A first-in-human oral dose study of mesdopetam (IRL790) to assess its safety, tolerability, and pharmacokinetics in healthy male volunteers.

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Abstract

The management of Parkinson's disease (PD) is frequently compromised by complications induced by dopaminergic treatment such as involuntary movements (dyskinesias) and psychosis. Mesdopetam (IRL790) is a novel dopamine D3 receptor antagonist developed for the management of complications of therapy in PD. Aim To evaluate safety, tolerability and pharmacokinetics of escalating single and multiple doses of mesdopetam Method We conducted a prospective, single-centre, randomized, double-blind, placebo-controlled phase I, first in human (FIH) study with mesdopetam administered to healthy male subjects. Results Overall, mesdopetam was well tolerated up to 120 mg single dose and up to 80 mg upon multiple dosing. AEs were mainly related to the nervous system and were dose dependent. No SAEs occurred and no AEs led to withdrawal. The results of the SAD and the MAD parts indicated dose- and time-independent pharmacokinetics with rapid absorption, maximum plasma levels generally reached within 2 hours after dosing. The average terminal half-life of mesdopetam ranged from 6.4 to 7.1 hours in the SAD part, and 6.3 to 7.3 hours in the MAD part. No accumulation was observed upon multiple dosing. Safety findings were unremarkable with no changes demonstrated in vital signs, ECG parameters or physical examination. Mesdopetam produced a dose-dependent increase in plasma prolactin, compatible with target engagement. Conclusion Mesdopetam was safe and well tolerated in healthy male volunteers. Pharmacokinetic analysis indicated rapid absorption and dose-linear pharmacokinetics of mesdopetam, with a plasma half-life around 7 hours, upon single and repeated dosing. The pharmacokinetics of mesdopetam supports twice daily use in patients.

Aim

To evaluate safety, tolerability and pharmacokinetics of escalating single and multiple doses of mesdopetam

Method

We conducted a prospective, single-centre, randomized, double-blind, placebo-controlled phase I, first in human (FIH) study with mesdopetam administered to healthy male subjects.

Results

Overall, mesdopetam was well tolerated up to 120 mg single dose and up to 80 mg upon multiple dosing.

AEs were mainly related to the nervous system and were dose dependent. No SAEs occurred and no AEs led to withdrawal.

The results of the SAD and the MAD parts indicated dose- and time-independent pharmacokinetics with rapid absorption, maximum plasma levels generally reached within 2 hours after dosing. The average terminal half-life of mesdopetam ranged from 6.4 to 7.1 hours in the SAD part, and 6.3 to 7.3 hours in the MAD part. No accumulation was observed upon multiple dosing.

Safety findings were unremarkable with no changes demonstrated in vital signs, ECG parameters or physical examination. Mesdopetam produced a dose-dependent increase in plasma prolactin, compatible with target engagement.

Conclusion

Mesdopetam was safe and well tolerated in healthy male volunteers. Pharmacokinetic analysis indicated rapid absorption and dose-linear pharmacokinetics of mesdopetam, with a plasma half-life around 7 hours, upon single and repeated dosing. The pharmacokinetics of mesdopetam supports twice daily use in patients.

INTRODUCTION

Parkinson's disease is a relatively common neurodegenerative disorder characterized by motor symptoms such as poorness and slowness of movement, tremors and loss of balance. Psychiatric symptoms such as anxiety and depression as well as other non-motor symptoms are also common (*1*). Treatments that restore dopamine deficits in the brain such as levodopa and dopamine agonists have been used since the 1970s to treat the motor symptoms in Parkinson's disease (PD), but are known to after a few years cause adverse effects such as wearing-off, on-off and dyskinesias (*2*). It is estimated that within five years of initiation of standard dopamine replacement therapy in PD, about 50% of patients (and after 10 years almost all patients) develop involuntary movements, so called Levodopa (L-dopa) Induced Dyskinesias (LIDs), in response to their medical treatment (*3*). LIDs are often the key complication limiting further dose increases in dopaminergic therapy.

Psychotic symptoms such as hallucinations and delusions are relatively common in patients with PD, where use of dopaminergic medication and cognitive impairment are the most important underlying factors (*4)* . In a systematic review, the prevalence of hallucinations alone in patients with PD was between 21% and 46% (*5).*

Mesdopetam (formerly IRL790, Mesdopetam x $\frac{1}{2}$ L-Tartrate (N-[2-(3-Fluoro-5-methylsulfonyl-phenoxy)ethyl]propan-1-amine) is a novel dopamine D3 receptor antagonist. In experimental animal models, mesdopetam displays both anti-dyskinetic and antipsychotic properties, while leaving normal behaviour largely unaffected, indicating a novel pharmacological profile with potential to alleviate several troubling complications of therapy commonly seen in the management of PD (6).

Mesdopetam is metabolized to two main metabolites in man; the dealkylated M1 (IRL902) via CYP450, which is further acetylated by N-acetyltransferase 2 (NAT2) to M2 (IRL872). Both metabolites are present in plasma and urine.

The objectives of this first-in-human study were to assess the safety, tolerability and pharmacokinetics of mesdopetam in healthy male volunteers after single and multiple oral dosing, including food effect on the pharmacokinetics after single dosing.

