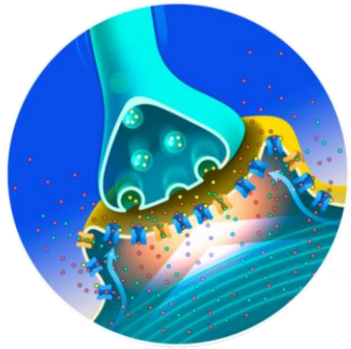
FENM, a Drug Candidate to cure Alzheimer's Disease (AD) and Post-Traumatic Stress Disorder (PTSD)

A platform addressing Neurological Diseases through NMDA GluN2D Receptor inhibition

12/10/2022

NMDA Receptor family is at the cross-road of several serious cerebral disorders



First Market Authorization for Memantine in AD granted in 2002

2017: Consensus statement of the PTSD psychopharmacology working group (US Experts & KOL)

AD

- NMDA-R plays a central role in the synaptic excitotoxicity underlying AD's cognitive impairment
- NMDA-R hyperactivation is also linked to the tau neurofibrillary degeneration in AD
- **NMDA-R antagonists with larger therapeutic index than Memantine are needed**

PTSD

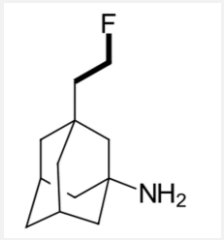
- NMDA-R is a key component of the synaptic plasticity underlying working & long-term memories
- Dysregulation of NMDA-R is critical in the physiopathology of PTSD
- **NMDA-R antagonist class ranks #1 as warranted drug developments**

ReST FENM significant milestones

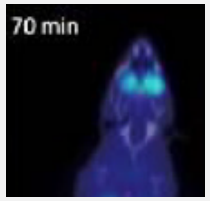
M2i, Lead the Change

ReST THERAPEUTICS | RECOVERY FROM STRESS AND TRAUMA

2013 — Design and first synthesis of FENM



2015 — FENM is a functional radiotracer



2021 — Preclinical POC and MOD for AD and PTSD

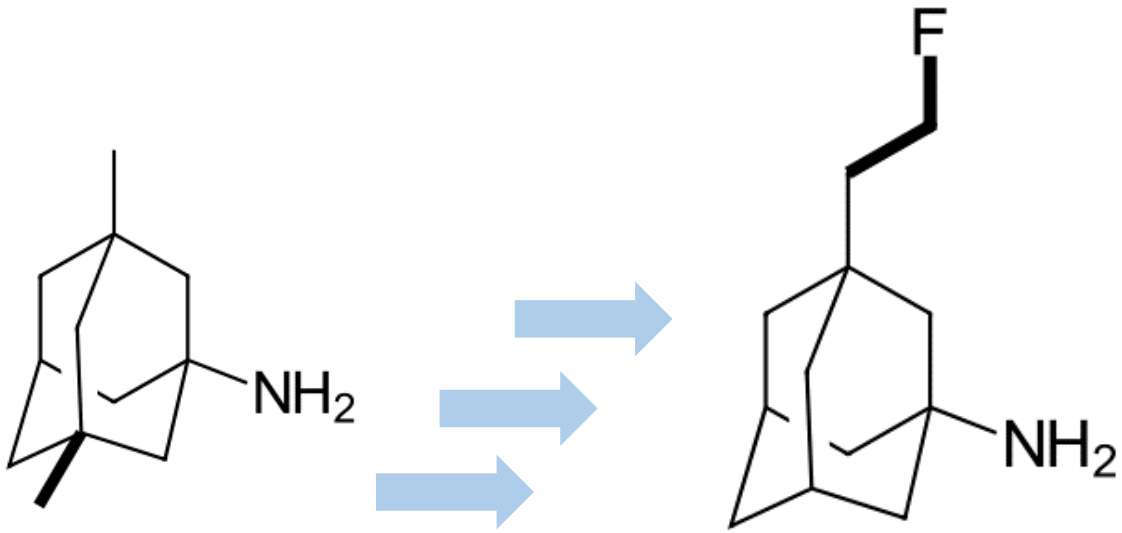
05-2022 — FENM passes all regulatory tests to enter Clinical Phase

10-2022 — GMP clinical batches of both API and FD produced for FIH

03-2023 — Positive EMA Scientific Advice on FIH

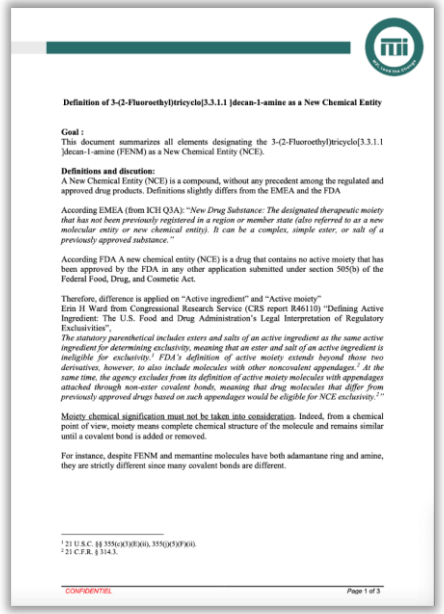
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FENM, a New Chemical Entity inspired by NMDA antagonist benchmark Memantine



Memantine

FluoroEthylNorMemantine



Definition of 3-(2-Fluoroethyl)tricyclo[3.3.1.1]decan-1-amine as a New Chemical Entity

Goal :
This document summarizes all elements designating the 3-(2-Fluoroethyl)tricyclo[3.3.1.1]decan-1-amine (FENM) as a New Chemical Entity (NCE).

Definitions and discution:
A New Chemical Entity (NCE) is a compound, without any precedent among the regulated and approved drug products. Definitions slightly differs from the EMEA and the FDA

According EMEA (from ICH Q3A): *"New Drug Substance: The designated therapeutic moiety that has not been previously registered in a region or number state (also referred to as a new molecular entity or new chemical entity). It can be a complex, simple ester, or salt of a previously approved substance."*

According FDA A new chemical entity (NCE) is a drug that contains no active moiety that has been approved by the FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

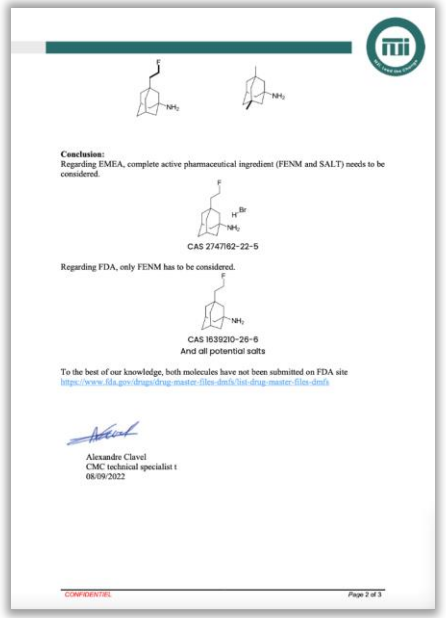
Therefore, difference is applied on "Active ingredient" and "Active moiety"
Erin H Ward from Congressional Research Service (CRS report R46110) "Defining Active Ingredient: The U.S. Food and Drug Administration's Legal Interpretation of Regulatory Exclusivities",
The statutory parenthetical includes esters and salts of an active ingredient as the same active ingredient for determining exclusivity, meaning that an ester and salt of an active ingredient is ineligible for exclusivity.[1] FDA's definition of active moiety extends beyond those two derivatives, however, to also include molecules with other noncovalent appendages.[2] At the same time, the agency excludes from its definition of active moiety molecules with appendages attached through non-ester covalent bonds, meaning that drug molecules that differ from previously approved drugs based on such appendages would be eligible for NCE exclusivity.[1]"

Moiety chemical signification must not be taken into consideration. Indeed, from a chemical point of view, moiety means complete chemical structure of the molecule and remains similar until a covalent bond is added or removed.

For instance, despite FENM and memantine molecules have both adamantane ring and amine, they are strictly different since many covalent bonds are different.

[1] 21 U.S.C. §§ 355(c)(3)(E)(ii), 355(j)(5)(F)(ii).
[2] 21 C.F.R. § 314.3.

CONFIDENTIEL Page 1 of 3



Conclusion:
Regarding EMEA, complete active pharmaceutical ingredient (FENM and SALT) needs to be considered.

CAS 2747162-22-5

Regarding FDA, only FENM has to be considered.

CAS 1639210-26-6
And all potential salts

To the best of our knowledge, both molecules have not been submitted on FDA site
https://www.fda.gov/drugs/drug-master-files-dmfs/list-drug-master-files-dmfs

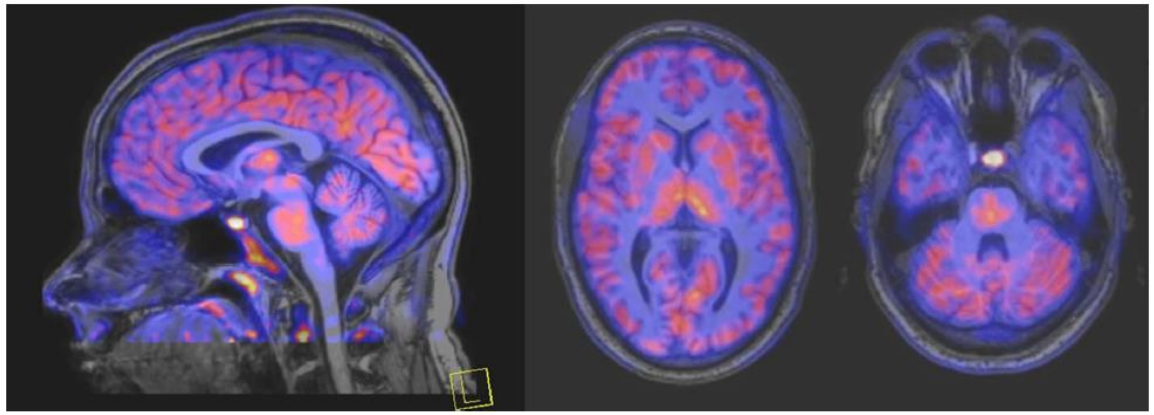
Alexandre Clavel
CMC technical specialist t
08/09/2022

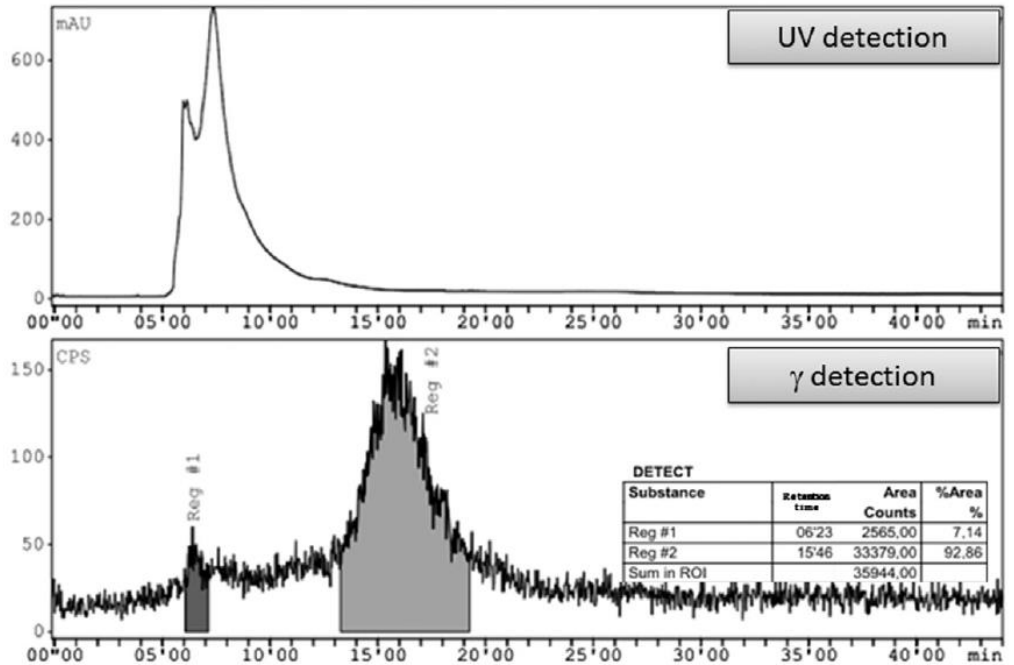
CONFIDENTIEL Page 2 of 3

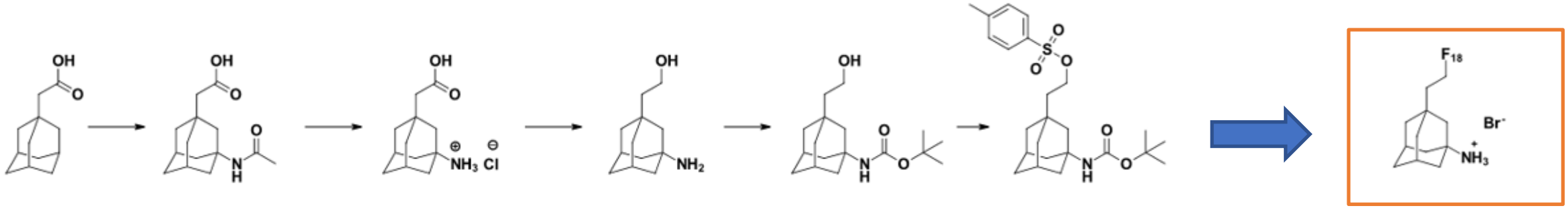
- Even though **FENM** and **Memantine** molecules have both adamantane ring and amine, they are strictly different since **FENM** has a **fluoro-ethyl group**
- Interestingly, **FENM** and **Memantine** share most *in vitro* and animal pharmacokinetics (*excellent gastrointestinal absorption, very low protein binding, unsignificant metabolization, renal elimination*)

FENM – API Chemistry - [^{18}F]FENM Radiotracer

CDMO : M2I Lifesciences







FENM – API Chemistry – FENM API

CDMO : M2I Lifesciences

CERTIFICATE OF ANALYSIS

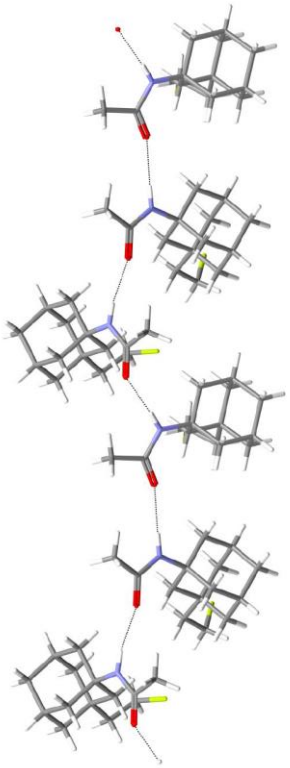
3-(2-fluoroethyl)adamantamine hydrobromide

