


ORIGINAL ARTICLE

Safety, pharmacokinetics and pharmacodynamics of TAK-418, a novel inhibitor of the epigenetic modulator lysine-specific demethylase 1A

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Aims: Dysregulation of histone methylation epigenetic marks may result in intellectual and developmental disability, as seen in Kabuki syndrome. Animal data suggest that increasing histone methylation by inhibiting lysine-specific demethylase 1A (LSD1) may improve cognitive outcomes in a model of Kabuki syndrome. TAK-418 is a novel LSD1 inhibitor, developed as a potential therapeutic agent for central nervous system disorders such as Kabuki syndrome. Here, we report safety, tolerability, pharmacokinetic and pharmacodynamic profiles of single and multiple doses of TAK-418 (ClinicalTrials.gov: NCT03228433, NCT03501069).

Methods: Two randomized, double-blind, placebo-controlled, phase 1 studies of oral TAK-418 were performed, a first-in-human single-rising-dose (SRD) study (5–60 mg) in healthy adult male and female volunteers (placebo, $n = 10$; TAK-418, $n = 30$), and an SRD (120–160 mg) and multiple-rising-dose (MRD) study (20–160 mg once daily for 10 days) in healthy female volunteers (placebo, $n = 2$ [SRD] and $n = 6$ [MRD]; TAK-418, $n = 6$ [SRD] and $n = 18$ [MRD]).

Results: TAK-418 was well tolerated. No clinically significant changes in laboratory test results or vital signs were observed and no serious adverse events were reported. TAK-418 had a nearly linear pharmacokinetic profile, with rapid absorption and short terminal half-life across the evaluated dose range. No obvious accumulation was observed after daily administration for 10 days. Administration with food delayed peak plasma concentrations but overall exposure was unaffected. TAK-418 rapidly crossed the blood–brain barrier and generally showed a dose-dependent response in the peripheral pharmacodynamic biomarker formyl-flavin adenine dinucleotide.

Conclusion: The brain-penetrant LSD1 inhibitor TAK-418 was well tolerated, with pharmacokinetic and pharmacodynamic effects that support further investigation.

KEYWORDS

healthy volunteer, histone demethylase, Kabuki syndrome, KMT2D protein, LSD1 inhibitor, phase 1 clinical trial, randomized controlled trial

1 | INTRODUCTION

Gene expression can be altered without changes in the underlying DNA sequence.¹ This process – referred to as epigenetic regulation – can be influenced by the environment or by mutation of regulatory factors, and the resulting changes in gene expression can be inherited.^{1,2}

Epigenetic alterations arise from remodelling of chromatin, driven by numerous mechanisms. The basic unit of chromatin is the nucleosome, composed of DNA wrapped around histone protein octamers.^{1,2} A number of epigenetic processes modulate chromatin and, therefore, gene expression, including DNA methylation and hydroxymethylation, phosphorylation, acetylation and ubiquitination, histone post-translational modification and changes in nucleosome positioning.^{1,2}

Impaired genetic regulation resulting from chromatin abnormalities is believed to contribute to some neurodevelopmental disorders, with regulatory proteins, such as histones, being involved in key phases of brain development.^{2,3} Mutations in genes encoding modulators of methylation at histone 3 lysine residue 4 (H3K4) have been reported in intellectual disability syndromes, schizophrenia and autism spectrum disorder.⁴ For example, Kabuki syndrome – a congenital intellectual disability disorder with distinctive facial features – is primarily associated with loss-of-function mutations in the lysine-specific methyltransferase 2D (*KMT2D*) gene.^{4,5} In this context, inhibition of H3K4 demethylation by **lysine-specific demethylase 1A** (LSD1; also known as KDM1A) may have therapeutic potential by restoring the balance of H3K4 methylation.

TAK-418 is a novel small molecule that irreversibly inhibits the activity of human LSD1 by targeting the catalytic **flavin adenine dinucleotide** (FAD) in the LSD1 active site. In a mouse model of Kabuki syndrome (generated by heterozygous deletion of the *KMT2D* gene⁶), TAK-418 rescued H3K4 histone modification defects and dose-dependently normalized adult neurogenesis in the hippocampus. Furthermore, visuospatial learning and memory defects were rescued after 2 weeks of treatment with TAK-418 compared with vehicle control.⁷ In addition, TAK-418 improved autism symptoms in two rodent models of neurodevelopmental disorder.⁸ These results support the hypothesis that LSD1 inhibition may be an effective method for the treatment of Kabuki syndrome.

We report first-in-human data from two studies evaluating the safety, tolerability and pharmacokinetic (PK) and pharmacodynamic (PD) profiles of single or multiple doses of TAK-418 to support further development of this molecule as a potential therapeutic agent for patients with central nervous system (CNS) disorders, such as Kabuki syndrome.

2 | METHODS

Two randomized, double-blind, placebo-controlled phase 1 studies of TAK-418 were performed in the USA: Study 1001 was a phase 1, single-centre, single-rising-dose (SRD) clinical trial in healthy

What is already known about this subject

- Until recently, development of LSD1 inhibitors has focused on the treatment of haematological and solid malignancies.
- Epigenetic modifications have a role in the manifestations of some central nervous system disorders, including Kabuki syndrome.
- Results of preclinical studies indicate that the lysine-specific demethylase 1A inhibitor TAK-418 may have utility for the treatment of certain neurodevelopmental disorders.

What this study adds

- TAK-418 demonstrated favourable safety and tolerability in healthy humans following daily dosing for up to 10 days.
- First-in-human studies show that TAK-418 penetrates the central nervous system with acceptable safety and pharmacokinetics at plasma concentrations that have a demonstrated peripheral target engagement.

male and female volunteers, and Study 1003 was a two-centre SRD and multiple-rising-dose (MRD) trial in healthy female volunteers. Key inclusion criteria were 18–55 years of age, and body mass index of 18.5–30.0 kg m⁻² (for non-Japanese participants) or 18.0–26.0 kg m⁻² (for Japanese participants). Health status was determined based on medical history, results of laboratory safety tests, physical examination, 12-lead electrocardiogram readings and vital sign measurements. Female participants in Study 1001 had to have no childbearing potential; those in Study 1003 had to have no childbearing potential or use at least one highly effective method of contraception throughout the trial. Key exclusion criteria included participation in another investigational study in the 4 weeks before screening. Detailed inclusion/exclusion criteria for both studies are provided in Table S1.

Both studies were conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines. All participants provided written informed consent before taking part. Study protocols and all amendments were approved by institutional review boards at all participating sites. These studies were prospectively registered with ClinicalTrials.gov (ClinicalTrials.gov identifiers: NCT03228433 [Study 1001] and NCT03501069 [Study 1003]).

