Title: First-in-human randomized trial to assess safety, tolerability, pharmacokinetics and pharmacodynamics of the KDM1A inhibitor vafidemstat

Short Title: First-in-Human of KDM1A inhibitor vafidemstat

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Online Resource 2

Supplemental Tables

Inclusion criteria
1. Healthy adult males (SAD) and healthy adult male or female subjects (MAD) aged 18 – 45 years (young) or >= 58 years (older adults).
2. Quetelet's index of 19 – 26 (young) or 19 – 30 (elderly) kg/m^2.
3. Normal clinical records and physical examination.
4. Laboratory tests (hematology and biochemistry) within the normal range according to Hospital laboratory reference values or with variations admissible according to the clinical criteria of the *CIM-Sant Pau*.
5. Clinically acceptable temperature, blood pressure and pulse rate in supine and standing position measured after a minimum of 3 minutes of resting (SBP between 100-140 mm Hg/ DBP between 50-90 mm Hg / HR between 50-100 bpm). For the elderly cohort, subjects with stable hypertension controlled for the past three months or subjects with diabetes mellitus II (no insulin users) stable and controlled for the past two months were also eligible.
6. Females must be of non-childbearing potential (i.e., surgically sterile) or have to use contraceptive measures (non-hormonal) such as condom, diaphragm or cervical/vault cap with spermicide until 28 days post-administration. Males should agree to abstain from sexual intercourse with a female partner or agree to use a condom with spermicide, in addition to having their female partner use some contraceptive measures as oral contraceptive drugs, intrauterine hormonal contraception, or cervical caps until 28 days post-administration.
7. Able to understand the nature of the study and comply with all their requirements.
8. Free acceptance to participate in the study and signed informed consent form approved by the CREC.
Exclusion criteria
1. History of alcohol dependence or drug abuse in the last year or > 24 g (women) or 40 g (men) alcohol /day.
2. Heavy consumer of stimulating beverages (> 5 coffees, teas, chocolate or cola drinks/day) and grapefruit juice
3. Background of allergy, idiosyncrasy or hypersensitivity to drugs
4. Intake of any medication 2 weeks prior to study treatment (except paracetamol in short-term symptomatic treatments or, in elderly, treatment of hypertension or diabetes mellitus II) including over-the counter products (food supplements, vitamins, medicinal plants), or enzymatic inductor/inhibitor in 3 months before drug administration.
5. Positive serology for hepatitis B or C, or HIV.
6. Background or clinical evidence of respiratory, renal, hepatic, gastrointestinal, hematological or neurological disease or other chronic diseases.
7. 12 lead ECG obtained at screening with PR ≥ 220 msec, QRS ≥120 msec and QTc ≥ 440 msec for men and ≥450 for women, bradycardia (<50 bpm) or clinically significant minor ST wave changes or any other abnormal changes on the screening ECG that would interfere with measurement of the QT interval.
8. Having undergone major surgery during the previous 6 months.
9. Smokers (refrained from any tobacco usage, including smokeless tobacco, nicotine patches, etc.) from 6 months prior to drug administration.
10. Pregnancy or lactation status (young volunteers in MAD only).
11. Participation in another clinical trial in the 3 months preceding the drug administration.
12. Donation of blood in the 4 weeks preceding the drug administration.
13. Acute illness in the 4 weeks preceding drug administration.
14. Clinically significant abnormal laboratory values (as determined by the PI) at the screening evaluation.
15. Existence of any surgical or medical condition which might interfere with the absorption, distribution, metabolism or excretion of the drug, i.e. impaired renal or hepatic function, chronic symptoms of pronounced constipation or diarrhea or conditions associated with total or partial obstruction of the urinary tract.
16. Positive results of the drugs at screening period or the day before starting treatment period. A minimum list of 6 drugs were screened for: amphetamines, cocaine, ethanol, opiates, cannabinoids and benzodiazepines (positive results may be repeated at the discretion of the PI).