MATERIALS AND METHODS

Study design. This was a single-centre, double-blind, randomized, placebo-controlled trial conducted between 23 November 2015 and 8 June 2016 at the CTC Clinical Trial Consultants Phase I unit in Uppsala, Sweden. Study code IRL790C001, EudraCT No 2015-003586-29.

The study comprised two parts.

Part 1 was designed as a partial cross-over single-ascending-dose (SAD) study with ascending dose levels of mesdopetam and one food interaction cohort. Sixteen (16) subjects were included in one of two cohorts, eight subjects in each cohort (six active treatment and two placebo), and the cohorts were dosed in a zig-zag manner (5 mg-40 mg-160 mg and 15 mg-80 mg-food/80 mg) with a wash-out period of at least one week between doses. Following a screening period of maximum 28 days, subjects were confined to the research clinic from the evening before each dosing (Day -1) until 24 hours post dose (Days 1-2) (food interaction group subjects until at least eight hours after administration (Day 1)). A follow-up visit was performed 5-10 days after last dose.

Part 2 examined multiple-ascending-dose (MAD) cohorts with study treatment once daily for 10 consecutive days. Twenty-four (24) subjects were included, twelve subjects in each dose cohort (nine on active treatment, three on placebo), and the cohorts were dosed with 40 mg and 80 mg, respectively. Following a screening period of maximum 28 days, subjects were confined to the research clinic from the evening before first dosing (Day -1) and during the four first administration days (Day 1-4). Following a safety and tolerability review before leaving the clinic on Day 4, the subjects visited the clinic daily for administration of doses 5-9 under medical surveillance (Days 5-9). In the evening of Day 9 the subjects were confined to the research clinic again until 24 hours after administration of dose 10 (Days 10-11). A follow-up visit was performed 5-10 days after the last dose.

This study was approved by the Ethics Review Board in Uppsala, Sweden and conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP). All subjects provided written, informed written consent before participating in any study procedures.

Treatments. Mesdopetam was provided as 5 mg, 20 mg and 40 mg (free base) hard gelatine capsules. Placebo was provided formulated as hard gelatine capsules identical in appearance to the mesdopetam capsules.

Subjects. Healthy male subjects 18-50 years of age, weighing at least 50 kg, with a body mass index between 18 and 30 kg/m^2 were eligible for the study. Good health was determined by medical history, physical examination, vital signs, electrocardiogram (ECG), and laboratory tests at screening. Main exclusion criteria included: history of any clinically significant disease which, in the opinion of the Investigator, could either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study; use of any prescribed or non-prescribed medication or herbal supplements within two weeks prior to the first administration of study treatment; administration of another new chemical entity or has participated in any other clinical study that included drug treatment within three months of the first administration of study treatment; regular use of tobacco products, and/or history of drug or alcohol abuse.

Primary objectives and endpoints (safety and tolerability). In both the SAD and MAD part of the study, safety assessments included: frequency, seriousness and intensity of Adverse Events (AEs), physical examination, 12-lead ECGs, Columbia Severity Suicidal Rating Scale (C-SSRS), vital sign measurements, laboratory measurements (clinical chemistry, hematology, and urinalysis). The SAD part also included telemetry. AEs were collected from signing the informed consent form (ICF) until the follow-up assessments. Serious Adverse Events (SAEs) spontaneously reported by a subject to the Investigator after the follow-up assessment, were to be handled in the same manner as SAEs that occurred during the study.

Secondary objectives and endpoints (pharmacokinetic parameters). In the SAD part, blood samples for measurement of plasma concentrations of mesdopetam and its metabolites IRL902 and IRL872 were collected at predetermined time points: pre-dose, 20, 40 minutes, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours after intake of mesdopetam (up to 8 hours only in the food interaction cohort). In the MAD part, blood samples were collected pre-dose, 20, 40 minutes, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours after the first and last dose of mesdopetam. A 48-hour sample was also taken after the first dose, and on Day 4 sampling was done pre-dose, 1, 2 and 3 hours post dose.

Urine was collected for measurement of the concentrations of mesdopetam and its metabolites in the single-dose cohorts (Part 1) at the predetermined interval 0 to 24 hours post dose.

Bioanalytical methods. Plasma samples were analyzed for mesdopetam and the metabolites IRL872 and IRL902 using ultra performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) performed by the National Veterinary Institute, Department of Chemistry, Environment and Feed Hygiene Section of Chemical Analysis, Uppsala, Sweden. A deuterated analogue of each molecule were used as internal standards. The method was validated according to EMA guidelines (7) and the bioanalytical experiments performed in accordance with the OECD Principles of Good Laboratory Practice (GLP). The validated concentration range was 6.00 to 6000 nmol/L for mesdopetam, and 3.00 to 1000 and 1.00 to 1000 nmol/L for IRL872 and IRL902 respectively.

Urine samples were analyzed for mesdopetam by ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) at MetaSafe AB, Sodertalje, Sweden. One analytical run with the samples from dose cohort 80 mg (without food) of the SAD part was done. The samples were diluted 10-fold with 0.1% formic acid and centrifuged before analysis. Calibration samples and quality control samples were prepared in placebo urine and treated as the unknown samples. Deuterated mesdopetam was used as internal standard. The regression coefficient $r^2$for the calibration curve, 2 to 12 μmol/L, was 0.9999. The accuracy of two quality controls of 2.5 and 5 μmol/L mesdopetam was 98 and 102%.