2.1 | Study 1001 design

Study 1001 had five cohorts, each comprising six participants randomized to receive TAK-418 and two randomized to receive placebo. Each cohort included at least four male volunteers. Study compound was administered after at least 10 hours of fasting. A sentinel dosing regimen was used for the TAK-418 5 mg cohort with the initial two participants (1:1, drug:placebo) to ensure adequate safety and tolerability. Post-dose safety and tolerability were assessed after a minimum of 72 hours and three additional participants were dosed with TAK-418 5 mg. Following evaluation of post-dose safety and tolerability after a minimum of 72 hours, the last three participants were dosed with TAK-418 5 mg. TAK-418 dosing started at 5 mg for the first cohort, with further cohorts receiving either TAK-418 15 mg, 30 mg, 40 mg or 60 mg. Dose escalation was based on blinded assessment of safety and tolerability data from the preceding cohort and was guided by PK data. From the TAK-418 15 mg cohort onwards, dose escalation was limited to dosing with a predicted maximum plasma concentration (C_{max}) or area under the concentration–time curve (AUC) that was no more than threefold higher than that of the previous cohort. Dosing continued as long as the predicted mean AUC within 24 hours of dosing (AUC_{0-24}) did not exceed the predetermined no-effect level ($\leq 1800 \text{ h} \cdot \text{ng mL}^{-1}$) and C_{max} did not exceed one-tenth of the no-effect level (2390 ng mL^{-1}) based on preclinical toxicological evaluations in male and female animals.

A preliminary investigation into the effect of food was conducted in the TAK-418 30 mg cohort, in which participants were administered TAK-418 with and without a high-fat/high-calorie breakfast 30 minutes before dosing, at least 7 days apart.

Participants were required to refrain from consuming alcohol or medications (defined as prescription and over-the-counter drugs, vaccines, supplements, nutraceuticals and oral herbal preparations) for 7 days before dosing, and to avoid consuming xanthine or caffeine for 24 hours before dosing. They also refrained from consuming grapefruit juice, grapefruits and products containing grapefruit, mustard greens (e.g., kale, broccoli and Brussels sprouts) or charbroiled meat for 7 days before the first administration of study compound until the final follow-up visit. In addition, participants refrained from drinking fruit juices 4 hours after dosing to avoid potential inhibitory effects on absorption mediated by organic anion transporters.⁹

Blood samples for PK analysis were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, 48 and 72 hours post-dose. Urine samples were collected pre-dose and at 0–12, 12–24 and 24–48 hours post-dose. Blood samples to evaluate formyl FAD (F-FAD) were also collected pre-dose and at 2, 8, 12, 24, 48 and 72 hours post-dose, and peripheral blood mononuclear cells (PBMCs) were extracted using standard techniques for PD analysis. TAK-418 reacts with the catalytic FAD on LSD1 to generate F-FAD, which was measured as a biomarker of target engagement in PBMCs. Briefly, PBMC samples were spiked with internal standard, processed by cell lysis extraction (each PBMC pellet was suspended

in 0.5 mL of medium [RPMI-1640 with 10% fetal bovine serum] and lysed by adding 1 mL of acetonitrile) and analysed using reverse-phase ultra-performance liquid chromatography with turbo ion spray tandem mass spectrometry detection (Triple Quadrupole MS [API 5000], AB-Sciex, Framingham, MA, USA). Positive (M + H)⁺ ions for F-FAD and methotrexate (internal standard) were monitored in the multiple reaction monitoring mode. Calibration standards were set at eight concentration levels between 30 pg mL^{-1} and 5000 pg mL^{-1} , and quality control samples at four concentration levels (90, 400, 2000 and 4000 pg mL^{-1}). Linear regression analysis calculations were performed with $1/x^2$ weighting using Watson LIMS™ software version 7.4.1 (ThermoFisher Scientific, Waltham, MA, USA). Analyte-to-internal standard peak area ratios for the standards were used to create a linear calibration curve using $1/x^2$ weighted least-squares regression analysis. The concentration of F-FAD was expressed as the amount of F-FAD in the medium (pg mL^{-1}).

During the single dose 1001 Study, results of preliminary toxicology studies indicated testicular findings in a single species that led to a careful evaluation of testicular health in male trial participants through analysis of standard semen analyses¹⁰ and serum follicle-stimulating hormone, luteinizing hormone, testosterone and inhibin B at baseline, and at one or two spermatogenic cycles post-dose. All male participants were followed up until day 184 (± 7 days).

2.2 | Study 1003 design

Study 1003 was conducted in women only, based on the preliminary toxicological findings noted above and pending results from the long-term (13- and 26-week) testicular health analyses in Study 1001. Thirty-two women (eight in the SRD cohort [120 mg on Day 1 and 160 mg on Day 10] and 24 in the MRD cohorts [20 mg, 60 mg, 160 mg non-Japanese, and 20 mg Japanese cohorts]) were enrolled and completed the study. One of the TAK-418 20 mg cohorts comprised only four Japanese women (who had not been away from Japan for over 10 years and who had Japanese parents and grandparents [see Table S1 for detailed inclusion/exclusion criteria for Japanese participants]).

Participants in the TAK-418 120/160 mg cohort received a single oral dose of TAK-418 120 mg (or matching placebo) in a double-blind manner, followed by a second single dose of TAK-418 160 mg (or matching placebo) after a washout interval of at least 14 days. In the MRD cohorts, participants received study compound once daily (q.d.) for 10 days in a double-blind manner. The TAK-418 20 mg and the TAK-418 60 mg non-Japanese cohorts each comprised six participants (four randomized to receive TAK-418 and two given placebo), and the TAK-418 160 mg non-Japanese cohort and the 20 mg Japanese cohort each comprised four participants (three randomized to receive TAK-418 and one given placebo).

Dosing continued as long as the predicted mean AUC_{0-24} did not exceed the predetermined no-effect level ($\leq 71\,500 \text{ h} \cdot \text{ng mL}^{-1}$) and

C_{\max} did not exceed one-tenth of the no-effect level ($\leq 1007 \text{ ng mL}^{-1}$) based on preclinical toxicology studies in female animals.

Participants refrained from consuming grapefruit juice, grapefruits and products containing grapefruit from approximately 2 weeks before the first administration of study compound until the final follow-up visit, and also from consuming all fruit juices 24 hours before and after administration of each dose of study compound on PK sampling days. Participants were also required to abstain from alcohol from 7 days before the screening visit and each follow-up visit, and from 7 days before blood sampling and until the last PK blood sample had been collected. At all other times, alcohol consumption was limited to no more than approximately two standard drinks per day. Participants also refrained from consuming caffeinated beverages from 24 hours before the screening visit and each follow-up visit, and from 24 hours before and until after the last PK blood sample had been collected. At all other times, caffeinated beverages or xanthine-containing products were limited to amounts of no more than 6 units per day (one unit contains 120 mg of caffeine).

