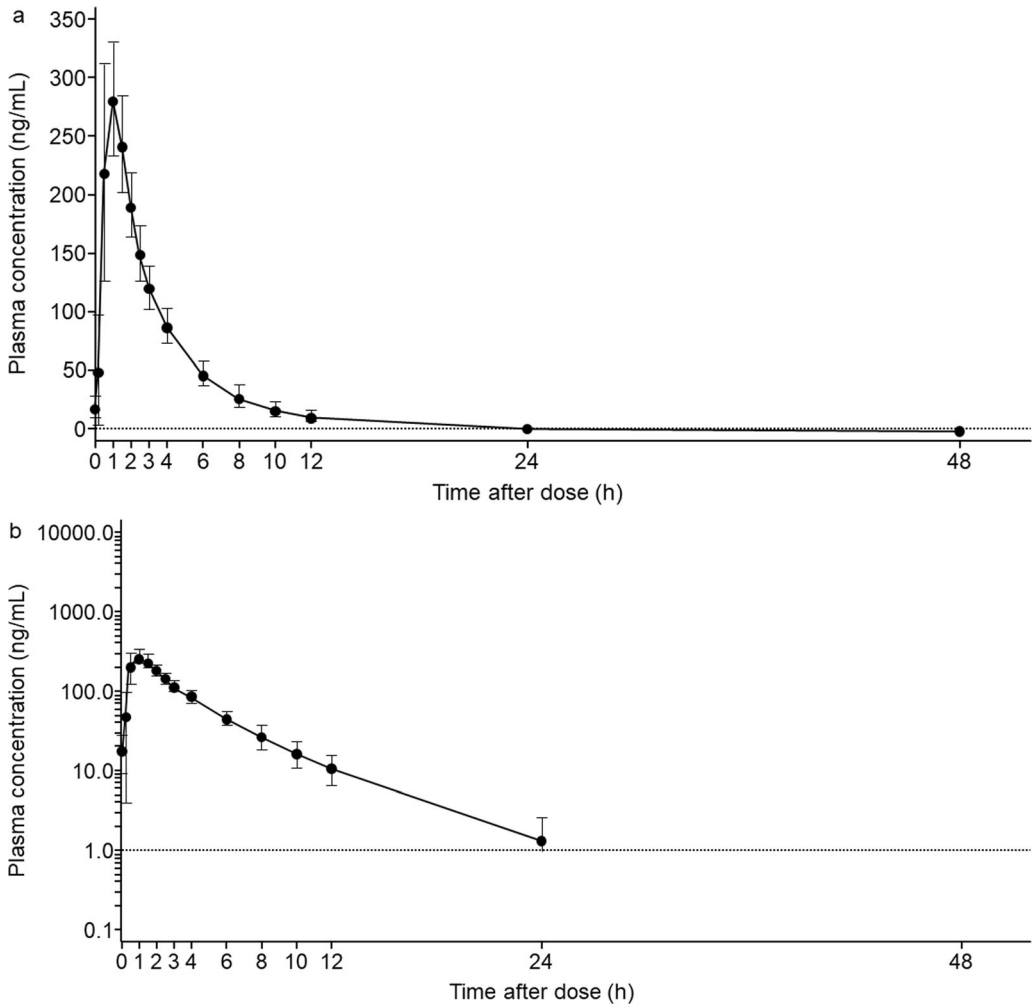

Fig. 3 Arithmetic mean plasma A200-0700 concentration versus time profiles following multiple oral doses of mirogabalin, up to 15 mg BID on Day 22. **a** Linear and **b** semi-logarithmic scales (PK analysis set); error bars represent SD; *BID* twice daily; *SD* standard deviation; *PK* pharmacokinetic

[33]. Therefore, we expect efficacy to be sustained for the dosing interval. Furthermore, the efficacy of twice-daily administration has been confirmed in clinical trials [34].

The efficacy and safety of mirogabalin have already been shown in DPNP and PHN in Asian studies, in which the majority of patients were Japanese [14, 16]. The present study shows that the PK do not differ between Chinese participants and those of other ethnicities. Therefore, the same dosing regimen of mirogabalin as in the above-mentioned studies is expected to have a similar effect in Chinese patients. The results of the present phase I study were used to establish the mirogabalin dosage regimen for a phase III, double-blind, placebo-controlled, randomized study (ClinicalTrials.gov: NCT04094662) evaluating the efficacy and safety of mirogabalin in Chinese patients with DPNP.

Limitations

The present study had several limitations, including that only healthy Chinese adults were enrolled, and that efficacy in Chinese patients with DPNP remains to be confirmed. Only a