Statistical analysis. No formal sample size calculation was performed for this study and thereby no hypothesis testing. The sample size was considered sufficient to provide adequate information for the study objectives.

The Full Analysis Set (FAS), comprising all subjects who received randomized study treatment and have available data, has been used for the safety and tolerability assessments. Evaluations have been done according to actual treatment regardless of randomization.

The Per Protocol (PP) analysis set comprises data from all randomized subjects who have received study treatment and have evaluable PK parameter data with no major protocol deviations with an impact on the PK data. All protocol violations were presented and discussed at the clean file meeting. The PP set has been used for presentation of PK endpoints.

All statistical calculations were performed using the SAS® program (Version 90.4, SAS Institute Inc., Cary, NC, USA). The statistical analyses include descriptive statistics reflecting the explorative nature of the study.

Pharmacokinetic calculations. The pharmacokinetic parameters were calculated by non-compartmental analysis (NCA) using the software Phoenix WinNonlin® version 6.3 or later (Pharsight Corporation, U.S.A.). Plasma concentration values below the lower limit of quantitation and missing values (e.g. no blood sample collected, or no value obtained at analysis) were excluded from the NCA. Actual time-points for blood sampling were used in the calculations of the individual parameters, while nominal time points were denoted for summary statistics. Dose proportionality of AUC and Cmax was estimated using a non-linear power model. As an estimate of the accumulation ratio (AR) the quotient of the AUC0-24h for the first and the last dose for each subject was calculated.

RESULTS

Subject demographics. A total of 40 subjects (17 subjects in Part 1 and 23 subjects in Part 2) were randomized to the study. All subjects were male Caucasians. One subject in Part 1 discontinued after 5 mg and was replaced for the subsequent dose levels, and one subject in Part 2 withdrew consent before randomization and was not replaced. Subject disposition is shown in Table 1. Subject demographics are shown in Table 2-3. The treatment groups within each study part were comparable with respect to demographic parameters as well as concomitant medication and medical history.

Safety and tolerability. All 40 subjects were included in the safety analysis. There were no SAEs in the study and no AEs led to withdrawal.

The first subject administered a single dose at the highest pre-defined dose level, 160 mg, experienced adverse central nervous system (CNS) symptoms of antidopaminergic character such as disturbance in attention,

dizziness, tremor, restlessness, nervousness and cold sweat. The main symptoms disappeared within seven hours post dose and the subject was fully recovered after one day. Due to these AEs the dose was reduced to 120 mg for the remaining subjects.

All AEs were coded according to MedDRA version 19.0. A detailed account of AEs occurring after first administration of IMP (Treatment Emergent AEs, TEAEs) is presented by SAD cohort (Part 1) in Table 4 and by MAD dose group (Part 2) in Table 5. During single dose escalation (part 1), the AEs most frequently represented were *Infections and infestations* (nasopharyngitis) and*Nervous system disorders* (headache being the most frequently reported event). Increased frequency or intensity of events by dose or by treatment (mesdopetam/placebo) was not seen in any of the AEs represented up to 120 mg mesdopetam. At the 160 mg dose level the only subject treated experienced disturbance in attention, dizziness, tremor, restlessness, nervousness and cold sweat. Disturbance in attention and restlessness was also experienced by one (20.0%) of the subjects given 120 mg mesdopetam.

In the part 2 (MAD) of the study the AEs most frequently represented were *Infections and infestations* (nasopharyngitis), *Nervous system disorders* (somnolence, disturbance in attention, headache and tremor), and *Respiratory, thoracic and mediastinal disorders*(nasal congestion, epistaxis and oropharyngeal pain). All 17 events reported within *Nervous system disorders* occurred after administration of 80 mg mesdopetam. Two subjects (25.0%) reported a total of eight events of somnolence whereof seven were assessed as probably related to the IMP and one as not related. One subject (12.5%) reported seven events of disturbance of attention, all assessed as probably related to IMP.

Any TEAE was experienced at all dose levels in part 1 of the study, including placebo. Of the TEAEs reported, 20/35 (57.1%) were assessed as not related to study treatment and 27/35 (77.1%) were of mild intensity. The one subject exposed to 160 mg mesdopetam experienced AEs of moderate intensity and one mild event, all assessed as probably related to the IMP.

In part 2 of the study, any TEAE was experienced in all dose groups, including placebo. The proportion of subjects experiencing any TEAE at doses 40 mg, 80 mg and placebo was 55.6%, 50.0%, and 16.7%, respectively. The average number of TEAEs reported by subject (m/n) was 1.2 and 5.8 at doses 40 mg, 80 mg and 1.0 for subjects given placebo. Following administration of 80 mg mesdopetam 16/23 events reported (69.6%) were assessed as possibly (2) or probably (14) related to the IMP whereas all events occurred following administration of 40 mg mesdopetam or placebo were assessed as not related. Of the totally 30 TEAEs reported 66.7% were of mild intensity.