Concomitant medications were not permitted during the study except for the occasional use of paracetamol (approximately $< 1 \text{ g}$ per day).

Blood samples for PK analysis were collected pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 8, 12, 24, 36, 48 and 72 hours post-dose in the SRD TAK-418/120/160 mg cohort, and pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 8 and 24 hours post-dose on Day 1 in the MRD TAK-418 20 mg, 60 mg, 160 mg non-Japanese, and 20 mg Japanese cohorts. Additional pre-dose samples for PK analysis were collected on Days 3 and 7 in the MRD study, and a similar sampling regimen to that of Day 1 was performed on Day 10, with additional sampling at 36 and 48 hours post-dose. Urine samples were collected pre-dose and at 0–6, 6–12 and 12–24 hours post-dose on Days 1 and 10 in the MRD cohorts. In the SRD cohort, blood samples were also collected pre-dose and at 4, 24, 72, 144 and 288 hours post-dose to evaluate F-FAD. Blood samples were also taken pre-dose and at 4, 12 and 24 hours post-dose on Day 1, pre-dose and at 4, 12, 24 and 48 hours on Day 10, and pre-dose on Day 7 for PD (F-FAD) analysis in PBMCs in all MRD cohorts. Cerebrospinal fluid (CSF) samples were collected from participants in the TAK-418 60 mg cohort pre-dose and at 1, 2, 4, 8, 12, 24, 36 and 48 hours post-dose on Day 10 using an indwelling spinal catheter inserted into the lower spinal canal by trained personnel at the clinical site per their standard operating procedure. All participants were followed up until day 60 (± 2 days) in the SRD cohort and day 70 (± 2 days) in all MRD cohorts.

Plasma, urine and CSF concentrations of TAK-418 were measured by validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods. The methods were validated successfully with respect to linearity, sensitivity, accuracy, precision, dilution, selectivity, haemolysed plasma (plasma only), lipemic plasma (plasma only), batch size, recovery, matrix effect, carryover and stability. TAK-418 in plasma, urine and CSF was isolated through protein precipitation extraction and analysed using reversed-phase ultra-performance liquid chromatographic (UPLC) with Turbo Ion Spray[®] MS/MS detection. The calibration range was $0.5\text{--}1000 \text{ ng mL}^{-1}$,

$1\text{--}2000 \text{ ng mL}^{-1}$ and $0.25\text{--}400 \text{ ng mL}^{-1}$ for TAK-418 in plasma, urine and CSF, respectively.

2.3 | Analyses

Safety was the primary endpoint in both studies, and data collected for evaluation included adverse events (AEs), findings from physical and neurological examinations, vital signs, clinical laboratory test results (with values flagged if they exceeded predefined thresholds), pregnancy monitoring and 12-lead electrocardiogram readings. A treatment-emergent AE (TEAE) was defined as an AE that occurred on or after the first dose of study compound and no more than 30 days after the last dose of study compound.

Secondary endpoints included plasma PK parameters C_{\max} and time to C_{\max} (t_{\max} ; all cohorts), AUC from time 0 to infinity ($AUC_{0\text{--}\infty}$; SRD cohorts), $AUC_{0\text{--}24}$ on Days 1 and 10 (MRD cohorts) and the effect of food on PK (Study 1001 TAK-418 30 mg cohort). The free base of TAK-418 (referred to henceforth as TAK-418F) was measured by liquid chromatography with tandem mass spectrometry, with lower limits of quantification of 0.5, 1 and 0.25 ng mL^{-1} for plasma, urine and CSF, respectively. CSF PK parameters at steady state in the TAK-418 30 mg cohort of Study 1003 were exploratory endpoints.

Changes in AUC and C_{\max} were considered to be dose-proportional if the bounds of the 90% confidence interval (CI) for proportionality were within the ranges 0.91–1.09 and 0.89–1.11 in Studies 1001 and 1003, respectively. For non-Japanese MRD cohorts (TAK-418 20 mg, 60 mg, and 160 mg), dose proportionality for C_{\max} and AUCs was tested using a power model. The power fit will be assumed as described by the following equation:

$$\ln(\text{PK Parameter}) = \beta_0 + \beta_1 \ln(\text{Dose}) + \varepsilon,$$

where β_0 is the intercept and β_1 is the slope with random error ε . Dose proportionality will be declared if the 90% CI for β_1 lies entirely within the critical region

$$\left(1 + \frac{\ln(0.80)}{\ln(r)}, 1 + \frac{\ln(1.25)}{\ln(r)} \right),$$

where r is the ratio of the highest and the lowest dose in the study.¹¹

PK parameters for TAK-418F were derived using noncompartmental analysis methods and determined from concentration–time data for all evaluable participants using Phoenix[®] WinNonlin[®] software version 6.3 (Certara, Princeton, NJ, USA). Actual sampling times were used in all plasma and CSF PK computations, while nominal time intervals were used for urine PK parameters. All measurements of concentrations below the lower limit of quantification were treated as zero.

The biomarker F-FAD concentration was evaluated in PBMCs to confirm peripheral pharmacodynamic activity of TAK-418 in a clinical setting. However, there is no known mechanistic link between F-FAD concentrations and efficacy, and thus F-FAD levels were not used for dose selection in further studies.

2.4 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.¹²

3 | RESULTS

3.1 | Participant disposition and baseline characteristics

In total, 40 participants were enrolled across five cohorts in Study 1001, which was initiated on 21 July 2017 and completed on 12 May 2018 (Figure S1A). One participant in the TAK-418 30 mg cohort discontinued study compound prematurely after testing positive for alcohol at the second admission (i.e., fed portion of the study) and one participant in the TAK-418 40 mg cohort who received placebo completed treatment but was lost to follow-up after Day 93. Participants

were predominantly male (80%) and had a mean age of 36.5 years; 55% were white (Table 1). No participants reported previous medication use.

Study 1003 was initiated on 30 May 2018 and enrolled 32 women across five cohorts before being prematurely terminated on 15 February 2019 as a result of a business decision (no human safety concern; evaluation of preclinical toxicology finding) (Figure S1B). All participants completed the study. The SRD TAK-418 120/160 mg cohort had a mean age of 38.0 years and 50% were white. MRD cohorts had a mean age of 45.2 years and most (75%) were white (Table 1).