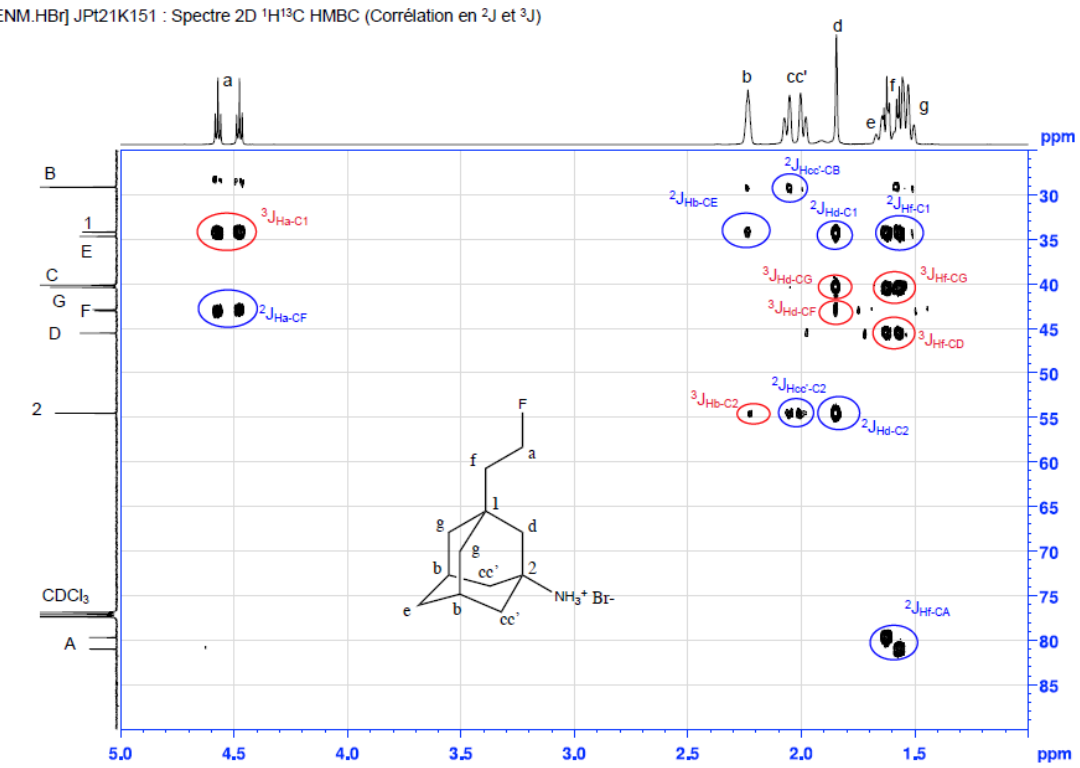
FENM.HBr

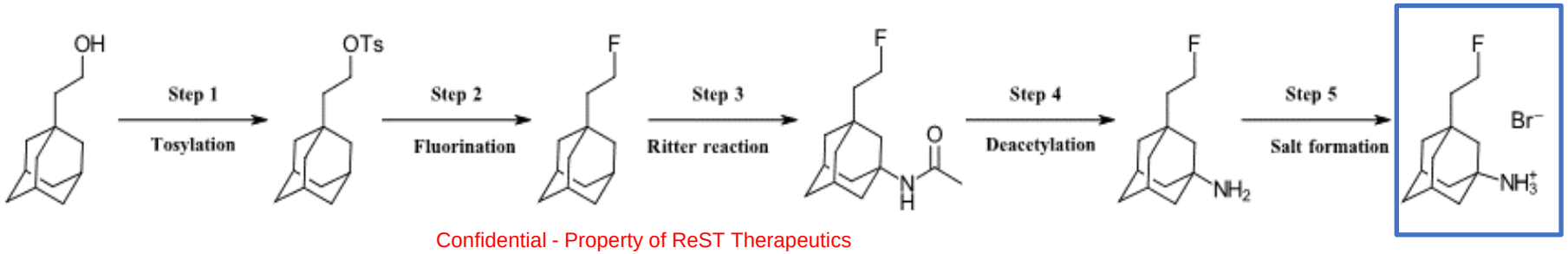
Batch MM N°: GIG209399
Inspection Batch QUA N°: 22SD1000802
Batch size: 4.7 kg

Manufacturing Date: August 18, 2022
Release Date: September 01, 2022
Retest Date: April 17, 2023
Version: 2

Test	Specification	Result
1. Characteristics		
Appearance	White to beige powder	Complies
2. Identification		
Identification / GC	Retention time identical to reference	Complies
Identification / IR	Identical with the reference spectrum	Complies
3. Purity		
Water content	≤ 0.5%w/w	0.1%
Sulphated ashes	≤ 0.1%w/w	0.0%
Purity by GC	For information	100.0%
Step 3 content	≤ 0.50%area	ND
Unspecified impurities (each)	≤ 0.2%area	0.0%
Sum of all impurities	≤ 1.0%area	0.0%
Propylene glycol content	≤ 5000ppm	ND
4. Assay		
Potentiometry	98.0 to 102.0%w/w	98.2%
5. Residual solvents		
- MTBE	≤ 5000 ppm	339 ppm
- Methyl THF	≤ 5000 ppm	ND
- Cyclohexane	≤ 3880 ppm	ND
- Dichloromethane	≤ 600 ppm	ND
- Acetonitrile	≤ 410 ppm	ND
- Pyridine	≤ 200 ppm	ND







FENM – FDF Stability testing

CDMO : EUROFINS

25°C/60%RH

9.1 - 10mg coated tablets, batch D220080, 25°C /60%RH

Parameters tested	Specifications	Initial	T1M	T3M	T6M	T9M
Appearance	White oblong tablet	White oblong tablet	White oblong tablet	White oblong tablet	White oblong tablet	
Average mass (mg)	315.0 mg ± 10 % (283.5 mg to 346.5 mg)	315.0	311.1	311.5	311.4	
Hardness (N)	140-210N	186	179	192	189	
Disintegration time (s)	Report the value	38	34	20	20	
Water determination (%)	For information	5.5	3.7	3.6	3.2	
In-vitro dissolution test						
Released (%) after 15 min	Q + 5% at 15 min at level S_1 (Q = 75%)	S1	S1	S1	S1	
Average value		98.2	101.6	102.8	106.1	
Minimum		95.3	98.1	97.3	101.7	
Maximum		102.8	104.3	108.0	111.0	
RSD (%)		3.2	2.3	3.9	3.8	
Assay (mg/tab)	9.00 – 11.00 mg/tab 90.0 – 110.0% LC	10.22 mg 102.2%	10.21 mg 102.1%	9.98 mg 9.98%	10.04 mg 100.4%	
Related substances (%)						
Unspecified impurity						
RRT 0.29	≤ 0.2 %	-	-	0.05	-	
Total impurities	-	-	-	0.05	-	

NP: not performed IP: In progress FENM.HBr: LOQ is 0.05 % - : Not detected or < Reporting Threshold (0.05 %)

40°C/75%RH

9.2 - 10mg coated tablets, batch D220080, 40°C /75%RH

Parameters tested	Specifications	Initial	T1M	T3M	T6M	T9M
Appearance	White oblong tablet	White oblong tablet	White oblong tablet	White oblong tablet	White oblong tablet	
Average mass (mg)	315.0 mg ± 10 % (283.5 mg to 346.5 mg)	315.0	311.9	311.5	312.6	
Hardness (N)	140-210N	186	181	193	187	
Disintegration time (s)	Report the value	38	31	16	13	
Water determination (%)	For information	5.5	3.7	4.1	3.6	
In-vitro dissolution test						
Released (%) after 15 min	Q + 5% at 15 min at level S_1 (Q = 75%)	S1	S1	S1	S1	
Average value		98.2	100.3	100.3	102.7	
Minimum		95.3	93.6	97.2	97.9	
Maximum		102.8	104.7	103.8	109.3	
RSD (%)		3.2	4.0	2.2	4.1	
Assay (mg/tab)	9.00 – 11.00 mg/tab 90.0 – 110.0% LC	10.22 mg 102.2%	10.03 mg 100.3%	10.15 mg 101.5%	10.04 mg 100.4%	
Related substances (%)						
Unspecified impurity	≤ 0.2 %					
RRT 0.29	≤ 0.2 %	-	-	0.05	-	
Total impurities	-	-	-	0.05	-	

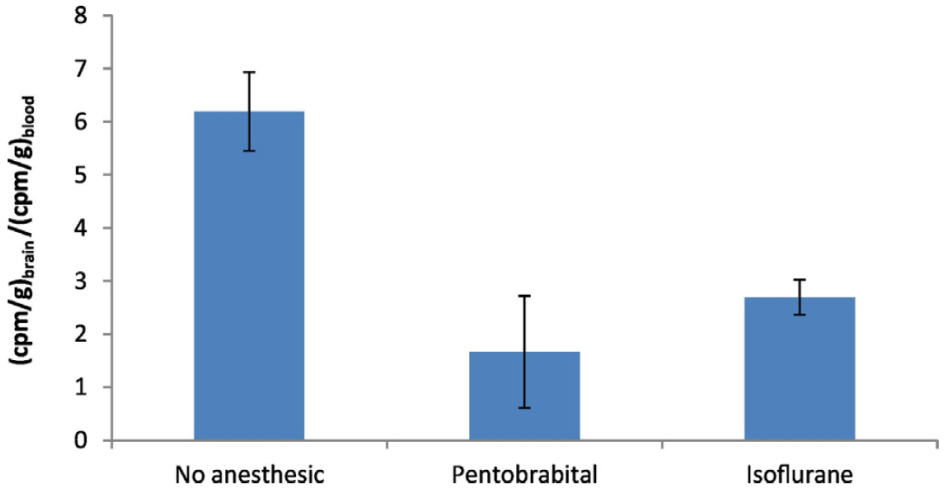
NP: not performed IP: In progress FENM.HBr: LOQ is 0.05 % - : Not detected or < Reporting Threshold (0.05 %)

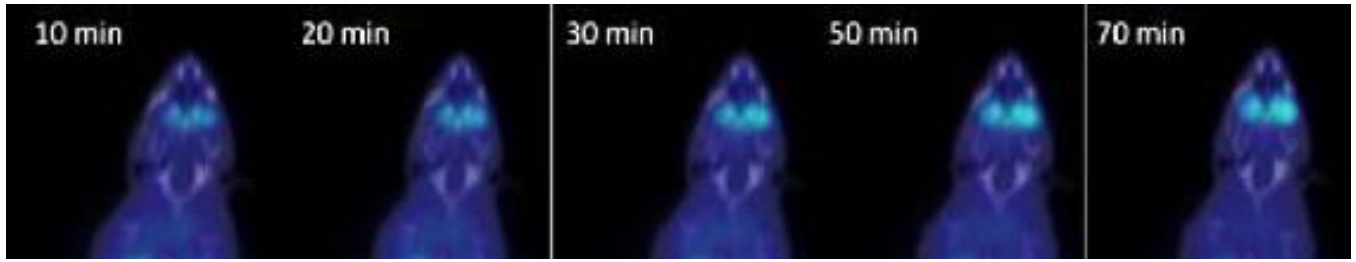
FENM was primarily designed to be a PET Radiotracer – [^{18}F]FENM

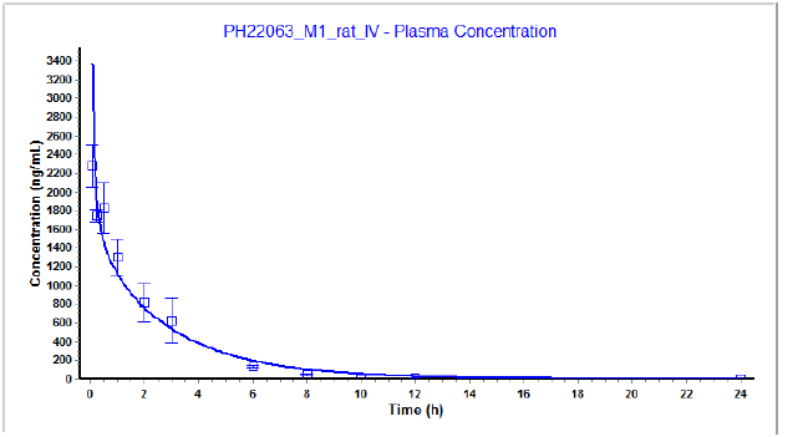
*([^{18}F]MEM shows no correlation with NMDA localization)**

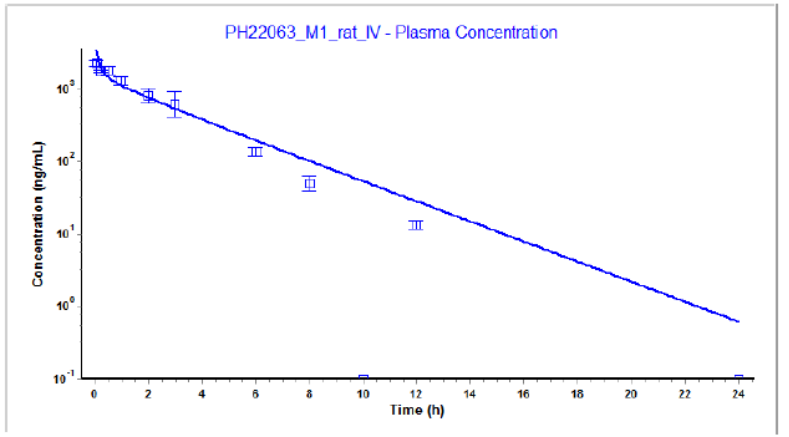
* S.M. Amatemey *et al*.,Nuclear Medicine et Biology, 29 (2002), 227-231

[^{18}F]FENM has a favourable bioavailability





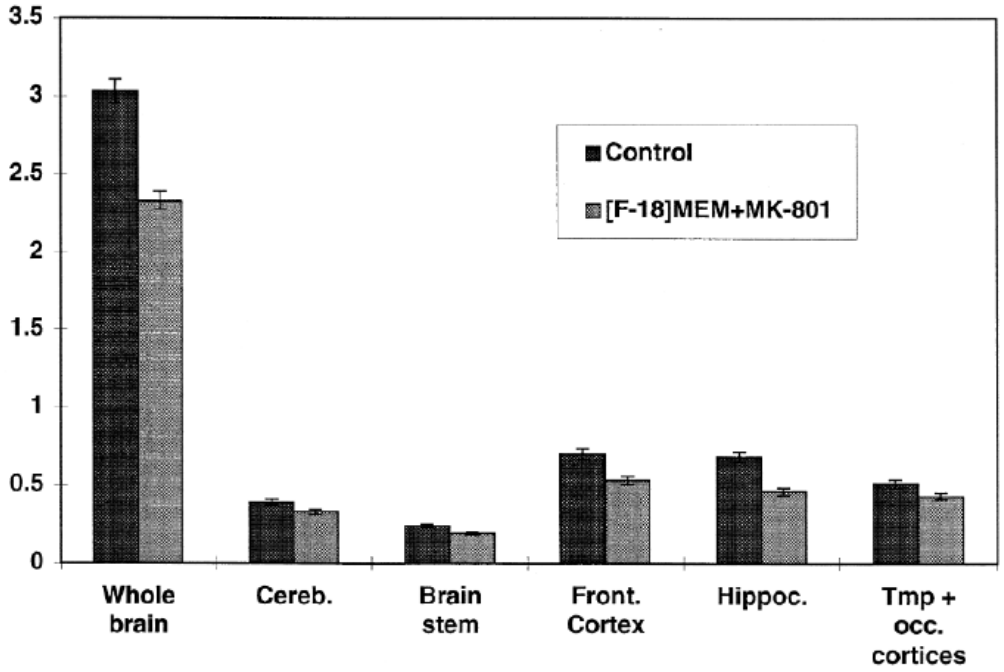




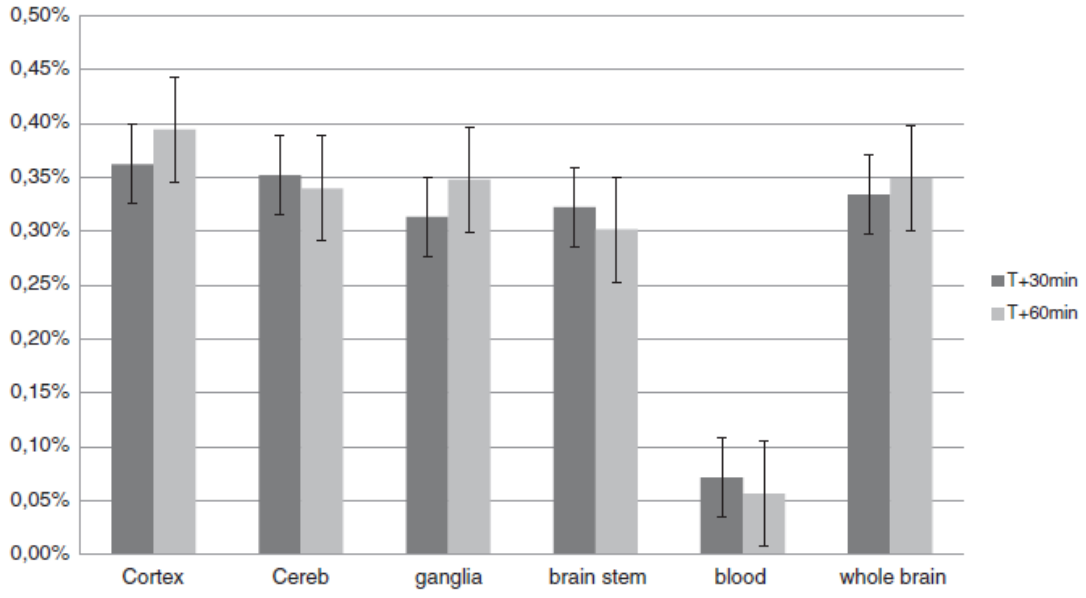
- The **BBB crossing** test showed that at 60 minutes after injection, 0.34% DI/g of **FENM** was in the brain, with the highest level of radioactivity in the **cortex**
- Uptake in the brain is **constant** after 40 min of injection. The highest uptake was found in the cortex and cerebellum, while the lowest was found in white matter.
- **Low residence time** of **FENM** in the body