Supplemental Table S1: Eligibility criteria

SAD: Single Ascending Dose, MAD: Multiple Ascending Dose, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, ECG: electrocardiogram, CREC: Clinical Research Ethics Committee, HIV: human immunodeficiency virus, PI: principal investigator.

	Inclusion - 4 weeks	D1																					D2	D3	D4	D5	Follow up (D5-7)
		Baseline	Time (h)																								
			Rx	0.25	0.5	1	1.25	1.5	1.75	2	2.25	2.5	2.75	3	4	5	6	8	10	12	13	16	24	48	72	96	
Informed consent	X																										
Inclusion / Exclusion criteria	X	X																									
Urine drug screening	X	X																									
Clinical History / Course	X	X																									X
Physical examination	X	X																					X				X
Vital signs	X	X				X		X		X		X		X			X			X			X	X	X	X	X
Laboratory tests *platelet and neutrophil count	X	X																					X*	X	X*	X*	X
Serology	X																										
ECG recording	X	X				X				X				X			X			X			X	X	X	X	X
Treatment administration			X																								
Blood sampling (PK)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	
Blood Sampling (Gene Expression)		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	
Blood Sampling (LSD1 target engagement)		X																		X					X		
Blood Sampling (platelet MAO-B activity)		X																		X					X		
AEs (check-list)	(training)	X				X		X		X		X		X			X			X			X	X	X	X	X
VAS	(training)	X				X				X				X			X			X			X	X	X	X	
LSEQ	(training)	X																					X				
AEs / Concomitant Medication																											
In-housing ([-13h] to [+48h])																											

Food intake was not allowed until at least +4 hours post-medication and from then on controlled lunches, dinners and snacks were given at specific time points.

Supplemental Table S2: Programmed interventions in the SAD

SAD: Single Ascending Dose, ECG: electrocardiogram, PK: pharmacokinetics, AEs: adverse events, VAS: visual analogue scale, LSEQ: Leeds Sleep Evaluation Questionnaire

	Inclusion	D1															D2								D3							
		Baseline	Time (h)																													
			Rx	0.5	1	1.5	2	2.5	3	4	5	6	8	10	12	13	24	Rx	26	28	30	34	36	37	48	Rx	50	52	54	58	60	61
Informed consent	X																															
Inclusion / Exclusion criteria	X	X																														
Urine drug screening / pregnancy test	X	X																														
Clinical History / Course	X	X																														
Physical examination	X	X																														
Vital signs	X	X			X	X	X	X	X			X			X		X		X				X		X		X				X	
Laboratory tests *platelet and neutrophil count	X	X															X*								X*							
Serology	X																															
ECG recording	X	X			X		X		X			X			X		X		X				X		X		X				X	
Treatment administration			X															X								X						
Blood sampling (PK)		X		X	X	X	X	X	X	X	X	X	X		X		X								X							
Blood Sampling (Gene Expression)		X		X	X	X	X	X	X	X	X	X	X		X		X								X							
Blood Sampling (LSD1 target engagement)		X													X																	
Blood Sampling (MAO-B activity on platelet)		X													X																	
AEs (check-list)	(training)	X			X	X	X	X	X			X			X		X		X				X		X		X				X	
VAS	(training)	X			X		X		X			X			X		X						X		X						X	
LSEQ	(training)	X															X								X							
WCST		X																														
Sternberg Test		X																														
AEs / Concomitant Medication																																
In-housing from [-13h]																																

Note: Food intake was not allowed until at least +4 hours post-medication and from then on controlled lunches, dinners and snacks were given at specific time points.