There were no remarkable mean changes over time or individual clinically significant abnormal findings with regards to any of the vital signs parameters and no abnormal findings upon physical examination were reported at any of the time-points assessed in the SAD or the MAD part of the study.

Electrocardiogram (Single 12-lead ECG in both part 1 and 2 and ambulatory ECG telemetry in part 1 only) showed no remarkable mean changes over time or individual clinically significant abnormal values with regards to any of the ECG parameters measured.

Safety laboratory parameters showed no remarkable changes in mean values over time for any of the parameters analysed.

Dopamine released from tuberoinfundibular dopamine neurons inhibits prolactin secretion from the anterior pituitary (8). As a biomarker for target engagement plasma prolactin was measured at regular intervals in both Part 1 and Part 2 of the study. Following single dosing, mesdopetam produced a dose-dependent increase in plasma levels of prolactin indicating target engagement. Also, in the MAD part of the study modest, dose dependent elevations of plasma prolactin were seen. Table 6 -7 shows the median plasma prolactin levels by dose and time after administration for the SAD and MAD parts of the study.

Pharmacokinetic assessments

Single dose pharmacokinetics

All available mesdopetam concentration values for all subjects in all dose groups were included in the PK calculations. Following oral single dose administration of mesdopetam the plasma concentration increased rapidly to reach a maximum 0.7 to 3 hours after dosing, with a subsequent log-linear decline (Figure 1). The single dose PK parameter results are presented in Table 8. In brief, for dose levels 5-120 mg fasted, the following ranges were obtained for mesdopetam:

- Mean $t_{1/2}$ from 6.4 +- 1.9 hours to 7.1 +- 1.0 hours with the highest mean value after 80 mg mesdopetam.
- Median t_{max} from 1.0 hour (range 0.7-3.0) to 2.0 hours (range 1.0-4.0) with the highest median value after 15 mg mesdopetam.
- Mean C_{max} from 73.6 +- 18.4 nmol/L to 1940 +- 326 nmol/L with the highest mean value after 120 mg mesdopetam.
- Mean $AUC_{0\text{-}[?]}$ from 786 +- 298 nmol[?]h/L to 17300 +- 4620 nmol[?]/L with the highest mean value after 120 mg mesdopetam.
- Mean CL/F from 23.8 +- 4.3 L/h to 32.5 +- 6.2 L/h with the highest mean value after 80 mg mesdopetam.
- Mean V_z/F from 223 +- 41.7 L to 328 +- 59.0 L with the highest mean value after 80 mg mesdopetam.

For dose levels 5-120 mg, the $t_{1/2}$ of IRL902 ranged from 6.3 +- 0.6 hours to 7.3 +- 1.1 hours and the plasma concentration-time profile was parallel to the profile for the parent compound.

For IRL872, the plasma concentration profiles were markedly different from those of the parent compound with median t_{max}values of 9.0 hours (range 8-24) to 12 hours (range 12-12) and a mean $t_{1/2}$ of more than 20 hours. The estimate of the $t_{1/2}$ is uncertain both due to the short observation period and the flat shape of the plasma profile.

Relative bioavailability after fed and fasting conditions. For the four subjects receiving mesdopetam both under fasting and fed conditions, a small food interaction was observed. The geometric mean ratio (fed/fasted) was 110.7% for $AUC_{0\text{-}8h}$ and 109.0% for C_{max}. Tmax was also delayed after food intake compared to fasting.

For the metabolites IRL902 and IRL872 the geometric mean ratio (fed/fasting) was 82.5% and 84.5% for $AUC_{0\text{-}8h}$ and 95.9% and 117.8% for C_{max}essentially reflecting the results for mesdopetam.

Dose proportionality after single dose. The analysis of dose linearity for AUCt, AUC0-[?], and Cmax showed a linear relationship with a proportionality constant (b) close to 1, indicating dose proportionality for the parent compound mesdopetam and the metabolite IRL902.

For the metabolite IRL872 dose linearity could only be calculated for Cmax. since there were too many likelihood evaluations detected for AUC0-[?] and convergence criteria was not met for AUCt. The analysis of dose linearity for Cmax showed a linear relationship with a proportional constant (b) close to 1, indicating dose proportionality.

Multiple dose pharmacokinetics. Mean plasma concentration-time profiles for mesdopetam after multiple dosing of 40 mg and 80 mg once daily are shown in Figure 2. The individual concentration-time profiles for the first and last dose of 40 mg mesdopetam show rapid absorption for the parent compound with median t_{max} at 2.0 hours (range 0.3-3.0) and 2.0 hours (range 0.7-8.0) and a mean C_{max} of 631 +- 54.0 nmol/L and 567 +- 95.7 nmol/L for the first and last dose, respectively. The $t_{1/2}$ was 6.8 +- 1.3 hours and 7.0 +- 1.4 hours for the first and last dose, respectively. Mean $AUC_{0\text{-}24h}$ after the first dose was 5580 +- 1650 nmol[?]h/L and mean AUC_{ss} was 6000 +- 1970 nmol[?]/L (Table 9).