3.2 | Safety

3.2.1 | Study 1001

Four participants (40%) receiving placebo and 13 participants (43%) receiving TAK-418 while fasting reported TEAEs. All TEAEs identified following a single dose of TAK-418 up to 60 mg were mild in severity

TABLE 1 Demographic and baseline clinical characteristics

Characteristic	Study 1001 (n = 40)	Study 1003	
		SRD cohort (n = 8)	MRD cohort (n = 24)
Age, years, mean (SD)	36.5 (9.43)	38.0 (10.94)	45.2 (10.08)
Sex, n (%)			
Men	32 (80)	–	–
Women	8 (20)	8 (100)	24 (100)
Race, n (%)			
White	22 (55)	4 (50)	18 (75)
Black or African-American	9 (23)	4 (50)	2 (8)
Asian	6 (15)	–	4 (17)
American Indian or Alaskan Native	1 (3)	–	–
Native Hawaiian or Pacific Islander	1 (3)	–	–
Multiple	1 (3)	–	–
Ethnicity, n (%)			
Hispanic or Latino	7 (18)	1 (13)	3 (13)
Not Hispanic or Latino	33 (83)	7 (88)	21 (88)
Weight, kg, mean (SD)	79.8 (11.0)	68.3 (7.6)	67.7 (10.1)
Height, cm, mean (SD)	174 (7.89)	165 (6.78)	164 (7.79)
BMI, kg m ⁻² , mean (SD)	26.32 (2.864)	25.03 (3.062)	25.20 (2.741)
Smoking status, n (%)			
Never smoker	35 (88)	NR	NR
Former smoker	5 (13)	NR	NR
Alcohol consumption, n (%)			
Never drinker	31 (77)	NR	NR
Current drinker	9 (23)	NR	NR
Current caffeine consumption, n (%)	28 (70)	NR	NR

BMI, body mass index; MRD, multiple rising dose; NR, not reported; SD, standard deviation; SRD, single rising dose.

and no participants discontinued involvement in the study because of a TEAE. The most common TEAE was upper respiratory tract infection ($n = 3$; 10%). Nausea was the most common TAK-418-related TEAE, reported in one participant administered TAK-418 15 mg and another administered TAK-418 40 mg.

There were no clinically relevant changes in semen parameters or serum hormone levels in the 23 male participants, but two men given TAK-418 reported testicular pain. One case of testicular pain (with TAK-418 15 mg) lasting 4 weeks was believed by the investigator to be unrelated to the study drug, while the second case (TAK-418 40 mg) lasting 31 weeks was considered study-drug related. Results of clinical examinations, including testicular examinations, were normal in both cases.

No clinically significant changes in laboratory test results, vital signs or electrocardiogram readings were observed, and no serious AEs (SAEs), suicidal ideation/behaviour or deaths were reported.

3.2.2 | Study 1003

In the SRD TAK-418 120/160 mg cohort, one participant (50%) receiving placebo and four participants (50%) receiving TAK-418 (120 or 160 mg) experienced TEAEs. In the TAK-418 SRD group, the TEAEs were mild in three women (38%) and moderate in one woman (13%). The most common TEAEs in individuals receiving TAK-418 were dizziness and headache ($n = 2$ each; 25%). Two participants had TEAEs considered to be related to treatment, which were mild in intensity.

In the TAK-418 20 mg, 60 mg, 160 mg non-Japanese, and 20 mg Japanese MRD cohorts, three participants (60%) receiving placebo

and 15 participants (83%) receiving TAK-418 (20, 60 or 160 mg q.d.) experienced TEAEs (Table 2). In the TAK-418 groups, the TEAEs were mild in nine participants (50%), moderate in five participants (28%; headache in three participants, TAK-418 60 mg; gastrointestinal disorder and nausea in two participants each, TAK-418 60 mg) and severe in one participant (6%; headache, TAK-418 60 mg). Twelve participants (67%) given TAK-418 had TEAEs considered to be treatment related, all of which were mild in intensity. TEAEs reported by at least three participants included headache ($n = 9$; 50%), nausea ($n = 4$; 22%), diarrhoea, dry mouth, vomiting, decreased appetite and somnolence ($n = 3$ each; 17%). Headache in five individuals (28%) and dry mouth in three individuals (17%) were considered to be treatment related. Procedural complications were experienced by three participants (injury, poisoning and procedural complications) receiving TAK-418 20, 60 or 160 mg. Procedural headache was experienced by one participant in the TAK-418 60 mg cohort, and arthropod bite was reported by two participants (one participant each for those given TAK-418 20 mg and TAK-418 60 mg). A higher number of non-Japanese participants (83%; TAK-418 20 mg, 60 mg, and 160 mg non-Japanese cohorts) than Japanese participants (33.3%; TAK-418 20 mg Japanese cohort) experienced TEAEs with TAK-418 20 mg.

No notably abnormal laboratory test parameters were documented in the MRD cohorts; in the TAK-418 120/160 mg SRD cohort, an increase in gamma glutamyl transferase level to more than three times the upper limit of normal (reaching 315 U/L) was recorded on Day 30 for one participant (13%) receiving TAK-418 160 mg, which gradually decreased up to the Day 60 follow-up (U/L). Overall, abnormalities in laboratory test parameters, vital signs and electrocardiogram findings were sporadic and not considered clinically

TABLE 2 TEAEs reported in more than one participant after multiple doses of TAK-418 (Study 1003)

Preferred term	Number (%) of participants						
	Non-Japanese participants				Japanese participants		
	Placebo ($n = 5$)	TAK-418 20 mg ($n = 6$)	TAK-418 60 mg ($n = 6$)	TAK-418 160 mg ($n = 3$)	Placebo ($n = 1$)	TAK-418 20 mg ($n = 3$)	TAK-418 all participants ($n = 18$)
Participants with any TEAE	3 (60.0)	5 (83.3)	6 (100.0)	3 (100.0)	1 (100.0)	1 (33.3)	15 (83.3)
Headache	1 (20.0)	4 (66.7)	5 (83.3)	0	1 (100.0)	0	9 (50.0)
Nausea	0	0	4 (66.7)	0	0	0	4 (22.2)
Decreased appetite	0	2 (33.3)	1 (16.7)	0	0	0	3 (16.7)
Diarrhoea	0	0	1 (16.7)	2 (66.7)	0	0	3 (16.7)
Dry mouth	1 (20.0)	0	1 (16.7)	2 (66.7)	0	0	3 (16.7)
Somnolence	1 (20.0)	2 (33.3)	1 (16.7)	0	0	0	3 (16.7)
Vomiting	0	0	3 (50.0)	0	0	0	3 (16.7)
Arthropod bite	0	1 (16.7)	1 (16.7)	0	0	0	2 (11.1)
Constipation	0	0	2 (33.3)	0	0	0	2 (11.1)
Dizziness	0	1 (16.7)	1 (16.7)	0	0	0	2 (11.1)
Myalgia	0	0	2 (33.3)	0	0	0	2 (11.1)

TEAE, treatment-emergent adverse event.

meaningful. No participants discontinued involvement in the study because of a TEAE, and no SAEs, suicidal ideation/behaviour or deaths were reported.

