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Data Article

Dataset for Phase I randomized clinical trial for safety and tolerability of GET 73 in single and repeated ascending doses including preliminary pharmacokinetic parameters

Carolina L. Haass-Koffler [a,b,*], Kimberly Goodyear [b], Victoria M. Long [b], Harrison H. Tran [b], Antonella Loche [c], Roberto Cacciaglia [c], Robert M. Swift [a], Lorenzo Leggio [b]

[a] Center for Alcohol and Addiction Studies, Department of Psychiatry and Human Behavior, Brown University, Providence, RI, USA
[b] Center for Alcohol and Addiction Studies, Department of Behavioral and Social Sciences, Brown University, Providence, RI, USA
[c] Laboratorio CT, San Remo, Italy

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ABSTRACT

The data in this article outline the methods used for the administration of GET 73 in the first time-in-human manuscript entitled "Phase I randomized clinical trial for the safety, tolerability and preliminary pharmacokinetics of the mGluR5 negative allosteric modulator GET 73 following single and repeated doses in healthy male volunteers" (Haass-Koffler et al., 2017) [1]. Data sets are provided in two different manners. The first series of tables provided includes procedural information about the experiments conducted. The next series of tables provided includes Pharmacokinetic (PK) parameters for GET 73 and its main metabolite MET 2. This set of data is comprised by two experiments: *Experiment 1* references a single ascending dose administration of GET 73 and *Experiment 2* references a repeated ascending dose administration of GET 73.

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* Corresponding author.
E-mail address: carolina_haass-koffler@brown.edu (C.L. Haass-Koffler).

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Specifications Table

Subject area	Pharmaceutical Sciences
More specific subject area	Phase I randomized clinical trial, first-time-in-humans, dose escalation
Type of data	Table
How data was acquired	Clinical assessments and blood sampling
Data format	Filtered
Experimental factors	The trial was approved by the Medicine and Healthcare products Regulatory Agency (MHRA). Participants ($N = 80$, total across the two experiments) are administered GET 73 either as single escalation dose [10, 30, 100, 300, 450, or 600-mg) or a repeated dose (100, 300, 450, 450-mg (twice a day)] over 14 days
Experimental features	This was a double-blind, placebo-controlled, ascending dose, Phase I randomized clinical trial conducted in healthy male volunteers in two Experiments. The primary aim was to look at the safety and tolerability of GET 73. In addition, preliminary pharmacokinetic data on GET 73 and its main metabolite MET 2 were collected
Data source location	LCG Bioscience, Cambridge, UK
Data accessibility	The data are available in this article

Value of the data

- Data provides safe doses for administration of GET 73.
- Data outlines the procedures tested for safe administration of GET 73 at safe doses in future study groups.
- Pharmacokinetic parameters were collected for GET 73 and MET 2 as reference data to evaluate the bioavailability of GET 73.

1. Data

The dataset presents an outline of the study and pharmacokinetic analytical data for GET 73: (N-[4-(trifluoromethyl)benzyl]-4-methoxybutyramide) (Haass-Koffler et al., 2017) [1]. Pharmacokinetic data for MET 2: (4-oxo-4-{[(4-trifluoromethyl)benzyl]amino}butanoic acid), a main metabolite of GET 73, is also included in the data set. Tables 1–5 present procedural outlines for the Phase I randomized clinical trial. Tables 6–10 provide pharmacokinetic data for GET 73, while Tables 11–14 provide pharmacokinetic data for MET 2.

In Tables 1 and 2, timetables were set for the administration of GET 73 and the collection of data for the safety and tolerability of GET 73 in single and repeated ascending doses in healthy male volunteers.

In Tables 3 and 4, a procedure was documented for both single and repeated ascending doses with the goal of collecting preliminary pharmacokinetic data and monitor the safety of participants.

Table 5 lists laboratory assessments for safety of GET 73 and potential factors that can affect its tolerability. Some tests were also used for inclusion/exclusion criteria (urine tests for drugs of abuse).

Table 6 data shows the extent of exposure of GET 73 plasma concentration in a single ascending dose. C_{max} and $AUC_{0\text{-}t}$ are measures of these factors respectively with t_{max} as a reference to the maximum concentration of GET 73 in the plasma.

Table 1
Experiment 1, single ascending dose schedule.

Phase	Screening	Inpatient period	Study drug administration	Outpatient visit	Follow-up
Days	–21 to –2	–1 to 3	1	3	15

Table 2
Experiment 2, multiple ascending dose schedule.