	D4								D5																D6	D7	D8	D9	
	72	Rx	74	76	78	82	84	85	96	Rx	97	97	98	98	99	99	100	101	102	104	106	108	109	112	120	144	168	192	Follow-up (D13-15)
Informed consent																													
Inclusion / Exclusion criteria																													
Urine drug screening / pregnancy test																													
Clinical History / Course									X																				X
Physical examination																										X			X
Vital signs	X		X				X		X			X	X	X	X	X			X			X			X	X	X	X	X
Laboratory tests *platelet and neutrophil count	X*								X*																X*	X	X*	X*	X
Serology																													
ECG recording	X		X				X		X			X		X		X			X			X			X	X	X	X	X
Treatment administration		X								X																			
Blood sampling (PK)	X								X		X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	
Blood Sampling (Gene Expression)	X								X		X	X	X	X	X	X	X	X	X	X		X		X	X	X	X	X	
Blood Sampling (LSD1 target engagement)																						X						X	
Blood Sampling (MAO-B activity on platelet)																						X						X	
AEs (check-list)	X		X				X		X			X	X	X	X	X			X			X			X	X	X	X	X
VAS	X						X		X			X		X		X			X			X			X	X	X	X	
LSEQ	X								X																X				
WCST														X															
Sternberg Test														X															
AEs / Concomitant Medication																													
In-housing from [-13h]																													

Supplemental Table S3: Programmed interventions in the MAD

MAD: Multiple Ascending Dose, ECG: electrocardiogram, PK: pharmacokinetics, AEs: adverse events, VAS: visual analogue scale, LSEQ: Leeds Sleep Evaluation Questionnaire

	Inclusion - 4 weeks	D1					D2	D3	D5	
		Baseline	Time (h)							Follow up (D5-7)
			Rx	2	6	12	24	48	96	
Informed consent	X									
Inclusion / Exclusion criteria	X	X								
Urine drug screening	X	X								
Clinical History / Course	X	X						X		X
Physical examination	X	X						X		X
Vital signs	X	X		X	X	X		X		X
Laboratory tests *platelet and neutrophil count	X	X						X		X
Serology	X									
ECG recording	X	X		X	X	X	X	X	X	X
Treatment administration			X							
Blood sampling (PK)		X		X	X	X				
CSF sampling (PK-TE) one timepoint/volunteer		X		X	X	X				
AEs (check-list)	(training)	X		X	X	X	X	X	X	X
VAS	(training)	X		X	X	X	X	X	X	X
LSEQ	(training)	X					X			
AEs / Concomitant Medication										
In-housing ([-13h] to [+48h])										

Food intake was not allowed until at least +4 hours post-medication and from then on controlled lunches, dinners and snacks were given at specific time points.

Supplemental Table S4: Programmed interventions in the CSF Pharmacokinetics Substudy

CSF: Cerebrospinal fluid, ECG: electrocardiogram, PK: pharmacokinetics, TE: target engagement, AEs: adverse events, VAS: visual analogue scale, LSEQ: Leeds Sleep Evaluation Questionnaire