After the first and last dose of 80 mg mesdopetam a mean C_{max} of 1490 +- 410 nmol/L and 1430 +- 393 nmol/L was reached at a median t_{max} of 0.8 hours (range 0.3-2.0) and 2.0 hours (range 0.4-3.0), respectively. The $t_{1/2}$was 7.1 +- 1.1 hours for the first dose and 7.2 +- 0.6 hours for the last dose. Mean $AUC_{0\text{-}24h}$ after the first dose was 11500 +- 2410 nmol[?]h/L and mean AUC_{ss} was 12200 +- 3150 nmol[?]h/L.

Plasma profiles for the major metabolites are shown in Figure 3. The time course of mesdopetam and IRL902 showed similar $t_{1/2}$with lower concentrations for IRL902. IRL872 showed a longer $t_{1/2}$ as compared to the parent compound and IRL902; 46 +- 43 hours and 40 +- 14 hours after the first and last 40 mg dose and 73 +- 70 hours after the last 80 mg dose. The variations in IRL872 levels between subjects were approximately 10-fold.

Dose proportionality after multiple doses. The proportionality constant for AUC_{ss} and Cmax of mesdopetam, for the last MAD dose, indicated dose proportionality for AUC_{ss} (1.06) and supra proportional increases of Cmax (1.3). The proportionality constants for AUC_{ss} and Cmax of IRL902 for the last MAD dose were AUC_{ss} (1.4) and Cmax (1.5), respectively. For metabolite IRL872 the proportionality constant was below 1 for both AUCss and Cmax indicating a less than dose proportional increase in exposure.

Accumulation ratio (AR) after multiple doses. The mean AR for mesdopetam and IRL902 was close to 1 for both the 40 mg and 80 mg dose level indicating virtually no accumulation from the first to the last dose which is in good agreement with degree of accumulation calculated from the estimated half-lives and the dose interval. IRL872 showed accumulation at both dose levels, around 2-fold, in line with its longer half-life.

Urine excretion

Urine was collected for the 0-24 h post dose interval in the SAD part of the study, and mesdopetam was analyzed in the 80 mg cohort. The average urine recovery of mesdopetam was 27% of the dose (f_e), range 18-47%.

DISCUSSION

Mesdopetam (formerly IRL790) is a novel compound for the treatment of dyskinesia and psychosis in PD. This was a FIH study investigating the safety, tolerability, and pharmacokinetics after single and repeated oral administrations of mesdopetam.

During the initial single dose escalation five escalating doses of IRL790 were tested in 16 male subjects included in two alternating cohorts with eight subjects in each. At each dose level two subjects were given placebo and six subjects were given IRL790, using a partial cross-over design.

The multiple dose escalation included 23 healthy male subjects. IRL790 was administered as once daily doses for 10 consecutive days in doses 40 mg and 80 mg.

Overall, IRL790 was well tolerated up to 120 mg single dose and up to 80 mg multiple dose although an increased frequency of AEs within*Nervous system disorders* assessed as probably related to study treatment was seen after multiple dosing at the higher dose level (80 mg), as compared to 40 mg. No SAEs occurred and no AEs led to withdrawal.

The AEs that occurred in one subject administered a single dose of 160 mg were assessed as being probably related to the study drug as antidopaminergic symptoms, and the dose was reduced to 120 mg for the remaining subjects. These AEs were uncomfortable for the subject, but short-lasting and not serious.

There were no remarkable mean changes over time or individual clinically significant abnormal findings in vital signs, physical examination or ECG parameters at any of the time-points assessed in the SAD or the MAD part of the study. Safety laboratory parameters did not show any significant abnormal changes. A modest, dose dependent increase in s-prolactin was observed after both on the SAD and MAD parts of the study, consistent with target engagement at pituitary dopamine receptors.

Pharmacokinetics

Following single doses of mesdopetam AUCt, AUC0-[?] and Cmax showed a dose-linear relationship indicating dose proportionality for mesdopetam. Urine recovery analysis showed that renal excretion amounted to around 30% of the dose administered, indicating renal excretion of unchanged compound as one of the mayor pathways for the elimination of mesdopetam. The mean $t_{1/2}$ of the parent compound mesdopetam

ranged from 6.4 to 7.1 hours. The plasma concentration-time profile of the metabolite IRL902 was similar to the profile for the parent compound which points to formation rate limited pharmacokinetics while the plasma concentration profiles for metabolite IRL872 were markedly different with a mean $t_{1/2}$ of more than 20 hours indicating elimination rate limited pharmacokinetics for this metabolite. Since both IRL902 and IRL872 are pharmacologically inactive, no untoward pharmacological effects are expected from metabolites formed from mesdopetam.

A small food interaction suggesting slightly higher exposures under fed conditions was observed for mesdopetam. After multiple dose administration the pharmacokinetic profile was similar to single dose pharmacokinetics, with rapid absorption for the parent compound and a $t_{1/2}$ of ˜7 hours. The mean AR for mesdopetam and was close to 1 for both 40 mg and 80 mg dose level indicating virtually no accumulation from the first to the last dose. One possible explanation for the supra-proportional increases of IRL902 levels between the two MAD doses could be capacity limited metabolism to IRL872 (acetylation), which showed little change in exposure between the doses. The significance of the finding is however limited since only two dose levels were studied and was only observed in part 2 of the study. The overall pharmacokinetics of mesdopetam supports twice daily use in patients.