Phase	Screening	Inpatient period	Study drug administration	Outpatient visits	Residency period	Follow-up
Days	–21 to –2	–1 to 3	1 to 14	5, 7, 9, 11, and 13	13 to 16	28

Table 3
Experiment 1, assessments and procedures.

Phase	Screening		Pre-dose	Dose											Follow-up
Day	-21 to -2	-1			1								2	3	15
Hours				0	0.5	1	1.5	2	4	6	8	12	24	48	
Procedure and/or Data Collection															
Breath alcohol content (BrAC)															
Written informed consent															
Medical history and demographics															
Physical examination															
Vital signs, Electrocardiogram															
Blood and urine analysis															
Virology															
Urine drug screen															
Randomization															
Study drug administration															
Pharmacokinetic sampling															
Previous/concomitant medication															
Adverse events															
Outpatient regimen															
Inpatient regimen															

Time 0-hour: single GET 73 dosing

Table 4
Experiment 2, assessments and procedures.

Phase	Screening		Pre-dose	Dosing																			
Dose	-21 to -2	-1		1									2	3	4	5	6	7	8	9	10	11	12
Hours				0	0.5	1	1.5	2	4	6	8	12[a]	24	48	72	96	120	144	168	192	216	240	264
Procedure																							
Breath alcohol Content (BrAC)																							
Informed consent																							
Medical history and demographics																							
Physical examination																							
Vital signs																							
ECG																							
Blood and urine analysis																							
Virology																							
Urine drug screen																							
Randomization																							
Study drug administration																							
Study drug home administration																							
PK sampling																							
Previous/concomitant medication																							
Adverse events																							
Outpatient regimen																							
Inpatient regimen																							

Time 0 hour: Start GET 73 dosing; [a]Study drug administration at 12 h, applies only for the 450 mg BID dosing regiment

Phase			Pre-dose													
Dose	13	13 (pm)					14[a]						15	16	28	
Hours	288			312	312.5	313	313.5	314	316	318	320	324	336	360		
Procedure																
Breath alcohol Content (BrAC)																
Informed consent																
Medical history and demographics																
Physical examination																
Vital signs																
ECG																
Blood and urine analysis																
Virology																
Urine drug screen																
Randomization																
Study drug administration																
Study drug home administration																
PK sampling																
Previous/concomitant medication																
Adverse events																
Outpatient regimen																
Inpatient regimen																

Time 312 hour: continue, GET 73 dosing; [a]Study drug administration at 12 h, applies only for the 450 mg BID dosing regiment

Table 5
Clinical laboratory assessments.

Clinical chemistry	Haematology
γ Glutamyl Transferase	Haematocrit
Alanine Transaminase	Haemoglobin
Aspartate Transaminase	Mean Corpuscular Haemoglobin
Alkaline Phosphatase	Mean Corpuscular Hemoglobin Concentration
Potassium	Mean Cell Volume
Sodium	Platelet count
Calcium	Red Blood Cell count
Bilirubin – Direct (only if Total Bilirubin was outside the normal range)	Urinalysis
Bilirubin – Total	pH
Albumin	Leukocytes (2)
Protein – Total	Nitrite
White Blood Cell count (1)	Glucose
Creatinine	Ketones
Glucose (fasting)	Protein (2)
Inorganic Phosphate	Blood (2)
Triglycerides	Urine test for drugs of abuse
Cholesterol	Amphetamines
Urea	Ecstasy
Uric Acid	Barbiturates
Serum virology	Benzodiazepines
Hepatitis B Core Antibody	Cannabis
Hepatitis B Surface Antigen	Cocaine
Hepatitis C Virus	Methadone
HIV-I / HIV-2	Opiates

1 White blood cell count included differential white blood cell count. 2 Direct microscopy was performed if the sample was positive for any of these parameters.

Table 6
Experiment 1, GET 73 Pharmacokinetics parameters: C_{max} (ng/mL), $AUC_{0\text{-}t}$ (ng*h/mL) and t_{max} (h) by dose/treatment and day.

Dose GET 73	C_{max} (ng/mL)	$AUC_{0\text{-}t}$ (ng*h/mL)	t_{max} (h)
10-mg	48.35 (27.47–69.23)	60.04 (25.97–94.11)	0.50 (0.5–1.0)
30-mg	309.67 (211.46–407.88)	387.36 (224.72–550.01)	0.50 (0.50–1.02)
100-mg	721.33 (250.65–1192.01)	1246.80 (690.63–1802.98)	0.75 (0.50–1.50)
300-mg	1384.67 (510.79–2258.54)	3624.01 (1451.26–5796.77)	0.75 (0.50–1.50)
450-mg	3891.67 (2442.82–5340.52)	6931.90 (3314.19–10,549.62)	0.50 (0.50–1.00)
600-mg	5015.0 (3061.38–6968.62)	13,338.25 (7495.02–19,181.48)	0.75 (0.50–1.50)

Results reported as *M* and lower to upper 95% (*CI*) and for t_{max} as median (min-max values).