3.3 | PK properties following a single dose of TAK-418 (study 1001 and study 1003)

The mean plasma TAK-418F concentration over time profiles following single doses of TAK-418 are presented in Figure S2. Near dose-proportional increases in C_{\max} were found for TAK-418F at doses ranging from 5 mg to 60 mg in Study 1001 (slope, 1.06; 90% CI, 0.96–1.17) and from 20 mg to 160 mg in Study 1003 (slope, 1.02; 90% CI, 0.85–1.19). The TAK-418F C_{\max} following a high-fat meal was 58.0% (90% CI, 43.1–78.1%) of the C_{\max} observed in a fasting state (Table S2, Figure S3).

TAK-418F also produced near dose-proportional increases in AUC_{0-24} at doses ranging from 5 mg to 60 mg in Study 1001 (slope, 1.11; 90% CI, 1.01–1.22), and from 20 mg to 160 mg in Study 1003 (slope, 0.98; 90% CI, 0.84–1.12). Likewise, the TAK-418F $AUC_{0-\infty}$ increased near proportionally at doses ranging from 5 mg to 60 mg in Study 1001 (slope, 1.11; 90% CI, 1.00–1.22). The TAK-418F $AUC_{0-\infty}$ was 4.9% lower with a high-fat meal than in a fasted state (90% CI of the ratio of the least-square geometric means, 82.5–109.7), indicating equivalence and no effect of a high-fat meal (Figure S3).

Renal excretion of TAK-418F was moderate, with 13.3–19.5% recovered unchanged from urine after 20–160 mg dosing, and renal clearance was consistent across this dose range (5.81–8.68 L h⁻¹) (Tables 3 and 4). The amount of TAK-418 urinary excretion was similar for participants administered study drug in a fasted and fed state (Table S2).

3.4 | PK properties following multiple doses of TAK-418

At steady state (Day 10), the median t_{\max} after TAK-418 20–160 mg administration (1.00–1.26 h) was similar to the t_{\max} observed following a single dose, and C_{\max} was slightly to moderately higher on Day 10 than on Day 1 (accumulation ratio based on C_{\max} , 1.06–1.40) (Table 4; Figure 1). At steady state, the TAK-418F C_{\max} increased slightly less than dose-proportionally (slope, 0.87; 90% CI, 0.74–1.00), with the point estimate being slightly below the lower bound of the acceptance criteria for proportionality.

The AUC_{0-24} for TAK-418 was slightly to moderately higher on Day 10 than on Day 1 (accumulation ratio based on AUC_{0-24} , 1.08–1.33). PK linearity was evaluated and the point estimates for plasma AUC were 1.29, 1.13 and 1.06 for 20, 60 and 160 mg doses, respectively, when comparing Day 10 AUC_{0-24} with Day 1 $AUC_{0-\infty}$. At steady state, TAK-418F AUC_{0-24} increased slightly less than dose-proportionally over the 20–160 mg range (slope, 0.88; 90% CI, 0.73–1.03), with the point estimate being slightly below the lower bound of the acceptance criteria for proportionality.

At steady state, the mean TAK-418F terminal disposition phase half-life ($t_{1/2}$) was short (4.35–5.36 h) and the mean apparent clearance at steady state after extravascular administration (CL_{ss}/F) and apparent volume of distribution during the terminal disposition phase after extravascular administration (V_z/F) were 29.73–39.50 L h⁻¹ and 185.0–305.7 L, respectively. The renal excretion (15.45–20.06%) and clearance (5.12–7.81 L h⁻¹) of TAK-418F after multiple dosing (20–160 mg) were consistent with those observed after single dosing (Table 4).

Japanese participants had a 1.82-fold higher C_{\max} and 1.21-fold higher AUC_{0-24} than non-Japanese participants on Day 1. At steady state on Day 10, these differences were smaller, with C_{\max} being only 1.45-fold higher and AUC_{0-24} being approximately the same in Japanese compared with non-Japanese participants (Table 4).

3.5 | PK properties in CSF following multiple doses of TAK-418

Mean (standard deviation [SD]) CSF TAK-418F concentrations over time following multiple doses of TAK-418 60 mg at Day 10 are presented in Figure 2. TAK-418F absorption and brain penetration, as assessed by CSF concentration, following multiple oral doses was rapid (median t_{\max} in CSF, 1.82 h post-dose; range, 1.75–3.75 h), with a mean C_{\max} of 85.20 ng mL⁻¹ (percentage coefficient of variation [CV%], 24.7) and mean AUC_{0-24} of 611.0 h*ng mL⁻¹ (CV%, 26.5). TAK-418F geometric mean CSF/plasma ratios for C_{\max} and AUC_{0-24} were 0.26 (geometric CV%, 19.2) and 0.33 (geometric CV%, 16.4), respectively.

3.6 | Pharmacodynamic analysis: F-FAD

A dose-dependent increase in F-FAD area under the effect curve (AUEC) and C_{\max} was generally observed in participants receiving TAK-418 in Study 1001 and Study 1003 (Table 5; Figure S4). In Study 1003 (TAK-418 20 mg, 60 mg and 160 mg non-Japanese MRD cohorts), the F-FAD $AUEC_{0-24}$ on Day 10 at steady state increased with rising TAK-418 dose and exposure (Figure 3; Figure S5).

4 | DISCUSSION

Daily dosing with TAK-418 up to 160 mg had a favourable safety profile, was well tolerated and was not associated with dose-limiting toxicities. No study discontinuations, SAEs or clinically relevant changes in vital signs were observed.

Until recently, development of LSD1 inhibitors has focused on the treatment of haematological and solid malignancies because these compounds restrict haematopoietic progenitor proliferation, underpinning their efficacy in acute myeloid leukaemia therapy.¹³ However, treatment with an LSD1 inhibitor has been accompanied by thrombocytopenia,^{14,15} most likely caused by disruption of the

TABLE 3 PK properties of TAK-418 free base in plasma and urine after single doses of TAK-418