In conclusion, mesdopetam was generally safe and well tolerated in healthy male subjects up to 120 mg single dose and to 80 mg in the MAD part. There were no notable safety findings or indications of a safety risk. Mesdopetam displayed rapid absorption and linear pharmacokinetics with an apparent terminal elimination half-life around 7 hours upon single as well as repeated administration.

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Tables and Figures

Table 1. Subject disposition, SAD part (upper panel) and MAD part (lower panel. In SAD cohort 1, one subject withdrew after the first dose and was replaced for subsequent dosings. In the MAD part, one subject withdrew consent after Visit 5.

		Cohort 1	**Cohort 2**	**Total**
Number of subjects	Screened			23
	Screen Failures			3
	Not Randomized			3
	Randomized	9	8	17
	Randomized and not taken IMP	0	0	0
	Randomized and taken IMP	9 (100%)	8 (100%)	17 (100%)
	Study completion	8 (88.9%)	8 (100%)	16 (94.1%)
	Withdrawn	1 (11.1%)	0	1 (5.9%)
	Replacement subjects	1 (11.1%)	0	1 (5.9%)
Analysis sets	Full analysis set (FAS)	9 (100%)	8 (100%)	17 (100%)
	Per-protocol analysis set (PPAS)	9 (100%)	8 (100%)	17 (100%)

		40 mg	**80 mg**	**Placebo**	**Total**
Number of subjects	Screened				32
	Screen Failures				7
	Not Randomized				2
	Randomized	9	8	6	23
	Randomized and not taken IMP	0	0	0	0
	Randomized and taken IMP	9 (100%)	8 (100%)	6 (100%)	23 (100%)
	Study completion	9 (100%)	7 (87.5%)	6 (100%)	22 (95.7%)
	Withdrawn	0	1 (12.5%)	0	1 (4.3%)
	Replacement subjects	0	0	0	0
Analysis sets	Full analysis set (FAS)	9 (100%)	8 (100%)	6 (100%)	23 (100%)
	Per-protocol analysis set (PPAS)	9 (100%)	8 (100%)	6 (100%)	23 (100%)

Table 2. Demographics and baseline characteristics - SAD (FAS)

		Cohort 1		
(N=9)	**Cohort 2**			
(N=8)	**Total**			
(N=17)				
Age (years)	n/nmiss	9/0	8/0	17/0
	Mean (SD)	27.8 (7.8)	33.3 (11.5)	30.4 (9.8)
	Median (Min, Max)	23.0 (20,39)	30.0 (20,48)	28.0 (20,48)
Gender	Male	9 (100%)	8 (100%)	17 (100%)
Ethnicity	Hispanic or Latino	0	0	0
	Not Hispanic or Latino	9 (100%)	8 (100%)	17 (100%)
	Not Reported	0	0	0
	Unknown	0	0	0
Weight (kg)	n/nmiss	9/0	8/0	17/0
	Mean (SD)	75.60 (11.09)	72.84 (11.48)	74.30 (11.01)
	Median (Min, Max)	70.00 (64.7,96.1)	76.35 (55.3,87.8)	73.20 (55.3,96.1)
Height (cm)	n/nmiss	9/0	8/0	17/0
	Mean (SD)	179.78 (6.91)	175.81 (8.20)	177.91 (7.58)
	Median (Min, Max)	182.00 (171.0,190.0)	172.50 (166.0,189.0)	178.00 (166.0,190.0)
BMI (kg/m^2)	n/nmiss	9/0	8/0	17/0
	Mean (SD)	23.31 (2.34)	23.45 (2.37)	23.38 (2.28)

	Median (Min, Max)	23.29 (20.6,27.8)	24.18 (19.1,25.9)	23.77 (19.1,27.8)	

Table 3. Demographics and baseline characteristics - MAD (FAS)

		40 mg			
(N=9)	**80 mg**				
(N=8)	**Placebo**				
(N=6)	**Total**				
(N=23)					
Age (years)	n/nmiss	9/0	8/0	6/0	23/0
	Mean (SD)	26.4 (3.4)	30.9 (3.6)	28.0 (10.4)	28.4 (6.1)
	Median (Min, Max)	27.0 (22,32)	31.5 (24,36)	24.0 (22,49)	28.0 (22,49)
Gender	Male	9 (100%)	8 (100%)	6 (100%)	23 (100%)
Ethnicity	Hispanic or Latino	0	1 (12.5%)	2 (33.3%)	3 (13.0%)
	Not Hispanic or Latino	9 (100%)	7 (87.5%)	4 (66.7%)	20 (87.0%)
	Not Reported	0	0	0	0
	Unknown	0	0	0	0
Weight (kg)	n/nmiss	9/0	8/0	6/0	23/0
	Mean (SD)	81.81 (8.33)	79.35 (11.57)	77.90 (9.21)	79.93 (9.47)
	Median (Min, Max)	81.40 (72.8,94.2)	77.15 (62.9,97.2)	76.05 (67.3,91.8)	78.00 (62.9,97
Height (cm)	n/nmiss	9/0	8/0	6/0	23/0
	Mean (SD)	183.00 (7.26)	179.94 (4.77)	179.75 (7.06)	181.09 (6.34)
	Median (Min, Max)	184.00 (172.0,198.0)	181.00 (174.0,185.0)	177.25 (173.0,192.0)	183.00 (172.0,
BMI (kg/m^2)	n/nmiss	9/0	8/0	6/0	23/0
	Mean (SD)	24.45 (2.39)	24.54 (3.70)	24.13 (2.67)	24.40 (2.84)
	Median (Min, Max)	24.03 (21.5,29.8)	23.64 (20.3,29.0)	24.76 (19.9,27.9)	24.11 (19.9,29