Contrary to [^{18}F]MEM, [^{18}F]FENM is specific to NMDA dense regions

[^{18}F]MEM



[^{18}F]FENM



[^{18}F]FENM is a highly specific functional radiotracer

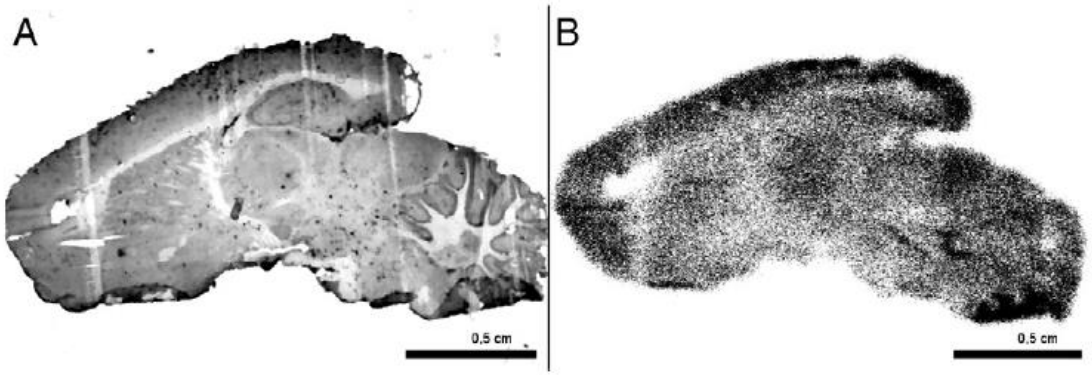
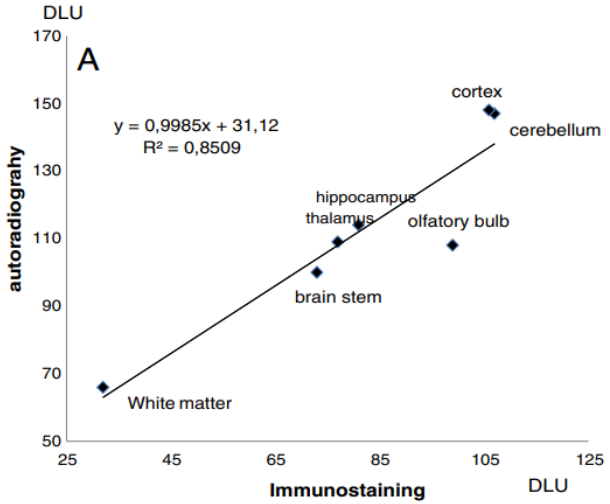


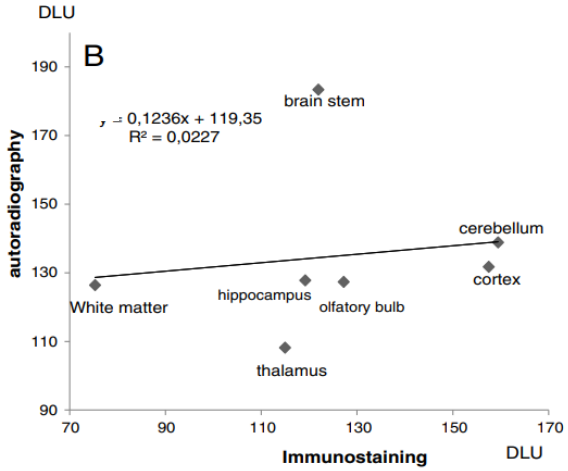
Fig. 7. Immunostaining (NMDAR1, A) and autoradiography ([^{18}F]-FNM, B) of two adjacent brain sections (20 µm thick) from a rat anesthetized with isoflurane.

[^{18}F]FENM colocalizes with NMDA-R



[^{18}F]FENM competes with Ketamine

a NMDA-R antagonist used as an anaesthetics



[^{18}F]FENM is today the only functional radiotracer, with demonstrated correlation with NMDA-R density

Clinical trial on Gilles de la Tourette syndrome*

Author	Brain correlation	Functional	Applied in human brain
Haradahira et al., 1998	ND	NO	NO
Ouyang et al., 1996	ND	NO	NO
Sobrio et al., 2010	ND	NO	NO
Owens et al., 1997	ND	NO	NO
Hartvig et al., 1995	ND	NO	YES
Ametamey et al., 1995	ND	NO	YES
Dumont et al., 2002	ND	NO	YES
Robins et al., 2010	ND	NO	YES
Leung, 2004	NO	NO	NO
Fuchigami et al., 2014	ND	NO	NO
Roger et al., 2003	ND	NO	NO
Labas et al., 2009	ND	NO	NO
Claiborne et al., 2003	ND	NO	NO
Salabert et al., 2015, 2018	**YES**	**YES**	**YES**

FENM →

NCT 0368179 - GlutaTour; Marie Beaurain et al.; **Front. Med. (2019)*

FENM in AD

Comparison with Memantine

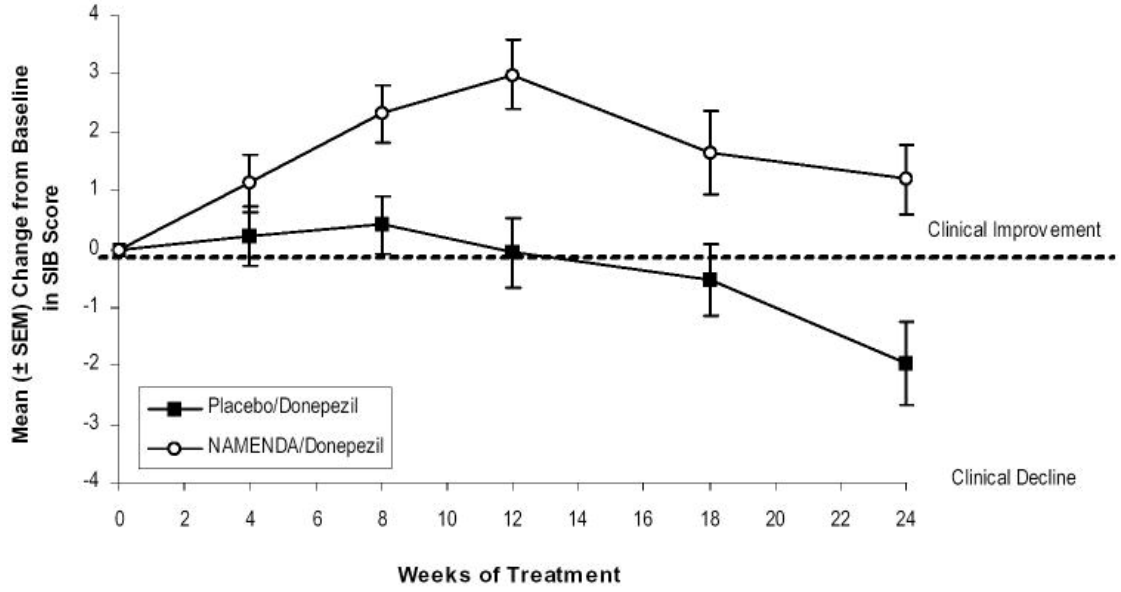
In AD patients, Memantine efficacy is lost over time

Results of the clinical trial in Namenda (FDA Summary of Product Characteristics)

Methodology

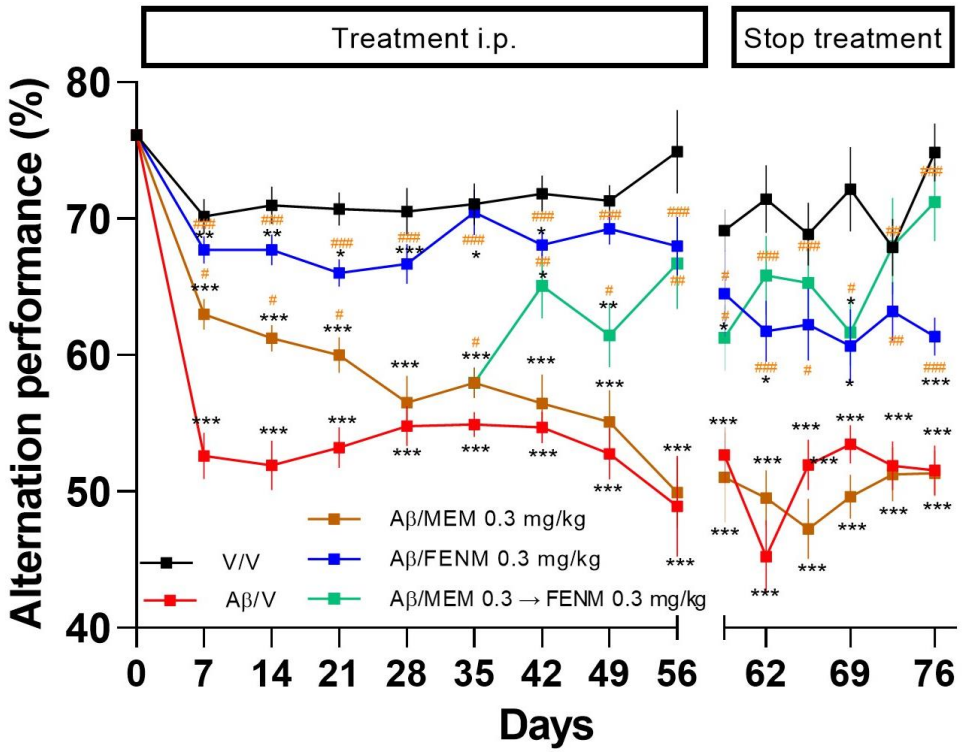
24 weeks duration, 404 patients with moderate to severe probable Alzheimer's disease who had been treated with donepezil … were randomized to memantine hydrochloride or placebo while still receiving donepezil. For patients randomized to memantine hydrochloride, treatment was initiated at 5 mg once daily and increased weekly by 5 mg/day in divided doses to a dose of 20 mg/day (10 mg twice a day).

Results



Neuroprotection by FENM is persistent and takes over when Memantine effects vanish in AD translational model

Persistent Neuroprotection by FENM



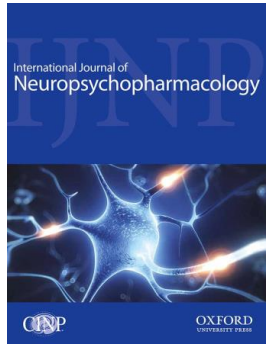
Neuroscience 2022

2020

Consistent Neuroprotection by FENM

Parameter	FENM	Memantine
Biochemical analyses[b]		
Cyt C release	+	+
Lipid peroxidation	++	+
IL-6 ELISA	++	+
TNFα ELISA	+	+
Bax/Bcl2 ELISA	++	+
Morphological analyses[b]		
Pyramidal cell loss (CV)	++	++
GFAP IHC—Rad	++	+
GFAP IHC—Mol	++	–
GFAP IHC—PoDG	++	+
GFAP IHC—Ctx	++	–
Iba1 IHC—Rad	++	+
Iba1 IHC—Ctx	++	–

FENM persistent effects are supported by its efficient neuroprotection that Memantine dose not have