		Plasma PK parameter						
		Median (range)		Mean (CV%)				
TAK-418 dose, mg	n	t _{max} , h	C _{max} , ng mL ⁻¹	AUC ₀₋₂₄ , h*ng mL ⁻¹	AUC _{0-∞} , h*ng mL ⁻¹	t _{1/2} , h	CL/F, L h ⁻¹	V _z /F, L
Study 1001								
5	6	1.00 (0.98–1.02)	22.67 (35.3)	89.3 (41.1)	92.2 (43.3)	3.133 (14.8)	64.0 (44.8)	274.5 (30.0)
15	6	1.00 (1.00–2.00)	63.50 (22.2)	295.8 (21.5)	302.2 (21.8)	4.375 (9.0)	51.7 (22.0)	324.0 (21.1)
30 ^a	6	1.00 (0.50–1.00)	166.33 (18.2)	646.3 (7.9)	661.3 (7.9)	4.772 (11.0)	45.6 (8.1)	313.5 (11.7)
40	6	1.25 (1.00–1.52)	162.23 (30.5)	690.2 (24.0)	700.0 (24.5)	3.868 (12.7)	60.6 (29.2)	333.3 (25.1)
60	6	1.00 (1.00–1.00)	324.17 (13.9)	1553.5 (29.4)	1584.3 (29.9)	4.220 (14.9)	41.3 (34.3)	243.0 (21.3)
Study 1003 SRD cohort^a								
120	6	1.50 (1.00–1.50)	727.8 (20.0)	3737.2 (19.9)	3828.3 (20.6)	5.188 (9.9)	32.47 (20.2)	240.2 (14.5)
160	6	1.25 (1.00–2.00)	796.3 (36.2)	4350.0 (31.0)	4466.8 (31.7)	4.847 (14.1)	40.62 (46.7)	276.7 (41.3)
		Urine PK parameter, mean (CV%)		f _{e,t} , %		CL _R , L h ⁻¹		
		Ae _b , mg						
Study 1001								
30 ^a	6	5.708 (13.0)	19.022 (13.0)	13.335 (18.8)	19.022 (13.0)	8.683 (16.3)	8.173 (38.1)	7.242 (13.4)
40	6	5.333 (18.8)	13.335 (18.8)	19.472 (35.2)	13.335 (18.8)	8.173 (38.1)	8.173 (38.1)	7.242 (13.4)
60	6	11.677 (35.2)	19.472 (35.2)		19.472 (35.2)	7.242 (13.4)	7.242 (13.4)	

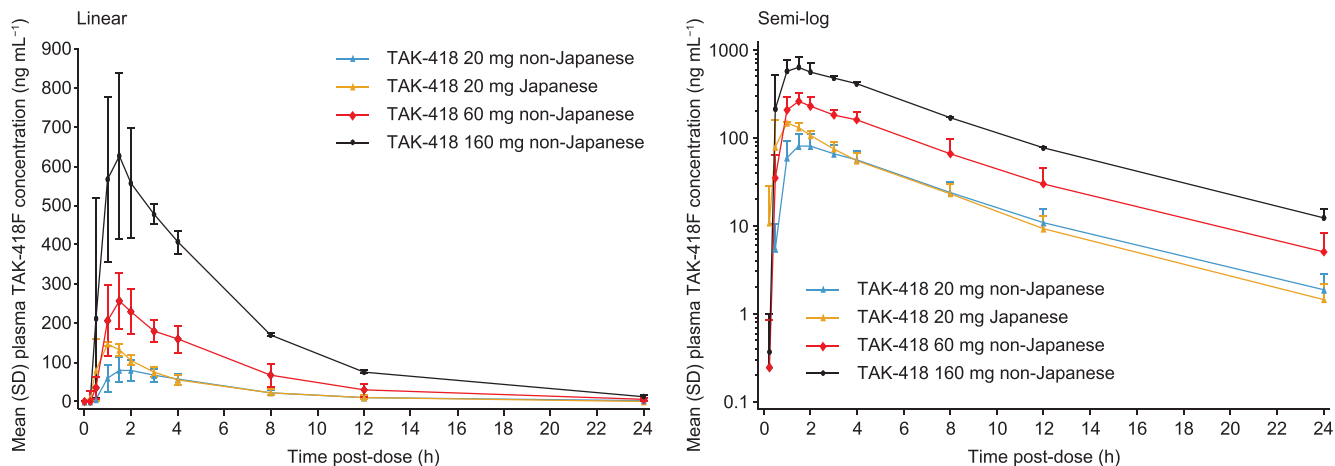
Ae_b, amount of drug excreted in urine from time 0 to the last collection time; AUC₀₋₂₄, area under the concentration–time curve from time 0 to 24 h; AUC_{0-∞}, area under the concentration–time curve from time 0 to infinity, calculated using the observed value of the last quantifiable concentration; CL/F, apparent clearance after extravascular administration; CL_R, renal clearance; C_{max}, maximum observed concentration; CV%, percentage coefficient of variation; f_{e,t}, fraction of administered dose of drug excreted in urine from time 0 to the last collection time; PK, pharmacokinetic; SRD, single rising dose; t_{max}, time of first occurrence of maximum observed concentration; t_{1/2}, terminal disposition phase half-life; V_z/F, apparent volume of distribution during the terminal disposition phase after extravascular administration. ^aFasted state.

TABLE 4 PK properties of TAK-418 free base in plasma and urine at Days 1 and 10 after multiple doses of TAK-418 (Study 1003)

Plasma PK parameter		Mean (CV%)																
Median (range)		C_{max} , ng mL ⁻¹		AUC_{0-24} , h*ng mL ⁻¹		$AUC_{0-\infty}$, h*ng mL ⁻¹		$t_{1/2}$, h		CL_{ss}/F , L h ⁻¹		V_z/F , L		Rac (C_{max})		Rac (AUC_{24})		
TAK-418 dose, mg	n	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	Day 1	Day 10	
20 (Non-Japanese)	6	1.75 (1.00–3.00)	1.26 (1.00–2.00)	85.2 (33.8)	117.8 (30.1)	503.3 (32.9)	668.2 (34.2)	515.3 (33.4)	4.997 (10.1)	33.00 (34.3)	231.8 (24.5)	1.402 (9.0)	1.325 (10.7)					
20 (Japanese)	3	1.00 (0.50–1.50)	1.00 (1.00–1.50)	154.7 (6.0)	171.3 (6.0)	610.3 (14.4)	677.3 (10.9)	619.0 (14.8)	4.350 (14.4)	29.73 (10.8)	185.0 (7.0)	1.110 (10.6)	1.117 (6.7)					
60 (Non-Japanese)	6	1.50 (1.00–4.00)	1.250 (1.00–3.00)	276.0 (21.6)	307.2 (17.0)	1445.5 (24.4)	1660.5 (25.4)	1476.7 (25.4)	4.923 (17.8)	37.80 (21.4)	262.2 (16.4)	1.144 (20.8)	1.150 (8.5)					
160 (Non-Japanese)	3	1.50 (1.00–3.00)	1.00 (1.00–1.50)	679.3 (28.8)	697.7 (14.7)	3747.3 (6.4)	4058.3 (6.1)	3822.0 (5.7)	5.357 (8.7)	39.50 (6.4)	305.7 (10.7)	1.062 (17.8)	1.083 (1.4)					
Urine PK parameter, mean (CV%)																		
Ae_b , mg		$f_{e,b}$, %		CL_R , L h ⁻¹														
Day 1	Day 10	Day 1	Day 10	Day 1	Day 10													
20 (Non-Japanese)	6	2.858 (25.1)	3.090 (28.4)	14.283 (25.1)	15.453 (28.4)	5.813 (16.4)	5.120 (38.2)											
60 (Non-Japanese)	6	11.423 (28.4)	11.087 (31.1)	19.050 (28.4)	18.475 (31.1)	8.365 (41.5)	6.740 (25.1)											
160 (Non-Japanese)	3	28.500 (11.0)	32.067 (37.3)	17.800 (11.0)	20.060 (37.2)	7.583 (4.9)	7.807 (32.7)											