		SAD					MAD						Older adults
		0.2 mg	0.6 mg	1.5 mg	2.5 mg	4.0 mg	0.2 mg	0.6 mg	1 mg*	1.5 mg	2.5 mg	4 mg	2.5 mg
	Age (years)	**27.6 (7.3)**	**25.1 (7.7)**	**29.9 (9.8)**	**25.3 (4.3)**	**24.6 (3.5)**	**29.5 (9.4)**	**30.0 (7.3)**	**29.1 (6.9)**	**29.4 (8.0)**	**31.0 (7.6)**	**27.8 (5.5)**	**63.8 (4.0)**
A	Mean (SD)	25.5 (3.6)	27.2 (7.9)	30.0 (9.4)	24.0 (2.1)	26.0 (2.4)	29.0 (7.4)	31.5 (6.35)	31.0 (6.9)	31.2 (8.5)	30.5 (7.2)	26.0 (5.2)	**63.3 (4.7)**
P	Mean (SD)	34.0 (14.1)	19.0 (0.0)	29.5 (14.9)	29.0 (8.5)	20.5 (3.5)	31.0 (18.38)	25.5 (10.6)	23.3 (1.2)	24.0 (2.8)	32.5 (12.0)	33 (-)	**65 (-)**
	Gender												
	Male (%)	**8 (100)**	**8 (100)**	**8(100)**	**8 (100)**	**8 (100)**	**4 (50)**	**5 (62.5)**	**7 (58.3)**	**4 (50)**	**6 (75)**	**2 (50)**	**3 (75)**
	Female (%)	**-**	**-**	**-**	**-**	**-**	**4 (50)**	**3 (37.5)**	**5 (41.7)**	**4 (50)**	**2 (25)**	**2 (50)**	**1 (25)**
A	Male (%)	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)	3 (50)	5 (83.3)	5 (55.6)	3 (50)	4 (66.6)	1 (33.3)	**2 (66.7)**
A	Female (%)	-	-	-	-	-	3 (50)	1 (16.7)	4 (44.4)	3 (50)	2 (33.3)	2 (66.7)	**1 (33.3)**
P	Male (%)	2 (100)	2 (100)	2 (100)	2 (100)	2 (100)	1 (50)	0 (0)	2 (66.7)	1 (50)	2 (100)	1 (100)	**1 (100)**
P	Female (%)	-	-	-	-	-	1 (50)	2 (100)	1 (33.3)	1 (50)	0 (0)	0 (0)	**0 (0)**
	BMI (kg/m2)	**23.6 (1.7)**	**24.6 (1.6)**	**24.2 (1.7)**	**24.1 (1.5)**	**22.6 (2.1)**	**23.1 (2.3)**	**24.0 (1.1)**	**23.2 (2.0)**	**24.0 (1.6)**	**23.5 (2.0)**	**22.3 (2.2)**	**26.8 (2.4)**
A	Mean (SD)	23.1 (1.6)	24.5 (1.5)	24.0 (2.0)	24.7 (1.1)	23.2 (2.2)	22.9 (2.7)	23.8 (0.9)	23.0 (2.2)	24.0 (1.9)	22.7 (1.7)	21.9 (2.5)	**26.5 (2.8)**
P	Mean (SD)	25.2 (0.6)	25.0 (2.5)	24.9 (0.0)	22.2 (0.0)	21.0 (0.5)	23.5 (0.7)	24.7 (1.6)	23.7 (1.8)	23.9 (0.6)	25.8 (0.3)	23.4 (-)	**27.7 (-)**

A Active treatment
P Placebo
* 8 + 4 substitutions

Supplemental Table S5: Baseline demographics.

SAD: Single Ascending Dose, MAD: Multiple Ascending Dose, SD: standard deviation, BMI: body mass index.

MedDRA AE term	Placebo (n=1)	Dose level III* 5 mg (n=3)
Dry Mouth		1 (7.7)
Asthenia		1 (7.7)
Feeling hot		1 (7.7)
Dizziness postural		1 (7.7)
Headache		1 (7.7)
Dyspepsia		1 (7.7)
Somnolence		1 (7.7)
Apathy		1 (7.7)
Abdominal discomfort		1 (7.7)
Nausea		1 (7.7)
Feeling abnormal		1 (7.7)
Feeling cold		1 (7.7)
Nervousness		1 (7.7)
TOTAL: 13 (100)		13 (100)

Supplemental Table S6: TEAEs related to the study drug in Dose Level III sub-cohort (dosing error)

Number of TEAEs (and percentage of total TEAEs) possibly or probably related to the study drug by preferred term and dose levels / (n= subjects) in a Dose level III sub-cohort that erroneously received 5 capsules of placebo or 1 mg vafidemstat on day 1 instead of one capsule on 5 consecutive days (dosing error). MedDRA: Medical Dictionary for Regulatory Activities, AE: Adverse Event, TEAE: Treatment Emergent Adverse Event.