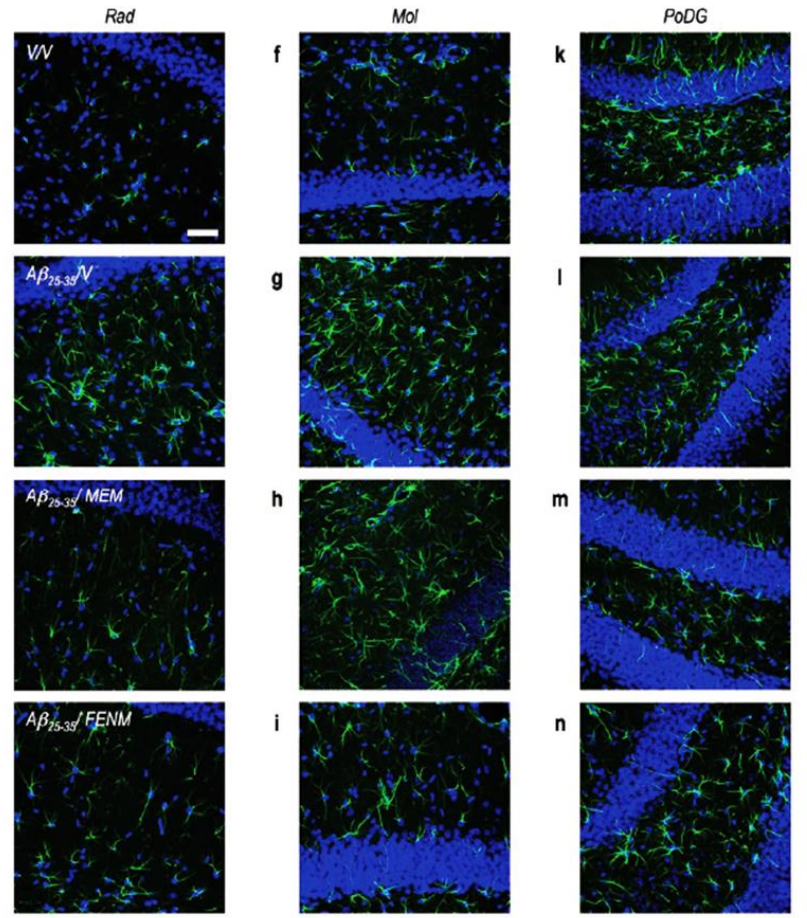
2020

In Aβ (25-35) paradigm

7days of treatment

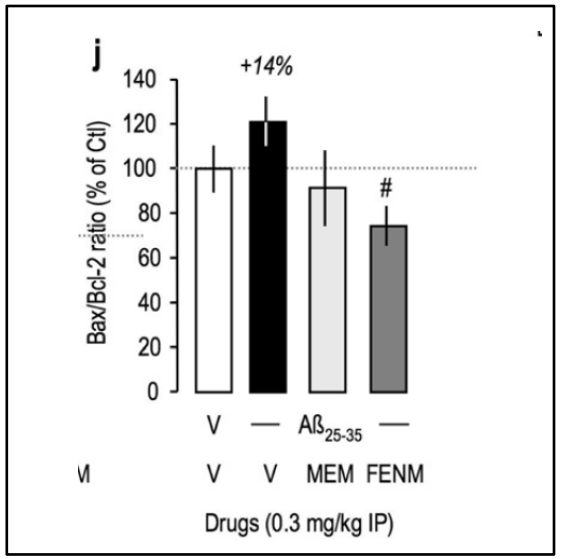
FENM
MEMANTINE
NaCl

Neuroinflammation

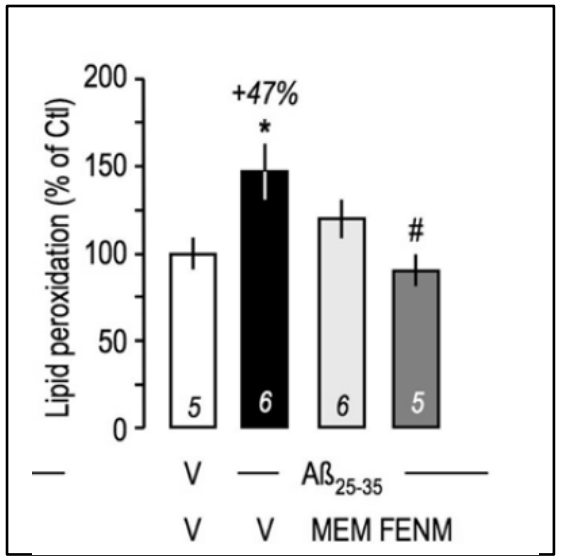


Astrocytes cells

Apoptosis



Oxydative stress



FENM persistent effects are supported by its efficient anti-amnesic effect

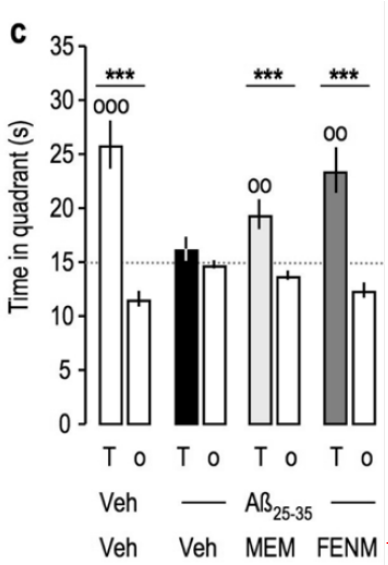
2020

In Aβ (25-35) paradigm

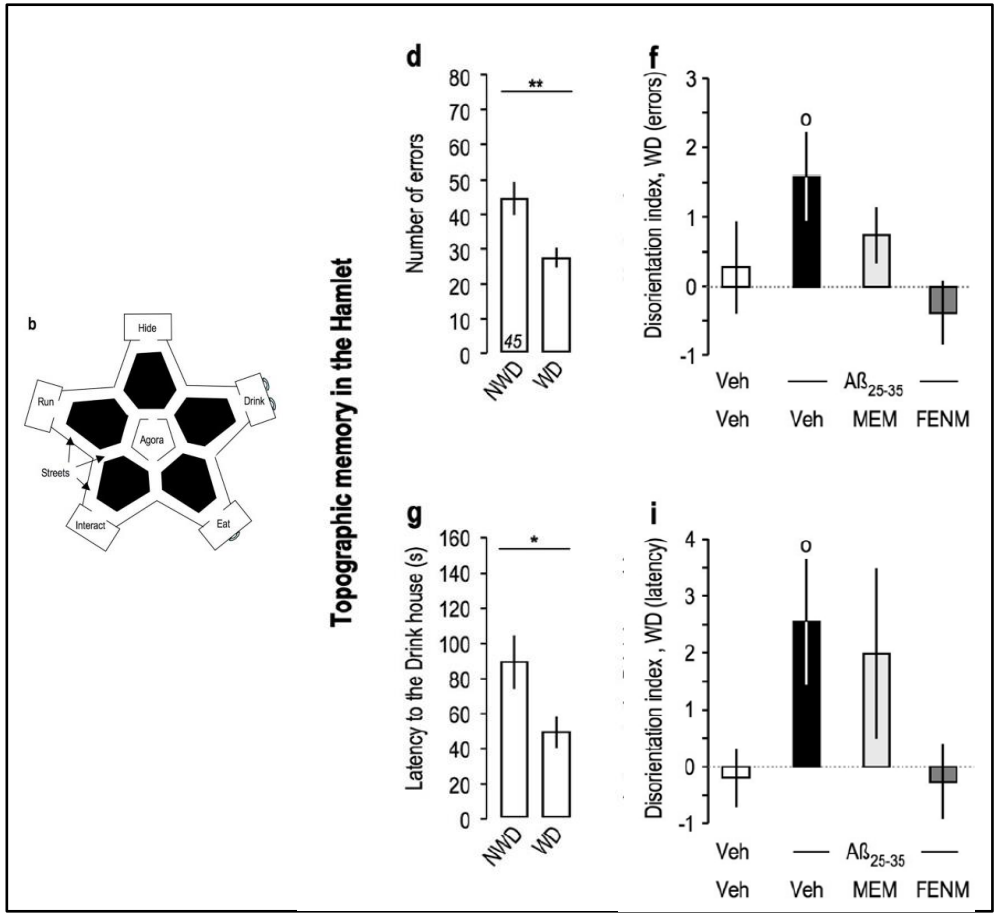
Treatment 7 days after Aβ25-35 induction

FENM
MEMANTINE
NaCl

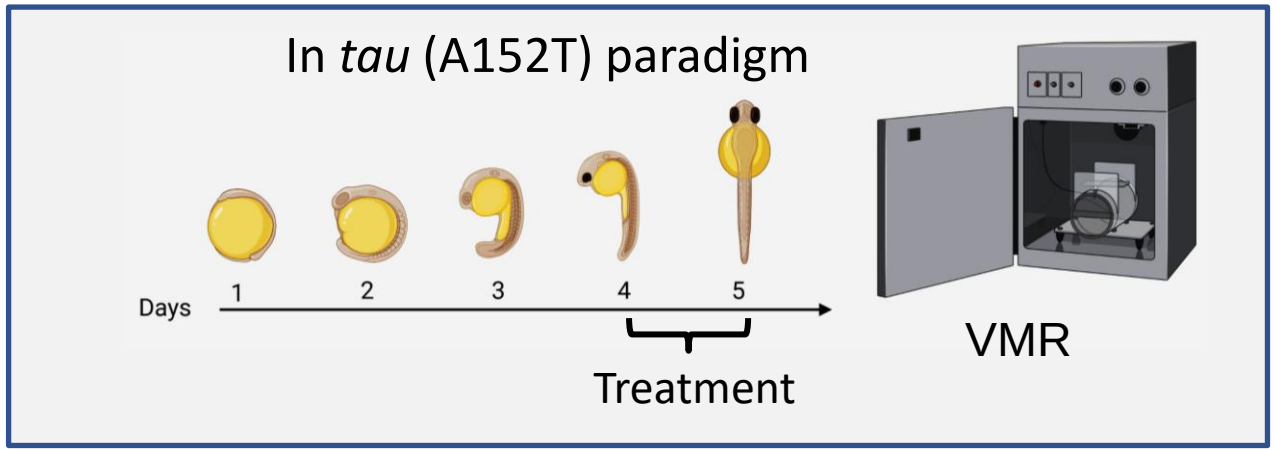
Place learning in the Water Maze

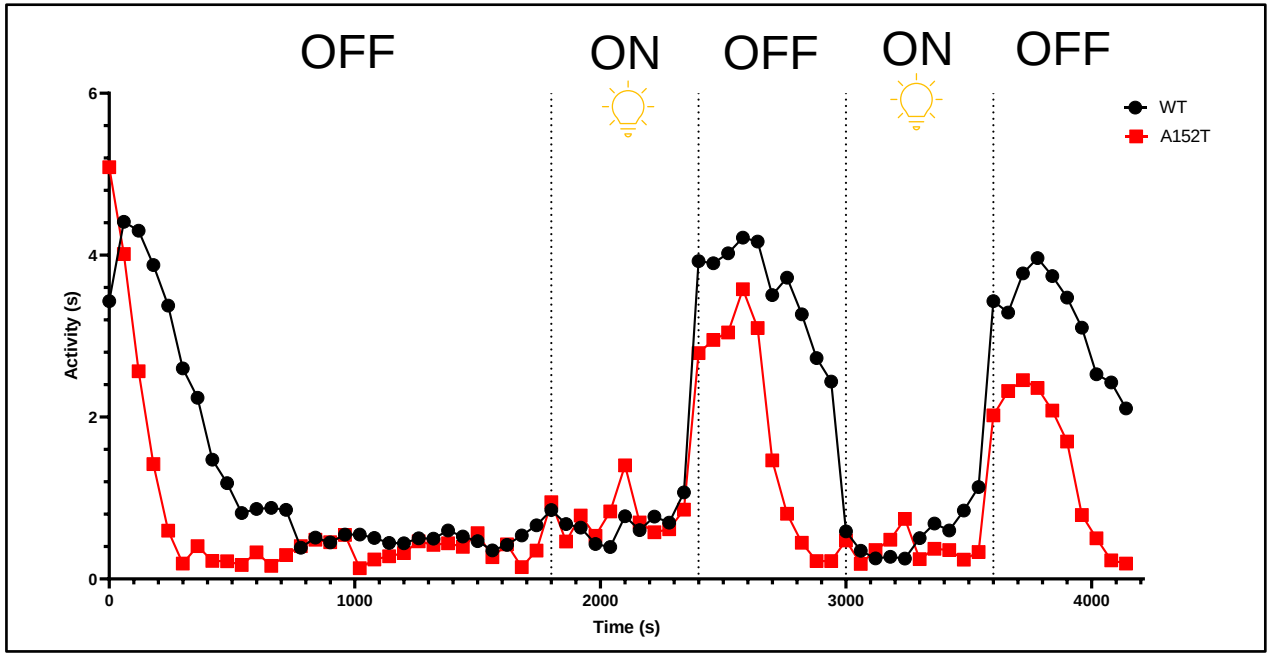


Topographic memory in the Hamlet

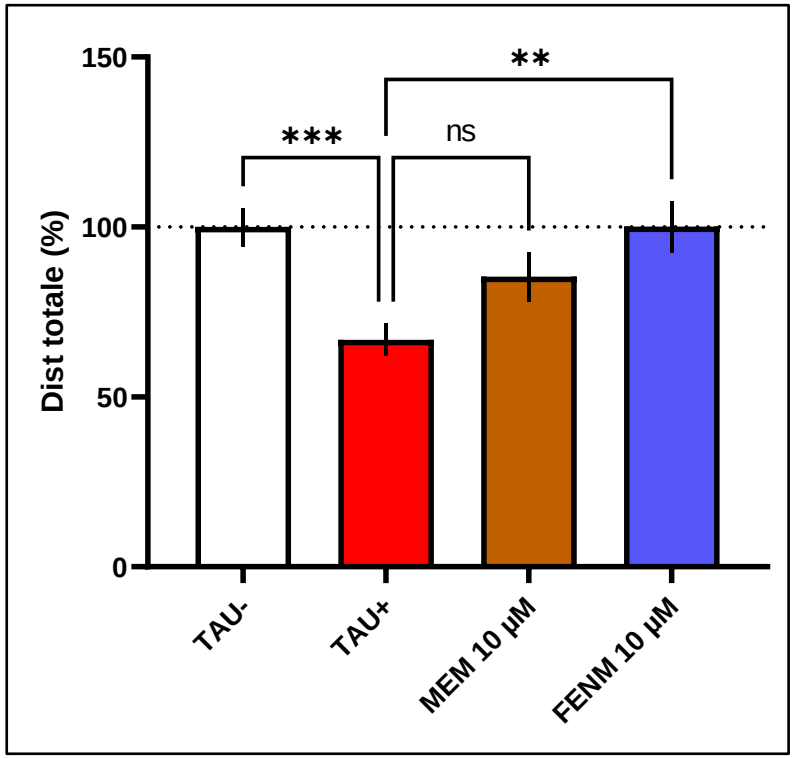


FENM persistent effects are supported by its efficient neuroprotection that Memantine dose not have





Locomotor response



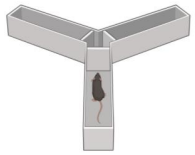
FENM persistent effects are supported by its efficient neuroprotection in Tg model

In APPsweePS1dE9 paradigm

Treatment (3 at 12 months)

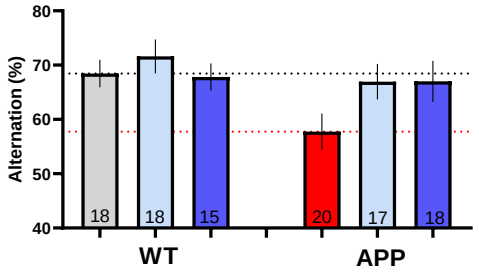
FENM 1 mg/kg/day
5 mg/kd/day

Short terme memory

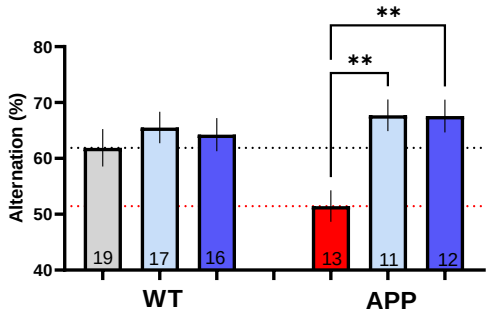


1 mg/kg
5 mg/kg

6 months

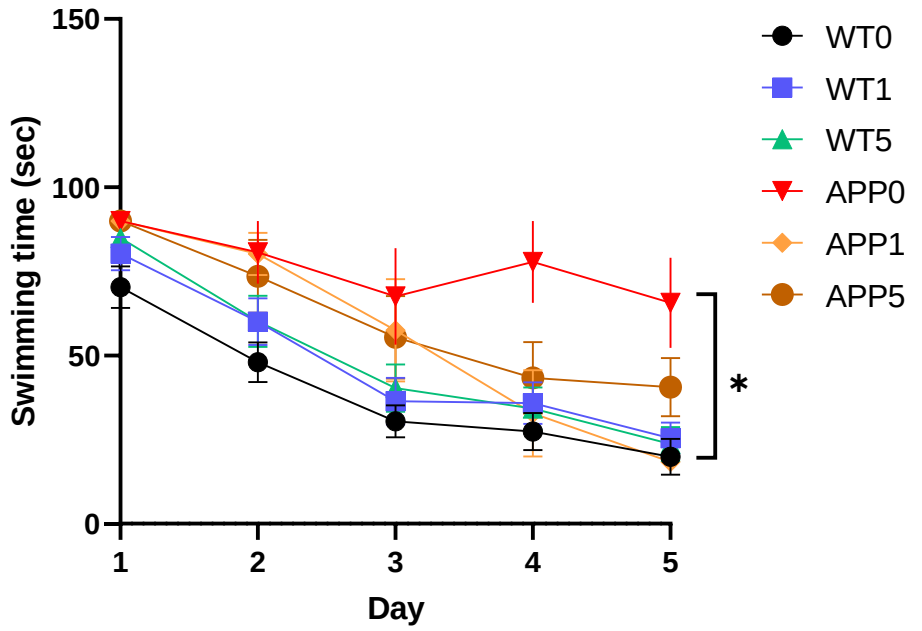


12 months



Place learning in the Water Maze

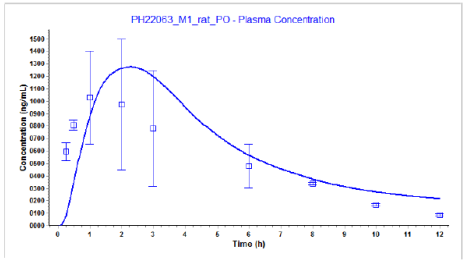
12 months

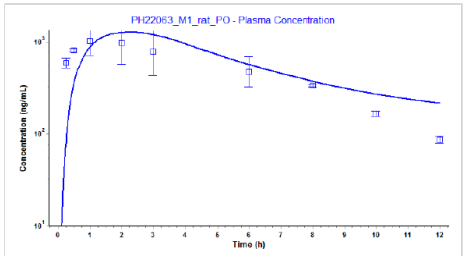


FENM PK and Synergies

FENM may have long ½ Life in Human when compared with animal PK (same as Memantine)