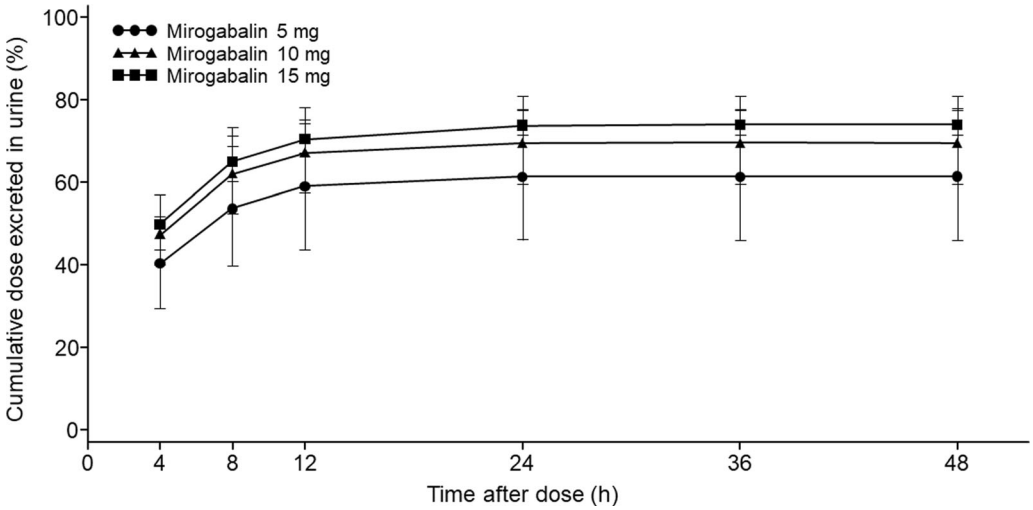

Fig. 4 Time course of cumulative percentage (arithmetic mean) of A200-0700 excreted in urine following single oral doses of 5-, 10-, and 15-mg mirogabalin (PK analysis set); error bars represent SD; *SD* standard deviation; *PK* pharmacokinetic

Table 5 Urinary pharmacokinetic parameters of A200-0700 following single oral doses of 5-, 10-, and 15-mg mirogabalin (PK analysis set)

	Mirogabalin		
	5 mg ***n*** **= 9**[a]	**10 mg** ***n*** **= 10**	**15 mg** ***n*** **= 10**
$Ae_{0-48\ h}$ (mg)	3.09 ± 0.796	7.02 ± 1.06	11.1 ± 0.455
$Fe_{0-48\ h}$ (%)	61.9 ± 15.9	70.2 ± 10.6	74.3 ± 3.03
CLr (L/h)	11.4 ± 3.65	12.8 ± 2.64	12.0 ± 2.14

Data are presented as mean ± SD for all parameters

$Ae_{0-48\ h}$ cumulative amount of A200-0700 excreted into urine up to 48 h; *CLr* renal clearance; *$Fe_{0-48\ h}$* cumulative percentage of dose excreted into urine up to 48 h; *PK* pharmacokinetic; *SD* standard deviation

[a]One participant was excluded from the PK analysis due to a positive pregnancy test

limited number of participants up to a maximum age of 45 years were eligible. The comparison of PK parameters reported in other ethnicities and age groups should be interpreted with caution because such comparisons were not the primary objective of the present study. Finally, this was a small, single-center study, and the safety profile of mirogabalin in Chinese individuals should be confirmed in larger, multicenter analyses.

CONCLUSIONS

Overall, this phase I study demonstrated that mirogabalin was safe and well tolerated at single doses of 5, 10, and 15 mg and at multiple doses of up to 15 mg BID in healthy Chinese participants. The data reported here are consistent with previous phase I studies in other populations, and confirmation of the efficacy and safety of mirogabalin in Chinese patients with peripheral neuropathic pain is eagerly anticipated.

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Author Contributions. All authors were involved in the study design and conduct, data analysis, and interpretation. All authors contributed to writing and reviewing the manuscript, and provided final approval of the manuscript for submission.

List of Investigators. Yi Li, Hailan Wu, Guoying Cao, Jicheng Yu, Yu Wang, Xiaofen Liu, Beining Guo, Jufang Wu, Peimin Yu, Zhen Hong (Co-principle Investigator), Jing Zhang (Principal Investigator), Xiaojie Wu, Aiqun Qiu, Dongyan Wu, Fengtao Liu, Guoyun Zhang, Jingjing Wang, JunZhen Wu, Lan Xu, Quling Li, Wei Lei, Xiaoli Yang, Xiaoyong Xu, Xin Li, Xingchen Bian, Yan Ge, Yaoguo Shi, Yi Wang, Yingying Hu and Zhiwei Huang were included as investigators in the data collection.

Disclosures. Kaoru Toyama, Takafumi Nakatsu, and Hitoshi Ishizuka are employees of Daiichi Sankyo, Co., Ltd., which funded this study. Yi Li, Hailan Wu, Guoying Cao, Jicheng Yu, Yu Wang, Xiaofen Liu, Beining Guo, Jufang Wu, Peimin Yu, Zhen Hong, Jing Zhang, and Xiaojie Wu declare that they have no competing interests.

Data Availability. All de-identified participant data relevant to this study are included in this article. Additional data and supporting documents pertaining to this study are provided upon reasonable request made via this web address (https://vivli.org/ourmember/daiichi-sankyo/) in accordance with the data sharing policy of Daiichi Sankyo Co., Ltd.

Compliance with Ethics Guidelines. Ethical approval for the study was obtained from the institutional review board at Huashan Hospital, Fudan University, on 24 January 2017, and the study was conducted in accordance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), the Chinese GCP, and all applicable regulatory requirements. All participants provided written informed consent prior to study participation.

Prior Presentation. The results of this study have not been previously presented at scientific meetings or published elsewhere.

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