Table 7
Experiment 2, GET 73 Pharmacokinetics parameters: C_{max} (ng/mL) by dose/treatment and day.

Dose GET73	Day 1 - single dose (ng/mL)	Day 14 - repeated doses (ng/mL)
100-mg	368.17 (218.85–517.48)	302.67 (151.32–454.02)
300-mg	2660.33 (1348.94–3971.73)	2075.67 (1016.19–3135.14)
450-mg	3723.33 (2774.58–4672.08)	3161.83 (2089.28–4234.39)
450-mg twice day	3271.67 (2140.81–4402.52)	4055.00 (2587.33–5522.67)

Results reported as *M* and lower to upper 95% (*CI*).

Table 8
Experiment 2, GET 73 Pharmacokinetics parameters: t_{max} (h) by dose/treatment and day.

Dose GET73	Day 1 - single dose (h)	Day 14 - repeated doses (h)
100-mg	1.00 (0.50–1.50)	1.00 (0.50–1.50)
300-mg	0.50 (0.50–1.00)	0.75 (0.50–1.50)
450-mg	1.00 (0.50–1.53)	1.00 (0.50–1.50)
450-mg twice day	0.75 (0.5–2.05)	0.75 (0.50–1.50)

Results reported as *Median* and minimum and maximum.

Table 9
Experiment 2, GET 73 Pharmacokinetics parameters: $AUC_{0\text{-}t}$ (ng*h/mL) by dose/treatment and day.

Dose GET73	Day 1 - single dose (ng*h/mL)	Day 14 - repeated doses (ng*h/mL)	Ratio day 14/day1
100-mg	657.3 (382.67–931.59)	598.75 (369.52–827.98)	0.91
300-mg	6348.74 (2297.78–10,399.70)	5938.89 (2193.79–9684.00)	0.94
450-mg	8541.24 (6244.42–10,838.07)	8102.90 (4724.25–11,481.55)	0.95
450-mg twice day	8639.29 (5811.59–11,467.00)	9704.90 (6053.12–13,356.68)	1.12

Results reported as *M* and lower to upper 95% (*CI*).

Table 10
Experiment 2, GET 73 Pharmacokinetics parameters: C_{min} (ng/mL) by dose/treatment and day.

Dose GET73	Day 1 - single dose (ng/mL)	Day 14 - repeated doses (ng/mL)
100-mg	0 (0–0)	0 (0–0)
300-mg	0.36 (−0.35 to 1.07)	0 (0–0)
450-mg	0.36 (−0.35 to 1.07)	0 (0–0)
450-mg twice day	49.99 (−5.45 to 105.42)	39.36(12.16–66.57)

Results reported as *M* and lower to upper 95% (*CI*).

Table 11
Experiment 2, MET 2 parameters: C_{max} (ng/mL) by dose/treatment and day.

Dose GET73	Day 1 -single dose (ng/mL)	Day 14 - repeated doses (ng/mL)
100-mg	1728.33 (1415.98–2040.68)	1491.33 (1042.06–1940.61)
300-mg	4193.33 (3550.43–4836.23)	4511.67 (3828.91–5194.42)
450-mg	6691.67 (5304.95–8078.38)	6003.33 (5664.54–6342.12)
450-mg twice day	7406.67 (6299.63–8513.71)	8820.00 (7482.47–10,157.53)

Results reported as *M* and lower to upper 95% (*CI*).

Table 7 tests for C_{max} in repeated ascending dose administration with data for Day 1 and Day 14.

For Table 8, t_{max} was collected in reference to when the C_{max} was reached in the repeated ascending dose administration group for both Day 1 and Day 14.

Table 9 measures the $AUC_{0\text{-}t}$ for repeated ascending dose administration experiment. $AUC_{0\text{-}t}$ ratio compares Day 14 to Day 1 levels.

Table 10 shows the C_{min} of GET 73 in the plasma over the repeated ascending dose administration. Data reported for Day 1 and Day 14.

Table 11 goes into data about MET 2, the main metabolite of GET 73. Data reported for Day 1 and Day 14.

Table 12 shows the t_{max} of MET 2 in the repeated ascending dose administration of GET 73.

Table 12
Experiment 2, MET 2 parameters: t_{max} (h) by dose/treatment and day.