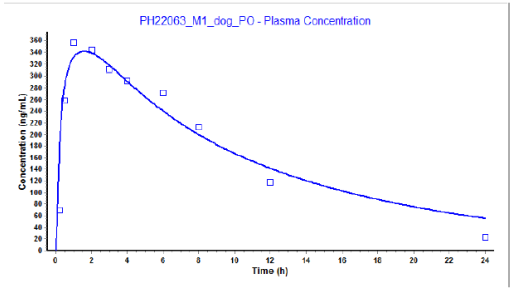
Results simulation of PO rats PK

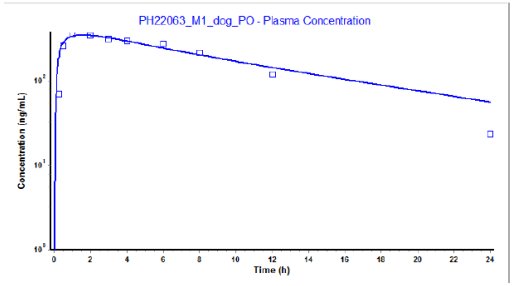




PK paramters	Observed	simulated
Cmax (ng/mL)	1030	1273.7
AUC0-t (ng.h/mL)	6050	7351.3
AUC0-∞ (ng.h/mL)	6321.5	9535.6

Results simulation of PO dogs PK





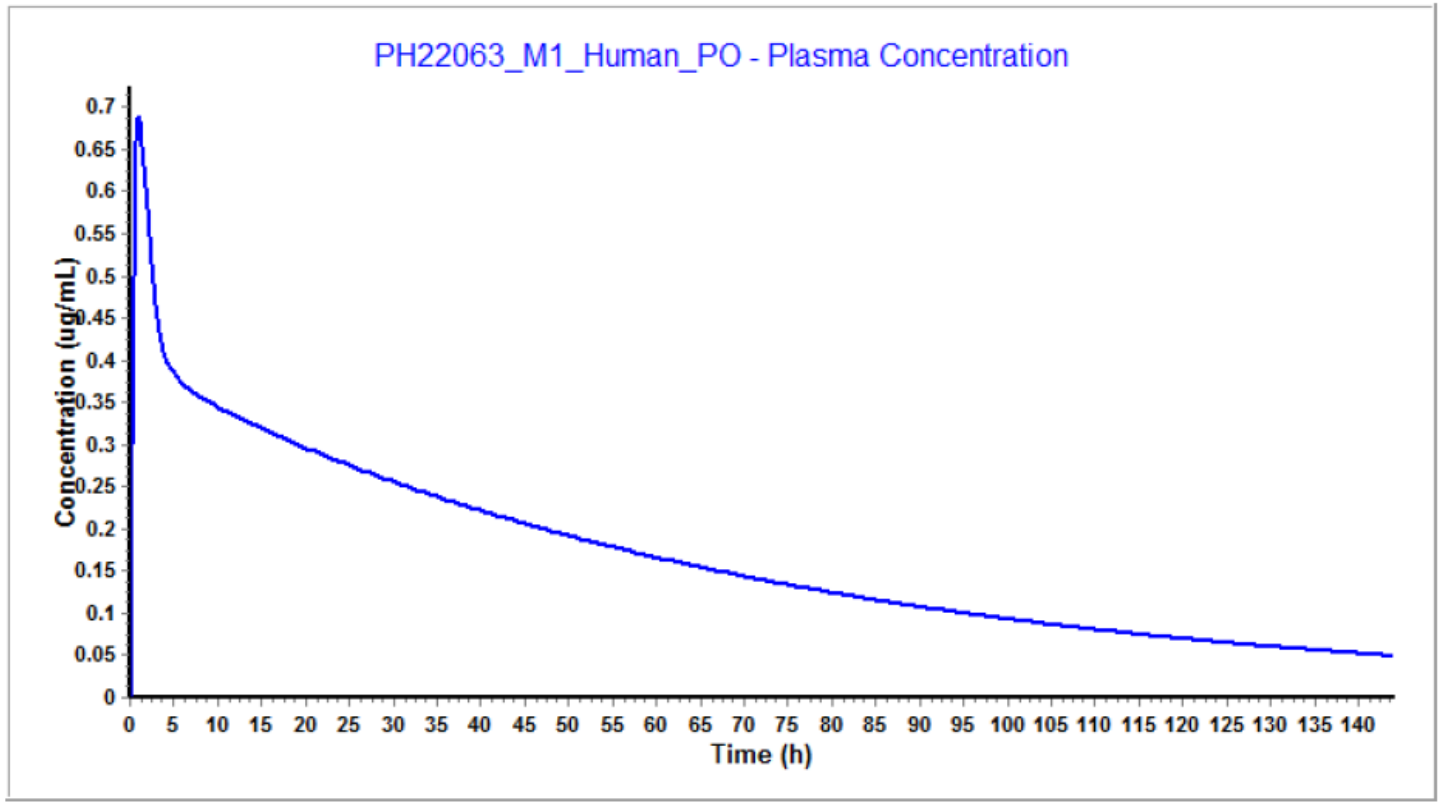
PK paramters	Observed	simulated
Cmax (ng/mL)	357	341.5
AUC0-t (ng.h/mL)	3739.1	3949.6
AUC0-∞ (ng.h/mL)	3910.3	4675.2

FENM may have long ½ Life in Human when compared with animal PK (same as Memantine)

		Species					Rodent: single dose in solution
		Rat		Mouse		Human	
Dose	**(mg/kg)**	1	10	1	10	10 mg	Human: BID
AUC $_{inf}$	**(uM hr)**	0.6	11.4	1.2	18.2		More than dose prop exposures
C $_{max}$	**(uM)**	0.1	3.7	0.5	7.6	0.47	in oral t1/2 suggest change in clearance mechanisms
C $_{min}$	**(uM)**		0.03		0.01	0.3	
C $_{max}$/ C $_{min}$ ratio			123		760	1.54	Much lower C_{max}/C_{min} ratio in human
T $_{max}$	**(hr)**	1	0.5 - 1	0.5	0.5 - 1	4 - 6	
		1 mg/kg (iv)		**1 mg/kg (iv)**			
Vd $_{ss}$	**(L/kg)**		8 - 9		8 - 9	9 - 11	
Cl $_{p}$	**(L/hr/kg)**		4.15		3.81	0.16	Much lower (estimated) clearance in human. Renal elimination in all species
GFR	**(L/hr/kg)**		**0.31**		**0.84**	**0.11**	Cl_p >> GFR suggests active elimination
t $_{1/2}$	**(hr)**		4		3	60 - 80	

Beconi MG, Howland D, Park L, Lyons K, Giuliano J, Dominguez C, Munoz-Sanjuan I, Pacifici R. Pharmacokinetics of memantine in rats and mice. PLoS Curr. 2011 Dec 15;3:RRN1291. doi: 10.1371/currents.RRN1291. PMID: 22307216; PMCID: PMC3269340.

FENM may have long ½ Life in Human when compared with animal PK (same as Memantine)



- Keeping all in vitro, a clearance set as fu*GFR predict a half life of 46h which comes closer to what was observed with memantine

PK parameters	Simulation
Cmax (µg/mL)	0.69
AUC0-24 (µg.h/mL)	24.45
AUC0-∞ (µg.h/mL)	27.84
$T_{1/2}$ (h)	46.2

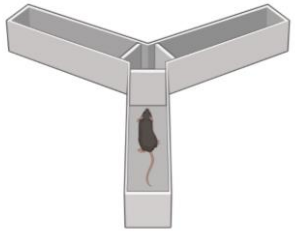
FENM Possible PK variations checked infusion administration

In Aβ (25-35) paradigm

Treatment 7 days after Aβ25-35 induction

FENM 0,1 mg/kg/day

Short term memory



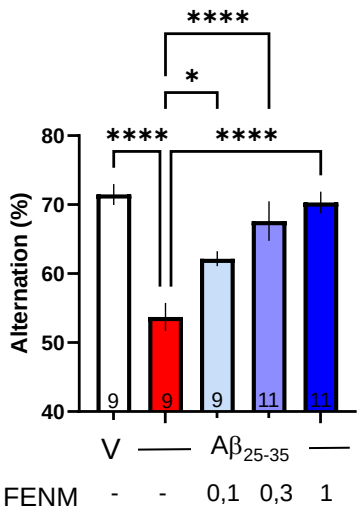
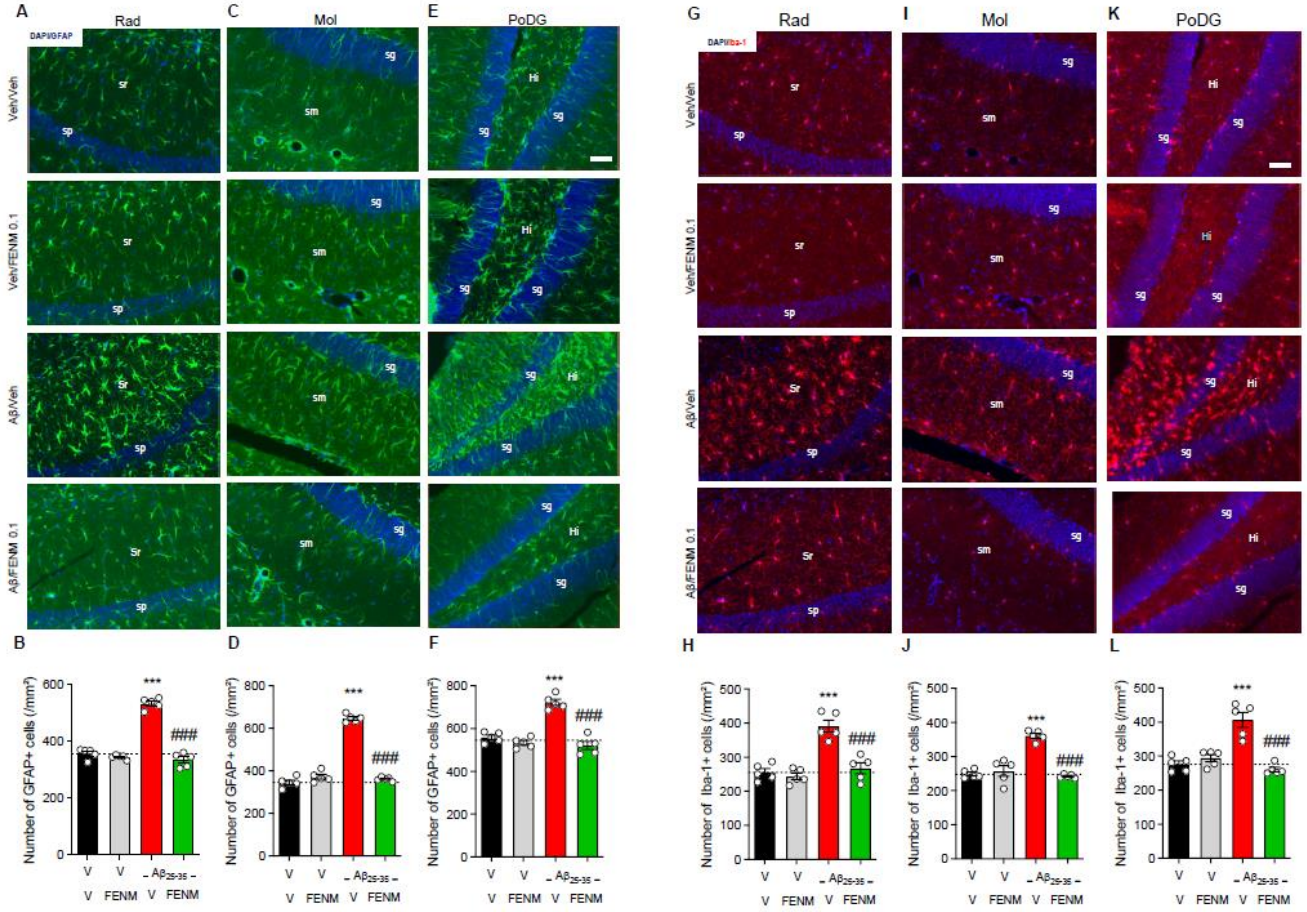


Figure 5. Infused FENM prevented $A\beta_{25-35}$-induced neuroinflammation in the hippocampus: immunofluorescence of GFAP (astroglia) and Iba-1 (microglia)



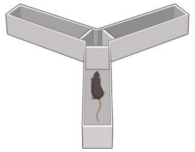
Synergistic protection against cognitive deficit using FENM