Ae_b , amount of drug excreted in urine from time 0 to the last collection time; AUC_{0-24} , area under the concentration–time curve from time 0 to 24 h; $AUC_{0-\infty}$, area under the plasma concentration–time curve from time 0 to infinity; CL_R , renal clearance; CL_{ss}/F , apparent clearance at steady state after extravascular administration; C_{max} , maximum observed plasma concentration; %CV, percentage coefficient of variation; $f_{e,b}$, fraction of administered dose of drug excreted in urine from time 0 to the last collection time; PK, pharmacokinetic; $t_{1/2}$, terminal disposition phase half-life; t_{max} , time of first occurrence of C_{max} ; Rac (AUC_{24}), accumulation ratio based on AUC_{0-24} ; Rac (C_{max}), accumulation ratio based on C_{max} ; V_z/F , apparent volume of distribution during the terminal disposition phase after extravascular administration.

(A)



(B)

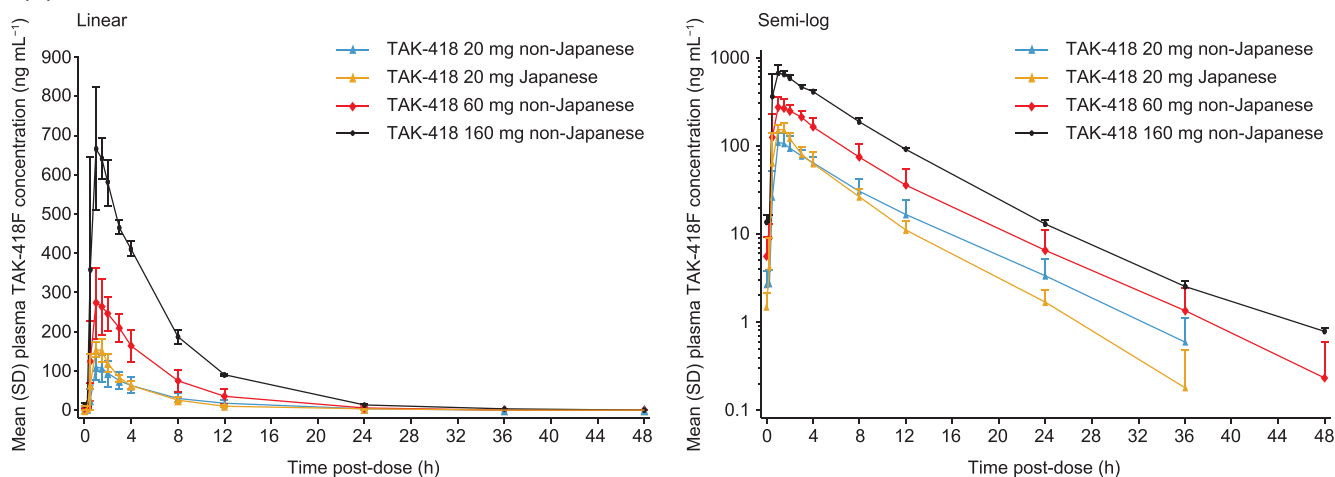


FIGURE 1 Mean (SD) plasma TAK-418F concentration over time following multiple doses of TAK-418 (Study 1003) on (A) Day 1 and (B) Day 10

SD, standard deviation; TAK-418F, TAK-418 free base

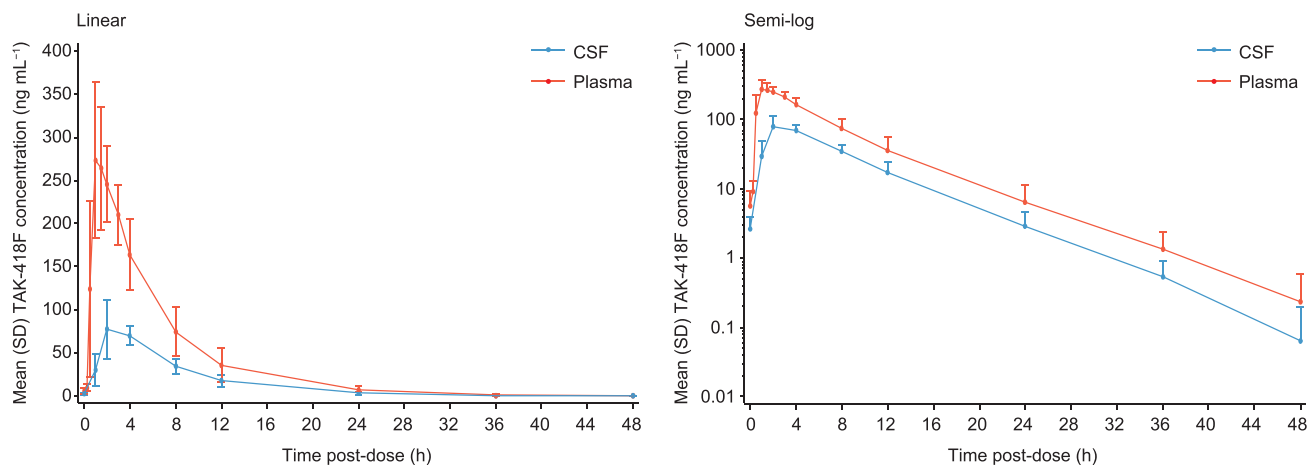


FIGURE 2 Mean (SD) CSF and plasma TAK-418F concentration over time following multiple doses of TAK-418 60 mg on Day 10

Note: $n = 6$ (female participants).