Dose GET73	Day 1 - single dose (h)	Day 14 - repeated doses (h)
100-mg	1.00 (0.50–1.50)	1.00 (0.50–1.50)
300-mg	1.00 (0.50–1.50)	1.50 (1.00–2.00)
450-mg	1.25 (1.00–2.00)	1.25 (1.00–1.50)
450-mg twice day	1.25 (1.05–2.05)	1.29 (1.00–1.60)

Results reported as *Median* and minimum and maximum.

Table 13
Experiment 2, MET 2 parameters: $AUC_{0\text{-}t}$ (ng*h/mL) by dose/treatment and day.

Dose GET73	Day 1 - single dose (ng*h/mL)	Day 14 - repeated doses (ng*h/mL)	Ratio day 14/day1
100-mg	3934.30 (3373.35–4495.25)	3790.54 (3086.52 - 4494.56)	0.96
300-mg	15,235.13 (11,392.92–19,077.34)	15,312.29 (11,615.23 - 19,009.35)	1.00
450-mg	21,051.64 (18,233.17–23,870.10)	20,693.28 (19,477.42 - 21,909.14)	0.98
450-mg twice day	30,443.09 (24,553.06–36,333.12)	32,251.41 (26,029.38 - 38,473.43)	1.06

Results reported as *M* and lower to upper 95% (*CI*).

Table 14
Experiment 2, MET 2 Pharmacokinetic parameters: C_{min} (ng/mL) by dose/treatment and day.

Dose GET73	Day 1 - single dose (ng/mL)	Day 14 - repeated doses (ng/mL)
100-mg	0 (0–0)	0 (0–0)
300-mg	0 (0–0)	0 (0 to 0)
450-mg	0 (0–0)	0 (0–0)
450-mg twice day	804.43 (–240.21 to 1849.08)	426.58 (85.56–767.71)

Results reported as *M* and lower to upper 95% (*CI*).

Data reported for Day 1 and Day 14.

Table 13 collects data on the $AUC_{0\text{-}t}$ of MET 2 in the plasma after repeated ascending dose administration of GET 73. Ratio compares Day 14 and Day 1 data are listed as well.

Table 14 measures the C_{min} of MET 2 in the plasma for repeated ascending dose administration of GET 73. Data was collected for Day 14 and Day

2. Experimental design, materials and methods

The method for collection of pharmacokinetic analytical data was validated at Quotient Bioresearch Ltd, UK. The procedures for the development and the validation of the method were based on the United States (US) Food and Drug Administration (FDA) recommendations Guidance for Industry Bioanalytical Method Validation - U.S. Department of Health and Human Services, FDA Center for Drug Evaluation and Research (CDER), Center for Veterinary Medicine (CVM), May 2001, BP.

Blood samples for pharmacokinetic evaluation in plasma were collected into tubes containing lithium heparin prior to dosing and at various time points after dosing up to 48 h for *Experiment 1* and up to 360 h for *Experiment 2*. The plasma samples were obtained from individuals from six single ascending dose groups in *Experiment 1* (10-mg, 30-mg, 100-mg, 300-mg, 450-mg and 600-mg) and four multiple ascending dose groups in *Experiment 2* (100-mg 300-mg, 450-mg and 450-mg twice a day).

Concentrations of GET 73 in human plasma samples were measured by LC–MS/MS after SLE+ (supported liquid extraction) over the calibration range of 2–1000 ng/ml according to the validated method and the relevant SOPs. Concentrations of MET 2 in human plasma samples were measured by LC–MS/MS after protein precipitation and dilution over the calibration range of 20–10,000 ng/ml. All instrument control, data collection, peak area integration and storage were performed using Analyst (versions 1.4.2 and 1.5.1, Applied Biosystems Inc., OA, US). Peak areas were then imported into Watson LIMS (version 7.2 Thermo Fisher Scientific Inc., MA, US) for regression and quantification. The mass spectrometer response (peak area ratio of analyte to internal standard) of each calibration standard was calculated by Watson LIMS and plotted against the nominal (prepared) concentration. A weighted linear regression analysis was used to calculate an equation of the calibration line. Concentrations of GET 73 and MET 2 in the plasma samples were back calculated from the calibration lines.

Values for the following pharmacokinetic parameters were estimated: 1) maximum plasma concentration (C_{max}), 2) the time to reach maximum plasma concentration (t_{max}) and 3) the area under the plasma concentration time curve over the dosing interval ($AUC_{(0\text{-}t)}$). Pharmacokinetic parameters were derived by noncompartmental analysis using WinNonlin (Version 4.1b, Pharshight Corporation, Mountain View, CA, US). Data in this article has not been published elsewhere.

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Transparency document. Supporting information

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Referenfces

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