Table 4. TEAEs by MedDRA SOC and PT for single ascending doses of mesdopetam (FAS). n= number of subjects, m= mentions

	5 mg (N=6) n (%)	**5 mg (N=6) m**	**15 mg (N=6) n (%)**	**15 mg (N=6) m**
Infections and infestations	3 (50.0%)	3	1 (16.7%)	1
Nasopharyngitis	3 (50.0%)	3	1 (16.7%)	1
Nervous system disorders	1 (16.7%)	1	2 (33.3%)	2
Headache	1 (16.7%)	1	2 (33.3%)	2
Disturbance in attention	0	0	0	0
Dizziness	0	0	0	0
Tremor	0	0	0	0
Gastrointestinal disorders	0	0	2 (33.3%)	2
Gastrointestinal hypermotility	0	0	1 (16.7%)	1
Toothache	0	0	0	0
Vomiting	0	0	1 (16.7%)	1
Psychiatric disorders	0	0	0	0
Restlessness	0	0	0	0
Nervousness	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (16.7%)	1	1 (16.7%)	1
Oropharyngeal pain	0	0	1 (16.7%)	1
Cough	0	0	0	0
Epistaxis	1 (16.7%)	1	0	0

Skin and subcutaneous tissue disorders	0	0	1 (16.7%)	1
Cold sweat	0	0	0	0
Eczema	0	0	1 (16.7%)	1
Metabolism and nutrition disorders	0	0	0	0
Decreased appetite	0	0	0	0
Musculoskeletal and connective tissue disorders	0	0	0	0
Back pain	0	0	0	0

Table 5. TEAEs by MedDRA SOC and PT-MAD (FAS)

	40 mg (N=9) n (%)	**40 mg (N=9) m**	**80 mg (N=8) n (%)**	**80 mg m**
Infections and infestations	3 (33.3%)	3	2 (25.0%)	2
Nasopharyngitis	3 (33.3%)	3	2 (25.0%)	2
Respiratory, thoracic and mediastinal disorders	1 (11.1%)	1	3 (37.5%)	3
Nasal congestion	0	0	2 (25.0%)	2
Epistaxis	0	0	1 (12.5%)	1
Oropharyngeal pain	1 (11.1%)	1	0	0
Nervous system disorders	0	0	4 (50.0%)	17
Somnolence	0	0	2 (25.0%)	8
Disturbance in attention	0	0	1 (12.5%)	7
Headache	0	0	1 (12.5%)	1
Tremor	0	0	1 (12.5%)	1
General disorders and administration site conditions	0	0	1 (12.5%)	1
Fatigue	0	0	1 (12.5%)	1
Musculoskeletal and connective tissue disorders	1 (11.1%)	2	0	0
Musculoskeletal pain	1 (11.1%)	1	0	0
Pain in extremity	1 (11.1%)	1	0	0

Table 6. Median plasma levels of prolactin (µg/L) at baseline (predose) and 2, 6, and 12 hours and following single doses of mesdopetam.

	Baseline	**2 hours**	**6 hours**	**12 hours**
Dose				
5 mg	15.0	20.5	8.3	10.0
15 mg	10.9	40.0	15.5	8.7
40 mg	12.5	54.0	23.0	13.5
80 mg	14.0	80.5	29.5	14.5
120 mg	12.5	68.0	29.5	19.5

Table 7. Median plasma levels of prolactin (µg/L) at baseline (predose) and 2 and 12 hours following multiple doses of mesdopetam

Dose/Day	**Baseline**	**2 h**	**12 h**
40 mg/Day 1	13	39	14
40 mg/Day 10	13	40	14
80 mg/Day 1	14	61	15

Dose/Day	Baseline	2 h	12 h
80 mg/Day 10	11	69	7

Table 8. Descriptive statistics for PK parameters of mesdopetam following single oral doses in the SAD part of the study.