CSF, cerebrospinal fluid; SD, standard deviation; TAK-418F, TAK-418 free base

TABLE 5 Effect of a single dose and multiple doses of TAK-418 on F-FAD levels in peripheral blood mononuclear cells (Study 1001 and Study 1003)

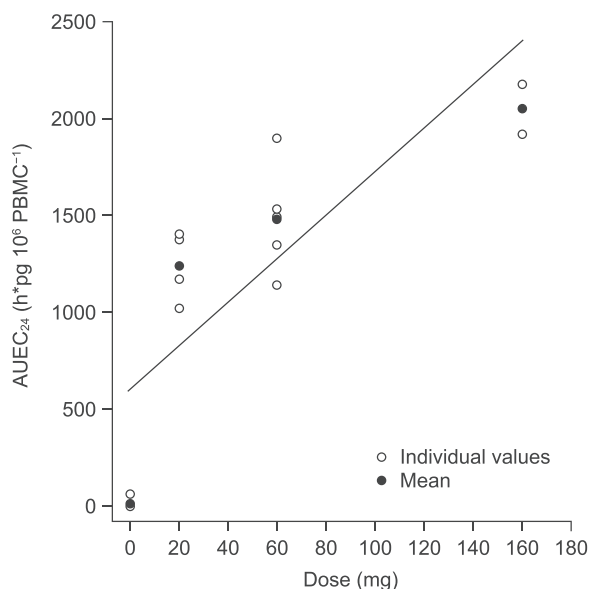
TAK-418 dose, mg	<i>n</i>	F-FAD AUEC ₇₂ (h*pg 10 ⁶ cells ⁻¹), mean (SD)	F-FAD C _{max} (pg 10 ⁶ cells ⁻¹), mean (SD)	F-FAD t _{max} (h), median (min, max)
Study 1001				
5 ^a	6	1666 (420)	52 (9)	24 (24, 48)
15	6	2837 (602)	52 (12)	48 (24, 72)
30	6	3534 (446)	67 (12)	48 (24, 72)
40	6	3062 (936)	56 (20)	24 (24, 72)
60	6	5295 (1243)	111 (22)	48 (48, 72)
Study 1003 – SRD				
120	6	6620 (1813)	132 (40)	72 (24, 72)
160	6	8112 (803)	172 (51)	4 (4, 72)
	<i>n</i>	F-FAD AUEC ₂₄ (h*pg 10 ⁶ cells ⁻¹), mean (SD)	F-FAD C _{max} (pg 10 ⁶ cells ⁻¹), mean (SD)	F-FAD t _{max} (h), median (min, max)
Study 1003 – MRD, Day 10				
20	6	1227 (184) ^b	95 (21)	36 (4, 288)
60	6	1478 (248)	73 (13)	24 (12, 96)
160	2	2043 (185)	127 (16)	24 (24, 24)

Note: Levels of F-FAD in the placebo groups were below the LLOQ (30 pg mL⁻¹).

AUEC, area under the effect curve; C_{max}, maximum observed concentration; F-FAD, formyl flavin adenine dinucleotide; LLOQ, lower limit of quantitation; t_{max}, time to reach C_{max}.

^aOwing to large variability at 72 hours for the 5 mg cohort, only data up to 48 hours are reported here.

^bBased on *n* = 4.

**FIGURE 3** Dose-dependent increase in F-FAD following multiple doses of TAK-418 (Study 1003; non-Japanese participants)

Note: A simple linear regression model was fitted to describe the relationship between AUEC₂₄ on Day 10 and the corresponding dose levels. AUEC₂₄, area under the effect curve at 24 hours; F-FAD, formyl flavin adenine dinucleotide; PBMC, peripheral blood mononuclear cells

association of LSD1 with growth factor-dependent 1B (GF11B), an important modulator of haematopoietic differentiation.¹⁶ Notably, no thrombocytopenia AEs were observed in the current study. This may

be related to differences in the extent of covalent modification of FAD by different LSD1 inhibitors.¹⁶ Some LSD1 inhibitors act by forming bulky FAD adducts, which disrupt the LSD1–GF11B interaction.¹⁵ TAK-418 forms a compact F-FAD adduct that may inhibit H3K4 methylation without disturbing this interaction, which overcomes a significant hurdle for the expanded use of LSD1 inhibitors as therapeutic agents beyond oncology.¹⁶

The PK profile of TAK-418 in healthy volunteers was well characterized in this study. TAK-418 was rapidly absorbed, with a short t_{1/2z} of 3.13–5.36 hours. The results of this study also suggest that TAK-418 displays first-order pharmacokinetics, with clearance not saturated at the doses investigated. Furthermore, there was little change in PK parameters including renal clearance after 10 days of daily TAK-418 administration. Interindividual variation was generally low and while administering TAK-418 with a high-fat meal delayed t_{max} and lowered C_{max}, overall exposure was not affected.

Approximately 20% of TAK-418 was recovered unchanged from urine within 24 hours, while largely being cleared from the circulation. TAK-418 also rapidly reached C_{max} in the CSF, indicating that the compound readily crossed the blood–brain barrier and would be suitable for treating patients with a CNS condition.

Exposure to TAK-418 with rising doses was approximately dose proportional (Study 1001) or slightly less than dose proportional (Study 1003); the difference in findings between these studies may be due to small sample sizes and differences in study populations. During the single dose 1001 Study, results of preliminary toxicology studies

indicated testicular findings in a single species that led to inclusion of female participants only in Study 1003.

Biomarker analyses indicated that TAK-418 had a pharmacodynamic effect. In Study 1003, the F-FAD on Day 10 at steady state increased with rising TAK-418 dose and exposure, and dose-dependent increases in F-FAD AUEC and C_{max} were observed in Study 1001 and Study 1003. These results observed in plasma suggest that target engagement could potentially be achieved at the dosing levels used in this study, while maintaining a favourable safety and tolerability profile.

4.1 | Limitations

The limited sample size and short dosing duration and follow-up in this study limit the generalizability of the results beyond informing dosing for future clinical studies. In addition, participants in Study 1003 were limited to women, preventing assessment of any reproductive AEs in men following daily administration. The biomarker analysis was conducted in plasma samples, and PD have not yet been demonstrated in the CNS.

5 | CONCLUSION

TAK-418 is a well-tolerated LSD1 inhibitor that penetrates the CNS with favourable safety and PK profiles and has a demonstrated pharmacodynamic effect that supports further clinical development.

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COMPETING INTERESTS

All authors are current or former employees of Takeda Pharmaceutical Company Limited and own stocks or stock options.

CONTRIBUTORS

J.R.W., W.Y., S.G., P.K., D.S.H. and L.R. conceived and designed the study. J.R.W., W.Y. and S.G. were responsible for the acquisition of data, which was analysed and interpreted by J.R.W., W.Y., S.G., M.S.Q., D.A., L.R. and M.M.B. The manuscript was drafted by W.Y., P.K., J.L., M.S.Q. and M.M.B. J.R.W., W.Y., L.R. and M.M.B. critically revised the manuscript for important intellectual content. Statistical analysis was carried out by P.K. W.Y., J.H., S.G. and M.S.Q. provided

administrative, technical or logistical support. The study was supervised by D.A., D.S.H., M.M.B. and L.R.

DATA AVAILABILITY STATEMENT

The redacted study protocols and redacted statistical analysis plans are available at ClinicalTrials.gov: NCT03228433, NCT03501069. The individual participant data supporting the results reported in this article will be available 3 months after the submission of a request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

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SUPPORTING INFORMATION

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

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