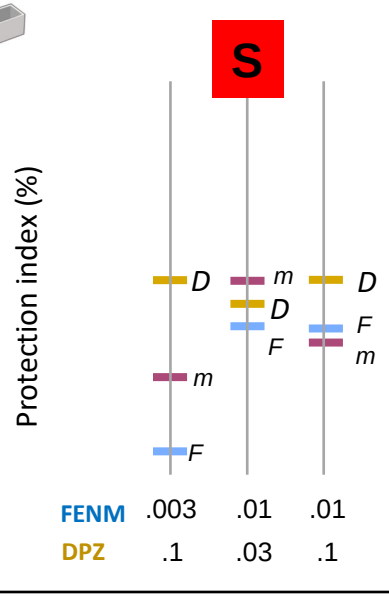
In Aβ (25-35) paradigm

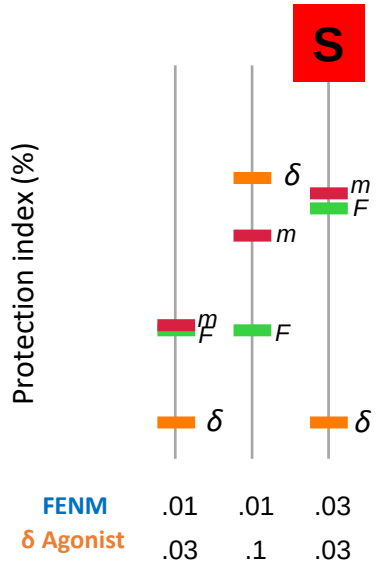
7 days of treatment

FENM + Donepezil
FENM + Sigma (δ) Agonist

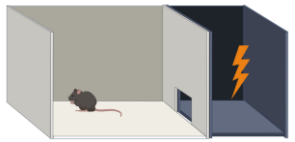
Short term memory

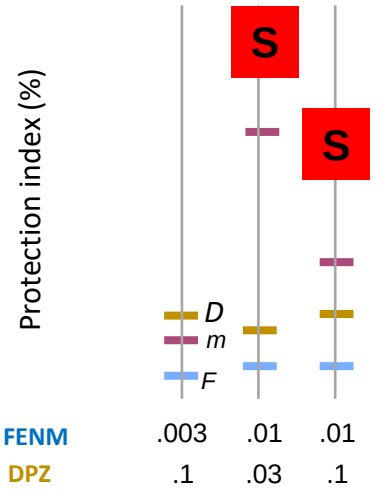


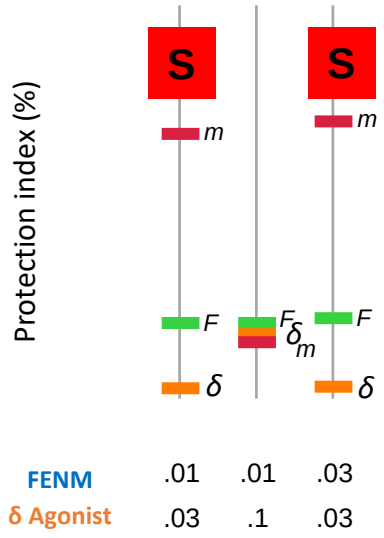




Long term memory





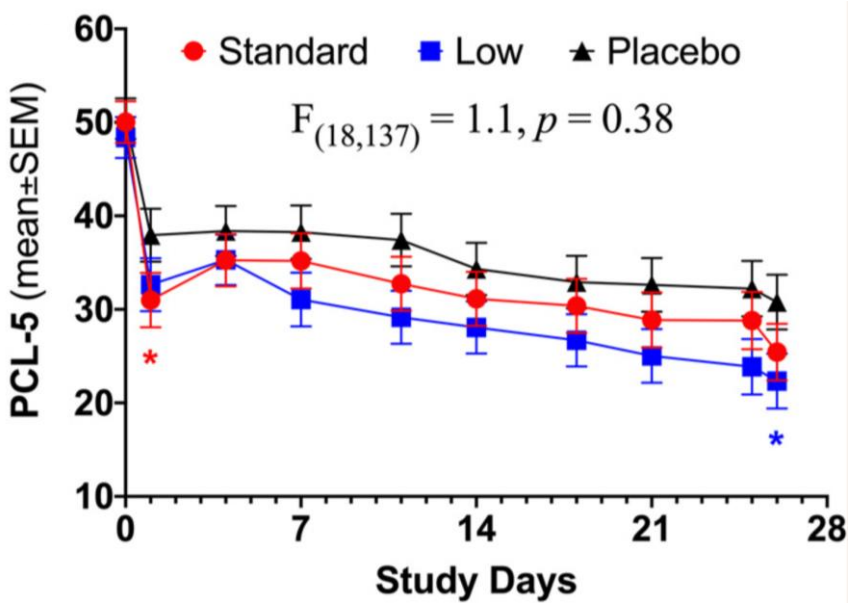


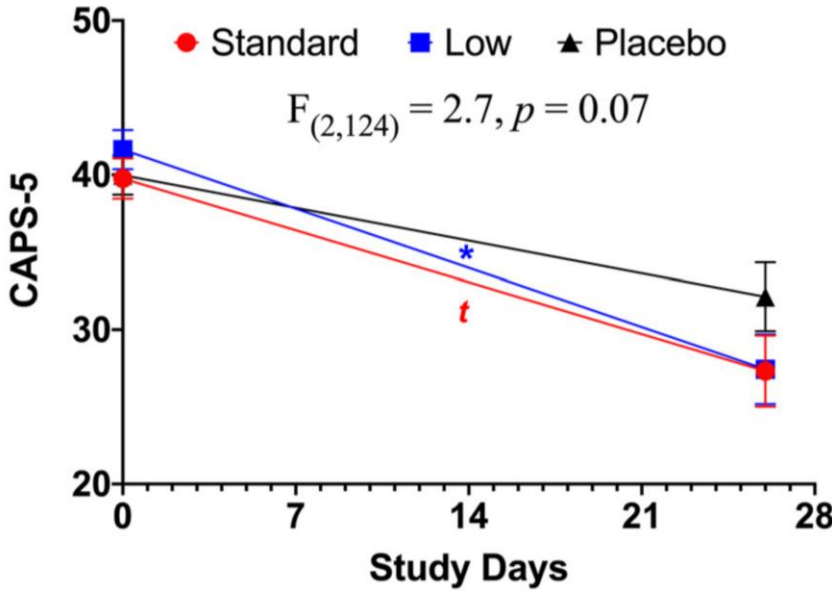
FENM in PTSD

Comparison with Ketamine

Promising Ketamine fails to demonstrate efficacy in PTSD

Even though this well-know NMDA-R Antagonist very efficiently treats depression





Methodology (multi-center randomized Phase III)

N=158 in 3 Veterans Affairs recruitment sites
Double-blind randomized trial

2 Doses :
low 0.2mg/kg and standard 0.5 mg/kg

Results

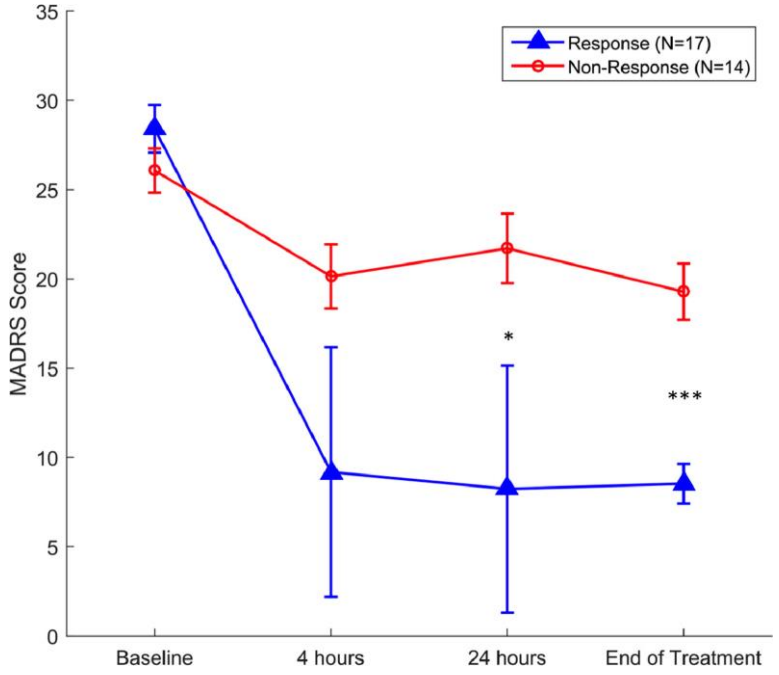
Higher doses could not be considered because of the dissociative (*already observed at 0.5mg/kg*) and anaesthetic effects

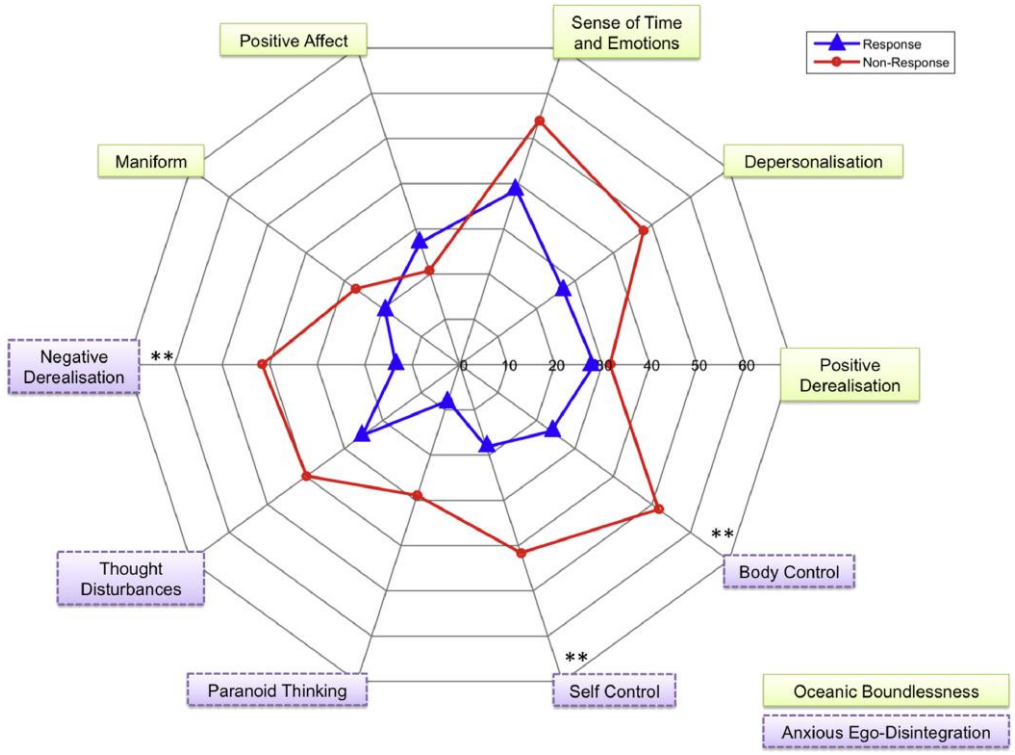
"*This clinical trial failed to find a significant dose-related effect of ketamine on PTSD symptoms*"

Published in Neuropsychopharmacology, July 2022, 47(8) : 1574-1581

As a fact, anxiety induced by Ketamine likely hampers its clinical potential in PTSD

Aust et al. Eur Neuropsychopharmacology (2019) 29, 529-538





Methodology

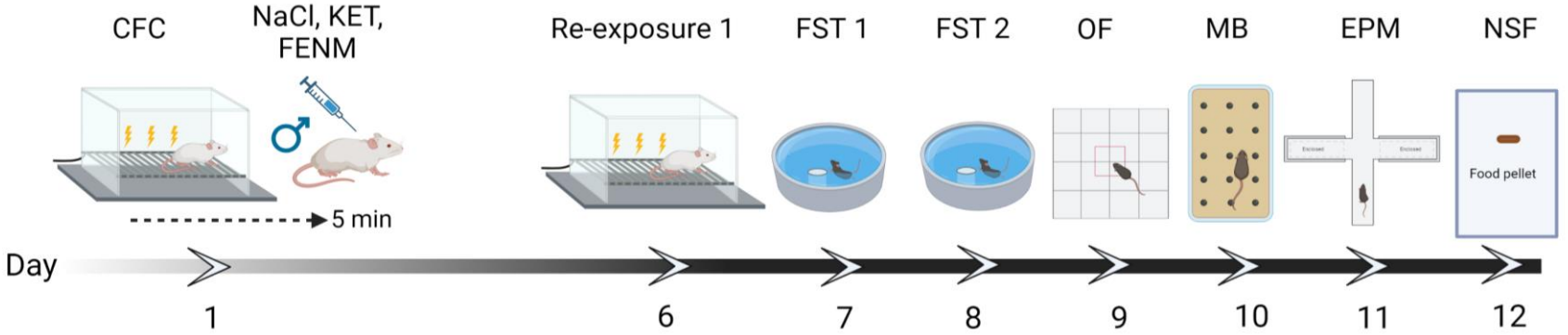
- 31 patients (16 women) with MDD primary diagnostic
- 3 ketamine infusions per weeks (0.5mg/kg) over 2 weeks.

Results

- Response to treatment measured by MADRS shows two different groups of responders and non-responders
- Which correlates with anxiety related experience during treatment session assessed by 5D-ASC

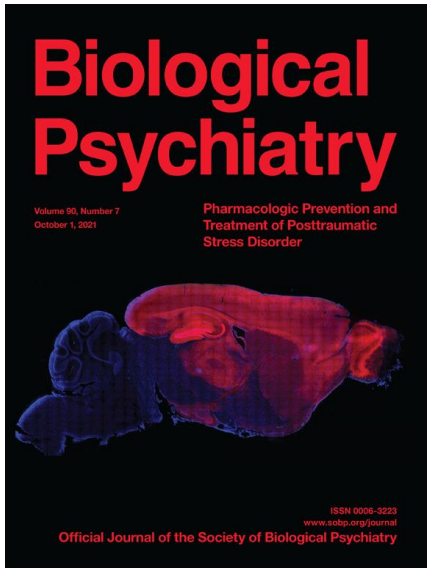
FENM is efficient in preclinical models for PTSD in a different and far superior way than Ketamine*

Methodology

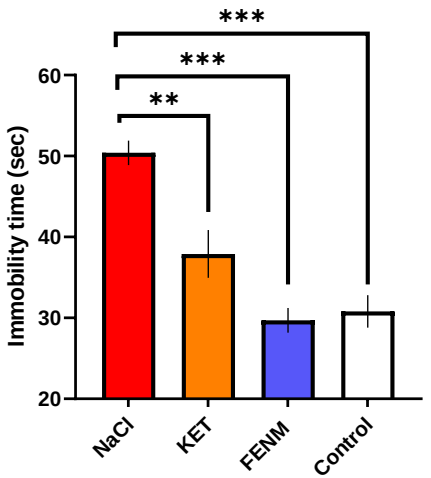


Results

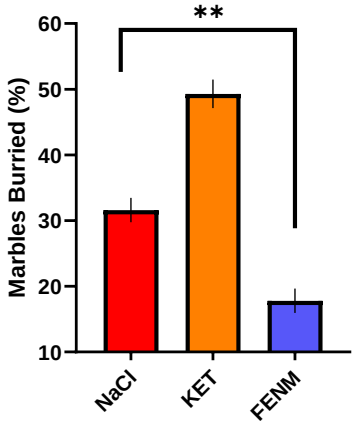
2021



FENM alleviates stress-induced despair better than Ketamine



FENM decreases anxiety ketamine doesn't

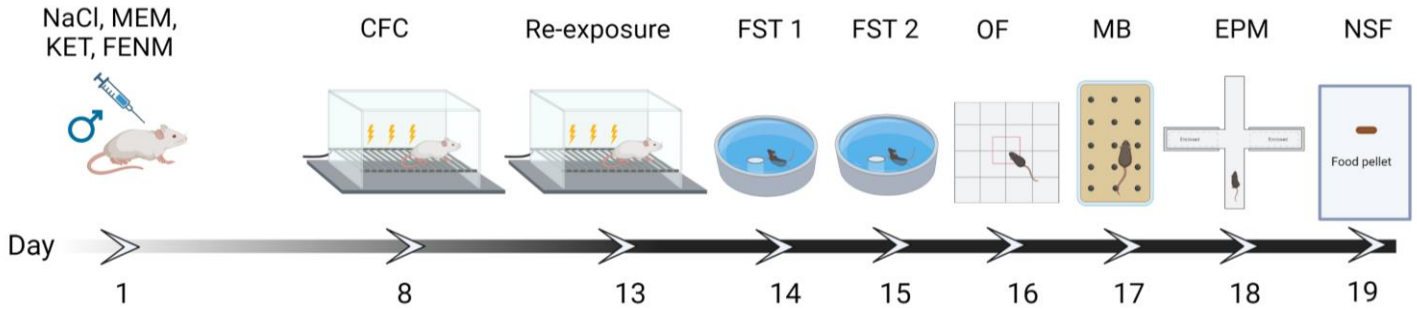


*Ketamine being used at a highly psychedelic dose level of 30mg/kg

FENM is also efficient in primary prophylaxis

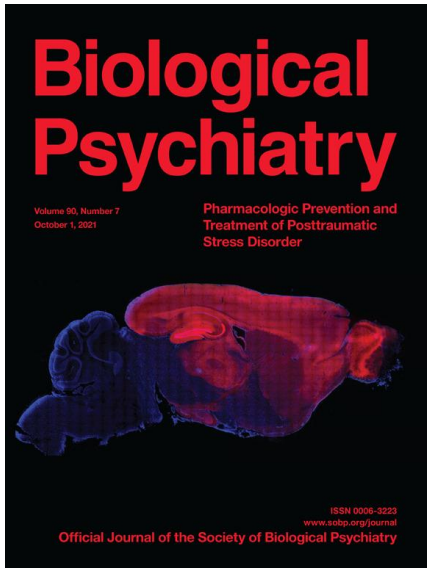
Methodology

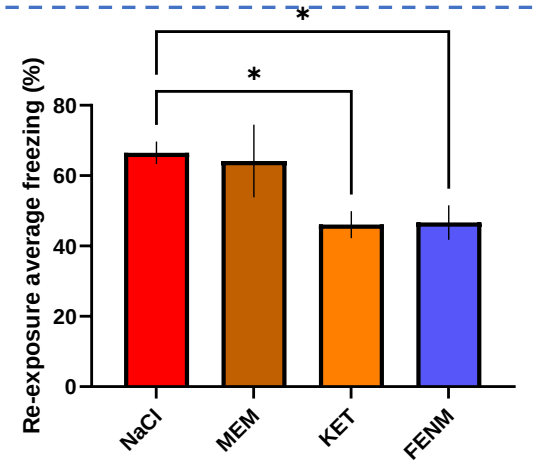
Saline, (*R,S*)-ketamine (30 mg/kg, highly psychedelic dose), or FENM (10, 20, or 30 mg/kg) was administered 1 week prior to Fear Conditioning