Parameter	Statistic	5 mg	15 mg	40 mg	80 mg
	n/nmiss	6/0	6/0	6/0	6/0
$AUC_{0-[?]}$ (nmol[?]h/L)	Mean (SD)	786 (298)	2360 (481)	6280 (1650)	9180 (1510)
	Median (Min, Max)	707 (516, 1280)	2150 (1970, 3120)	6490 (3660, 7960)	9400 (6570, 1
	Geometric mean	743	2330	6070	9060
	Geometric CV (%)	37.2	19.4	30.2	17.9
AUC_{0-t} (nmol[?]h/L)	Mean (SD)	633 (281)	2160 (412)	5760 (1500)	8260 (1230)
	Median (Min, Max)	544 (371, 1120)	1990 (1790, 2840)	5900 (3490, 7350)	8460 (6000, 9
	Geometric mean	588	2130	5580	8170
	Geometric CV (%)	43.2	18.2	29.1	16.4
AUC_{0-8h} (nmol[?]h/L)	Mean (SD)	NC	NC	NC	4900 (685)
	Median (Min, Max)				5070 (3580, 5
	Geometric mean				4850
	Geometric CV (%)				15.6
C_{max} (nmol/L)	Mean (SD)	73.6 (18.4)	227 (33.0)	756 (298)	936 (224)
	Median (Min, Max)	72.3 (51.6, 104)	233 (179, 276)	633 (469, 1240)	905 (678, 133
	Geometric mean	71.8	225	712	916
	Geometric CV (%)	25.0	14.9	38.3	23.2
t_{max} (h)	Median (Min, Max)	1.0 (0.7, 3.0)	2.0 (1.0, 4.0)	1.5 (0.7, 3.0)	1.0 (0.7, 3.0)
$t_{1/2}$ (h)	Mean (SD)	6.4 (1.9)	6.6 (0.9)	6.6 (0.9)	7.1 (1.0)
	Median (Min, Max)	6.3 (4.1, 9.0)	6.8 (5.1, 7.6)	6.5 (5.6, 7.6)	6.7 (6.2, 8.8)
CL/F (L/h)	Mean (SD)	25.7 (8.6)	23.8 (4.3)	24.9 (8.1)	32.5 (6.2)
	Median (Min, Max)	25.8 (14.2, 35.1)	25.4 (17.4, 27.7)	22.4 (18.2, 39.7)	31.0 (26.5, 44
	Geometric mean	24.4	23.4	23.9	32.1
	Geometric CV (%)	37.2	19.4	30.2	17.9
V_z/F (L)	Mean (SD)	225 (58.6)	223 (41.7)	234 (64.3)	328 (59.0)
	Median (Min, Max)	230 (159, 316)	227 (167, 275)	219 (160, 320)	304 (276, 430
	Geometric mean	219	220	226	324
	Geometric CV (%)	26.7	19.4	28.0	17.0

[a] in the 80 mg fed group n/nmiss is 3/3 for the parameters $AUC_{0-[?]}$, $t_{1/2}$, CL/F and V_z/F.

Table 9. Descriptive statistics for PK parameters of mesdopetam on Day 1 and Day 10 of dosing with 40 mg or 80 mg once daily in the MAD part of the study.

Parameter	Treatment Day	Statistic	40 mg	80 mg
		n/nmiss	Day 1 and 10: 9/0	Day 1: 8/0 Day 10: 7/1
AUC_{0-24h} (nmol[?]h/L)	Day 1	Mean (SD)	5580 (1650)	11500 (2410)
		Median (Min, Max)	5990 (3170, 8680)	1160 (8220, 16400)
		Geometric mean	5360	11300
		Geometric CV (%)	31.6	20.3
AUC_{ss} (nmol[?]h/L)	Day 10	Mean (SD)	6000 (1970)	12200 (3150)
		Median (Min, Max)	5920 (3690, 9360)	11900 (8150, 18200)
		Geometric mean	5730	11900

		Geometric CV (%)	32.8	25.2
C_{max} (nmol/L)	Day 1	Mean (SD)	630 (54.0)	1490 (410)
		Median (Min, Max)	630 (559, 729)	1370 (1010, 2220)
		Geometric mean	628	1440
		Geometric CV (%)	8.54	27.1
	Day 10	Mean (SD)	567 (95.7)	1430 (393)
		Median (Min, Max)	600 (438, 736)	1370 (881, 2150)
		Geometric mean	560	1380
		Geometric CV (%)	17.1	28.0
t_{max} (h)	Day 1	Median (Min, Max)	2.0 (0.3, 3.0)	0.8 (0.3, 2.0)
	Day 10	Median (Min, Max)	2.0 (0.7, 8.0)	2.0 (0.4, 3.0)
$t_{1/2}$ (h)	Day 1	Mean (SD)	6.8 (1.3)	7.1 (1.1)
		Median (Min, Max)	6.3 (5.4, 9.4)	6.7 (5.7, 8.7)
	Day 10	Mean (SD)	7.0 (1.4)	7.2 (0.6)
		Median (Min, Max)	6.7 (4.8, 9.5)	7.3 (6.1, 8.0)
CL/F (L/h)	Day 1	Mean (SD)	26.0 (9.44)	23.7 (5.12)
		Median (Min, Max)	22.2 (13.5, 43.5)	23.6 (15.2, 33.3)
		Geometric mean	24.6	23.2
		Geometric CV (%)	36.7	22.5
	Day 10	Mean (SD)	26.5 (8.1)	25.0 (6.1)
		Median (Min, Max)	24.5 (15.5, 39.3)	24.4 (15.9, 35.6)
		Geometric mean	25.4	24.4
		Geometric CV (%)	32.8	25.2
V_z/F (L)	Day 1	Mean (SD)	242 (54.5)	239 (43.0)
		Median (Min, Max)	222 (183, 356)	229 (180, 301)
		Geometric mean	237	236
		Geometric CV (%)	20.9	18.2
	Day 10	Mean (SD)	256 (53.3)	258 (63.4)
		Median (Min, Max)	232 (190, 349)	250 (159, 348)
		Geometric mean	251	251
		Geometric CV (%)	20.2	26.5

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