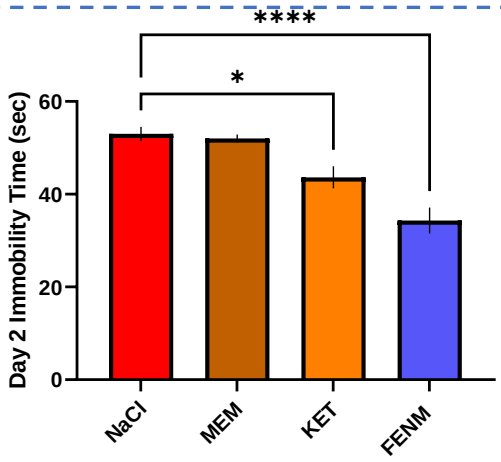


Results

2021





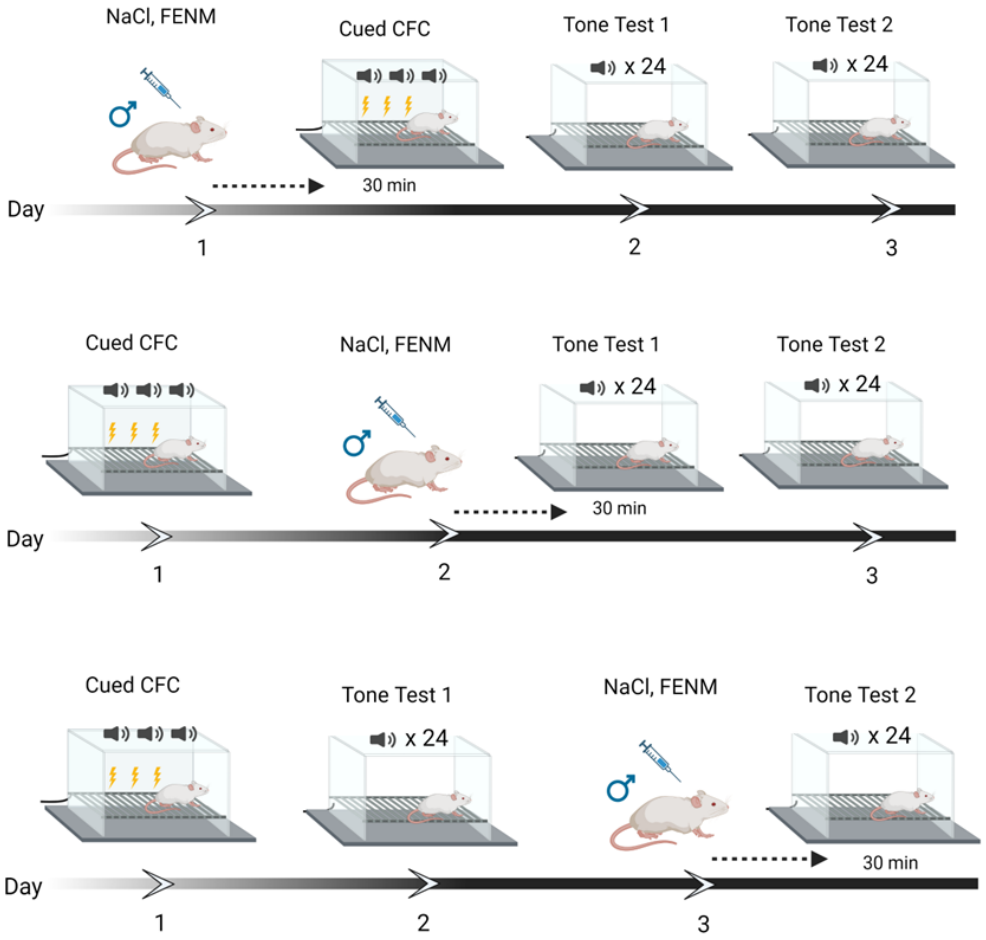


FENM attenuates learned fear and decreases stress-induced behavioral despair when administered as a prophylactic

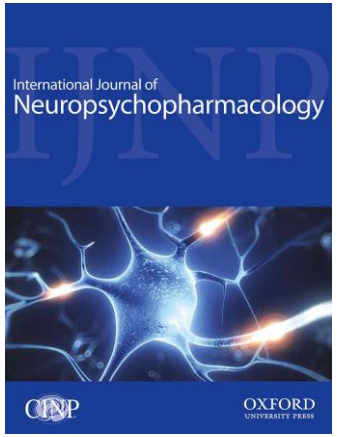
FENM also facilitates extinction of learned fear in preclinical models

where psychedelic Ketamine* could not even be applied, and Memantine** has no or negative impact

Methodology

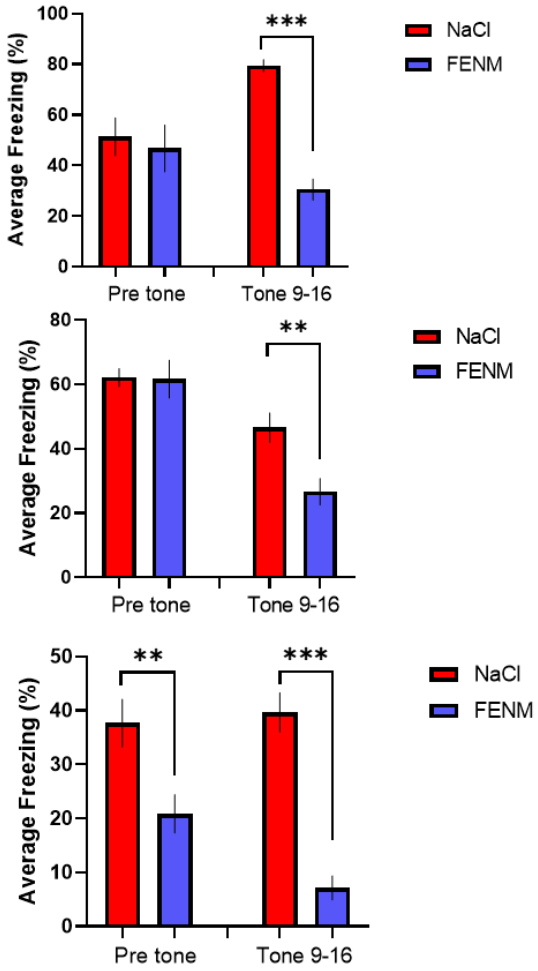


2021

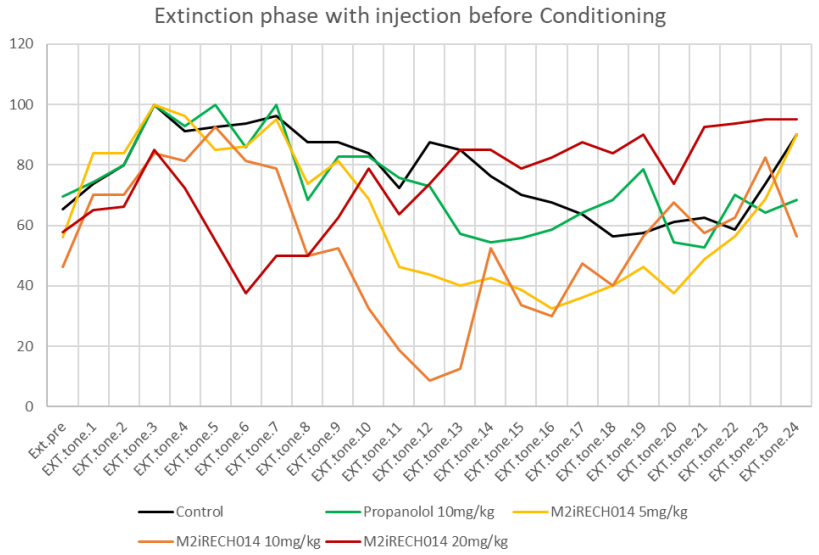


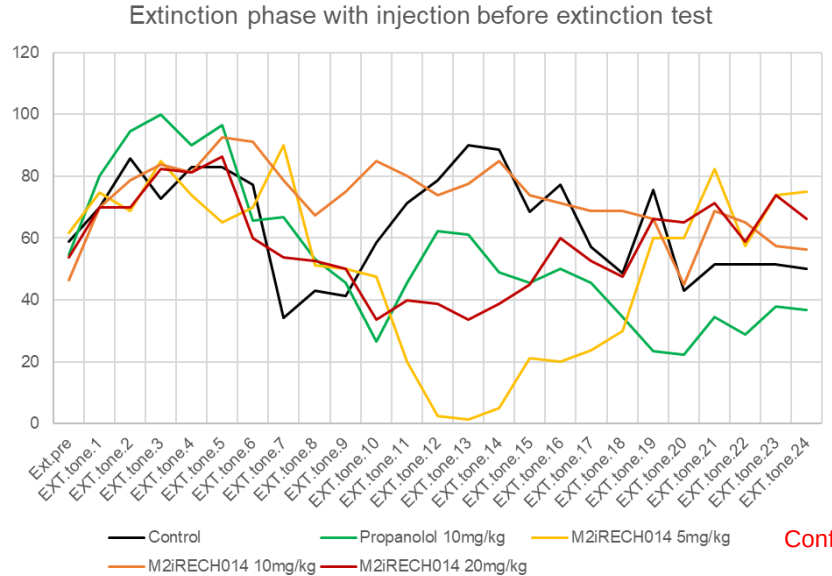
* *See Chen et al. (supp material)*
** *See Dong et al. and Ishikwa et al.*

Results (t2 session)

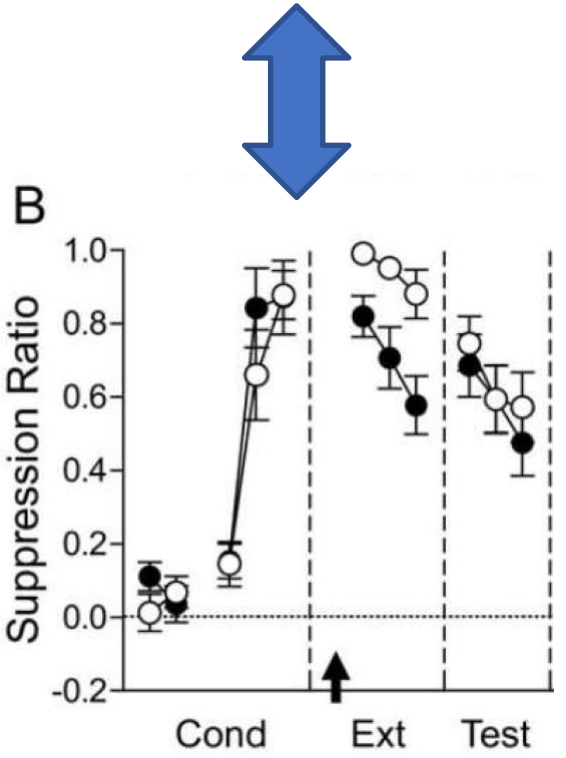


Fear Release – Focus on the Extinction phase and propranolol comparison





ReST has reproduced the results of [Rodriguez-Romaguera et al (2009)] on propranol, where injection before extinction only has effect during this stage

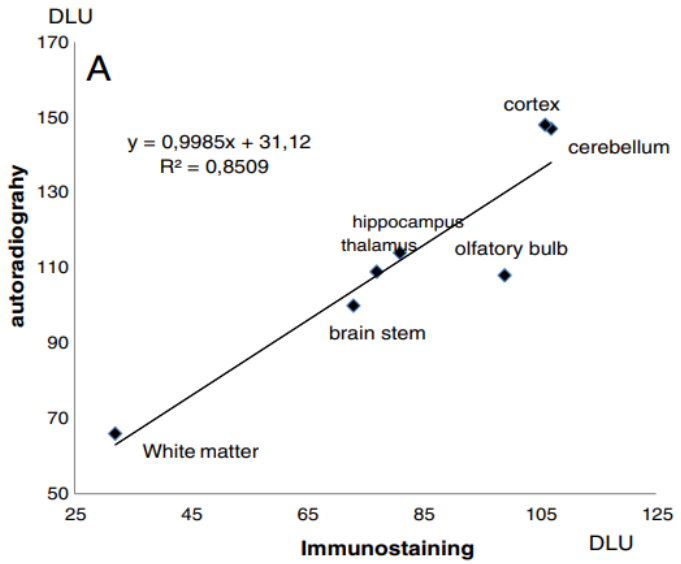


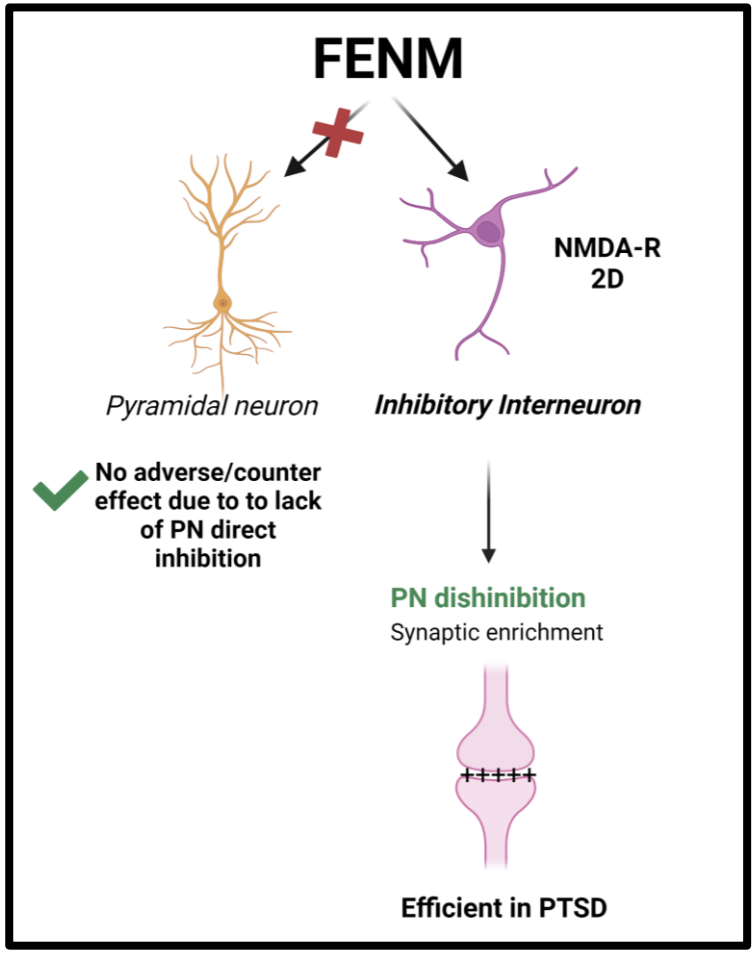
FENM MOA

Comparison the Memantine and Ketamine

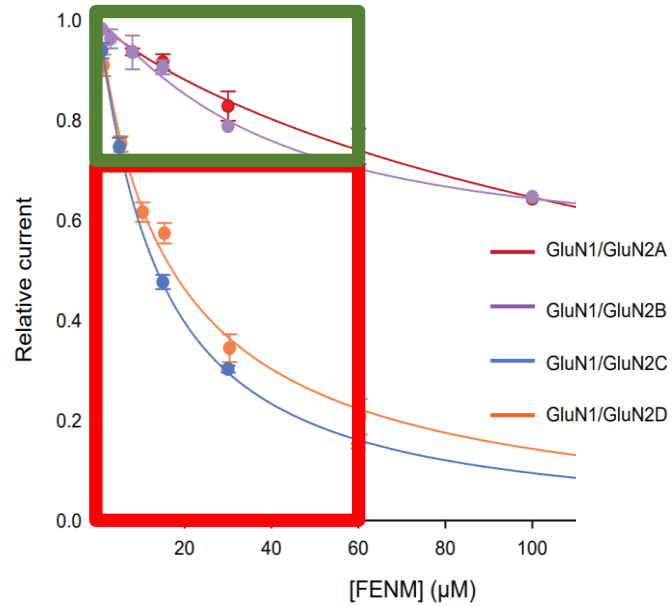
FENM targeted selective inhibition of NMDA-R GluN2D in inhibitory interneurons explains its efficacy

FENM accurately colocalizes with NMDA-R



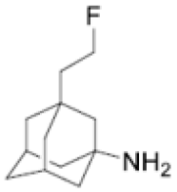
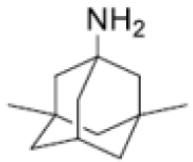
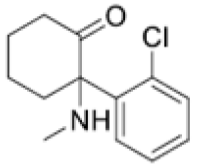


FENM selectively inhibits GluN2C & GluN2D



Mode of Action

Despite the fact that Ketamine & Memantine still have relative better affinity to 2C/2D than 2A/2B

	FluoroEthylNorMemantine 	Memantine 	Ketamine 
	IC_{50} 1mM Mg^{2+}	**IC_{50} 1mM Mg^{2+}**	**IC_{50} 1mM Mg^{2+}**
GluN1/ GluN2A	200 µM	20 µM	12,59 µM
GluN1/ GluN2B	200 µM	7,61 µM	6,97 µM
GluN1/ GluN2C	13,9 µM	1,02 µM	1,43 µM
GluN1/ GluN2D	17,88 µM	1,08 µM	1,27 µM

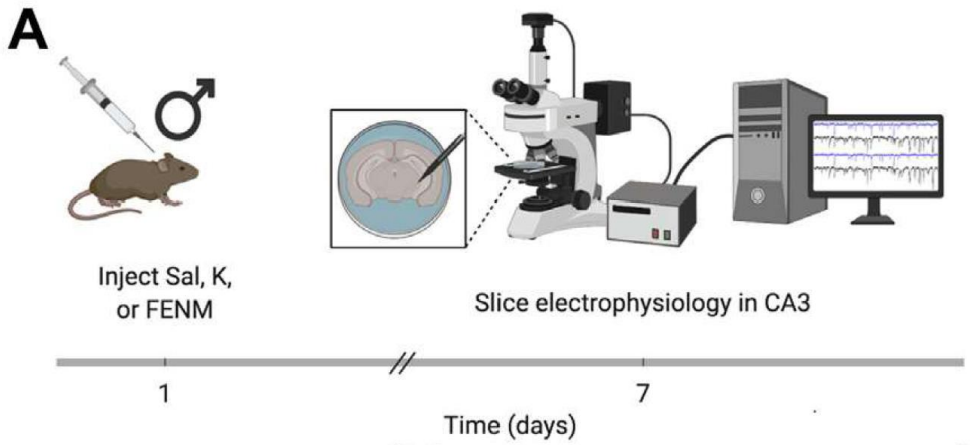
1-10µM

10-100µM

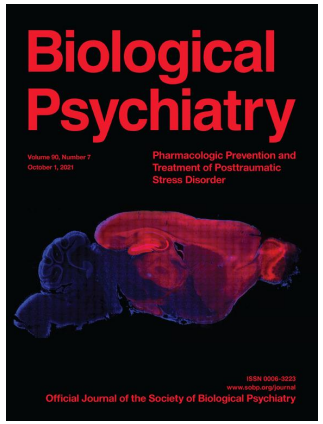
> 100µM

SPRAVATO (Janssen): "*The precise mechanism of action of ESK in MDD is unknown, but the prevailing theory is that it preferentially blocks NMDA receptors on inhibitory γ-amino-butyric acid (GABA)-ergic interneurons. Evidence within the literature suggests that this blockade transiently enhances the activity of glutamatergic neurons, including increasing the presynaptic release of glutamate, and stimulation of postsynaptic AMPA receptors".*

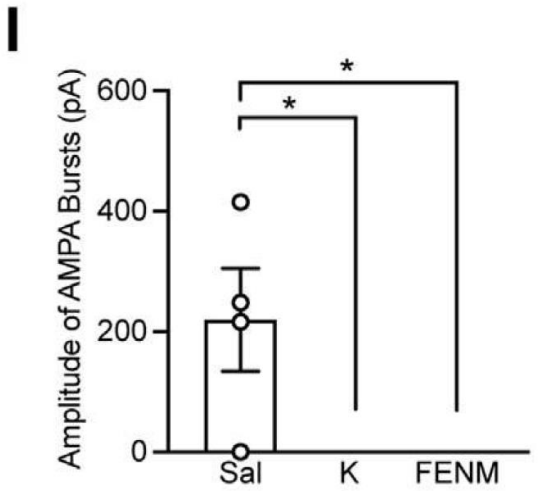
With a too high target engagment on 2A/2B, ketamine inhibits NMDA and AMPA bursts while FENM only acts on AMPA bursts ….

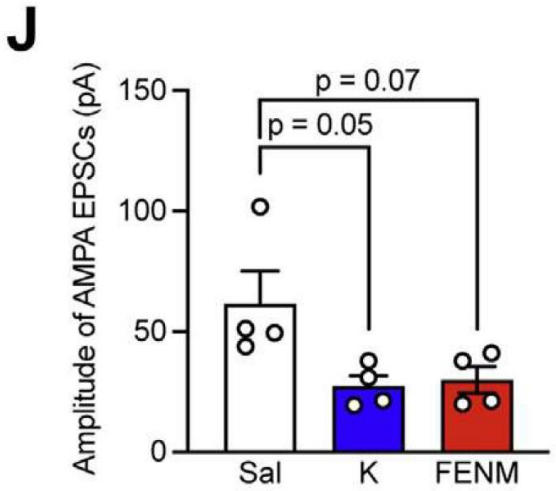


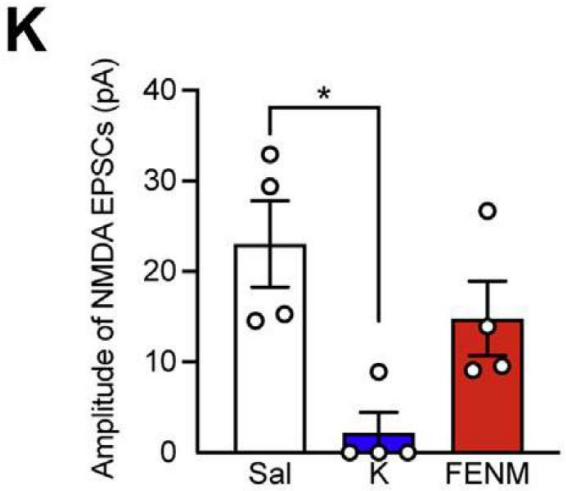
2021



	KETAMINE	FENM
Dose (mg/kg)	30	20
Brain Cmax in µmol	21	65
Estimated Target Engagment for pyramidal cells	70%	20%
Estimated Target Engagment for interneurones	95%	80%

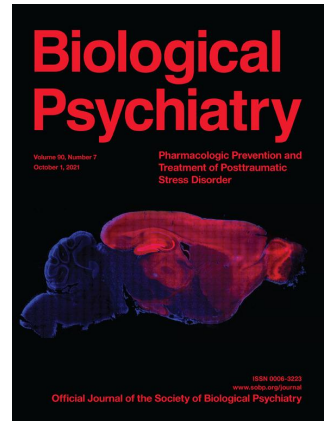


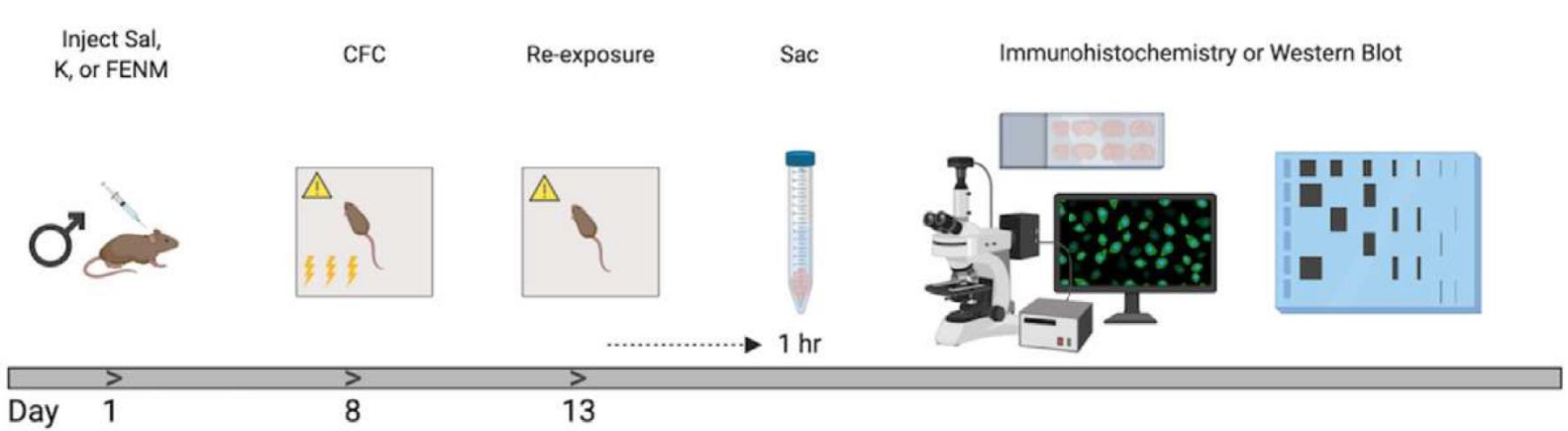


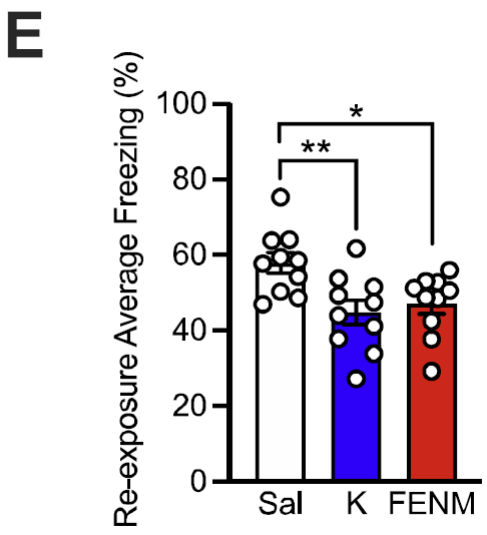


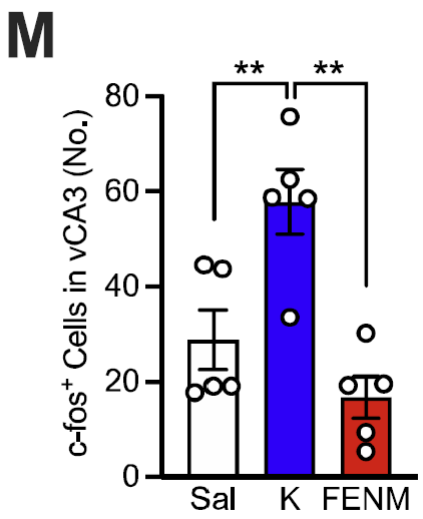
And with 2C/2D specificity, FENM does not affects the dissociative associated c-fos expression while ketamine does it

2021





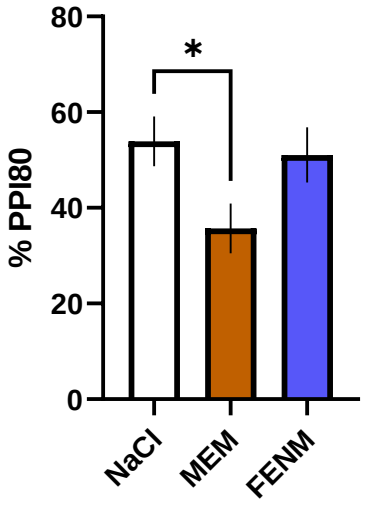




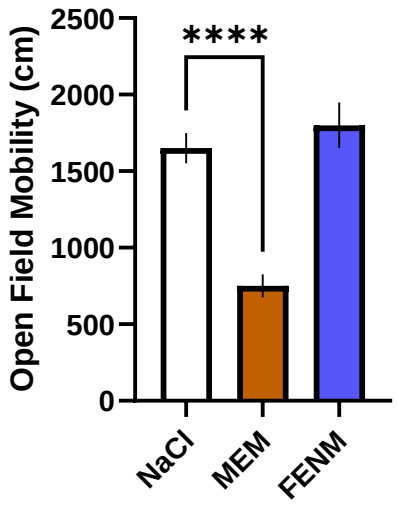
	KETAMINE	FENM
Dose (mg/kg)	30	20
Brain Cmax in µmol	21	65
Estimated Target Engagment for pyramidal cells	70%	20%
Estimated Target Engagment for interneurones	95%	80%

… which finally explains the lack of side effects for FENM

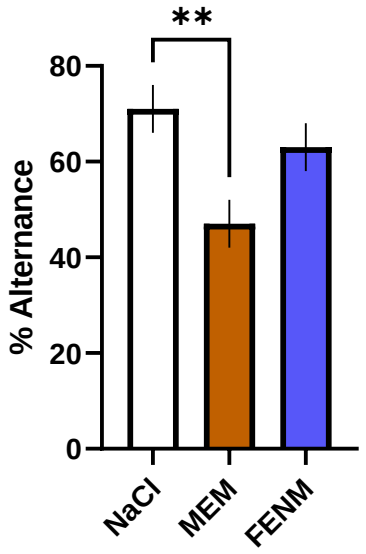
No sensory gating disruption



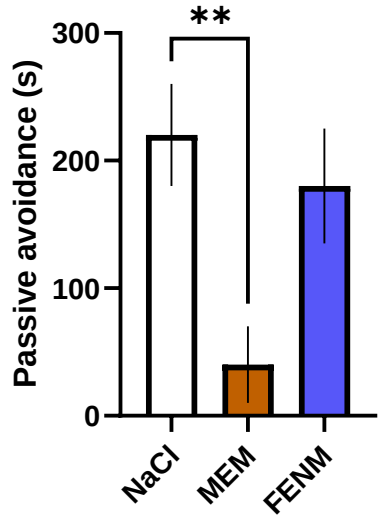
No sleepiness



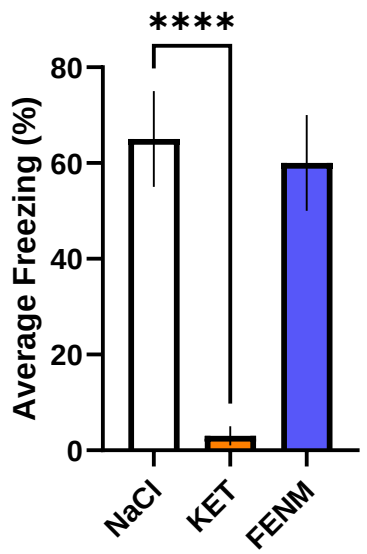
No working memory disruption



No long-term memory disruption



No memory encoding disruption



… and its highly favourable regulatory (FDA/EMA) toxicology/safety profile

- High 28D NOAEL in rodent and canine (**EMA scientific Advice allows for 3,2mg/kg in human**)
- High NOAEL in safety studies (FOB, Respiratory, Cardio)
- No genotoxicity

In the case of AD, the action of FENM goes through the reversion of NMDA 2A/B and PSD 95 impairments mediated by soluble amyloid peptides in synaptosomes

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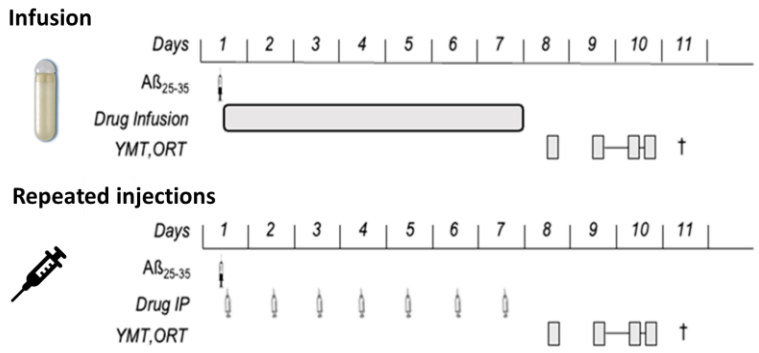
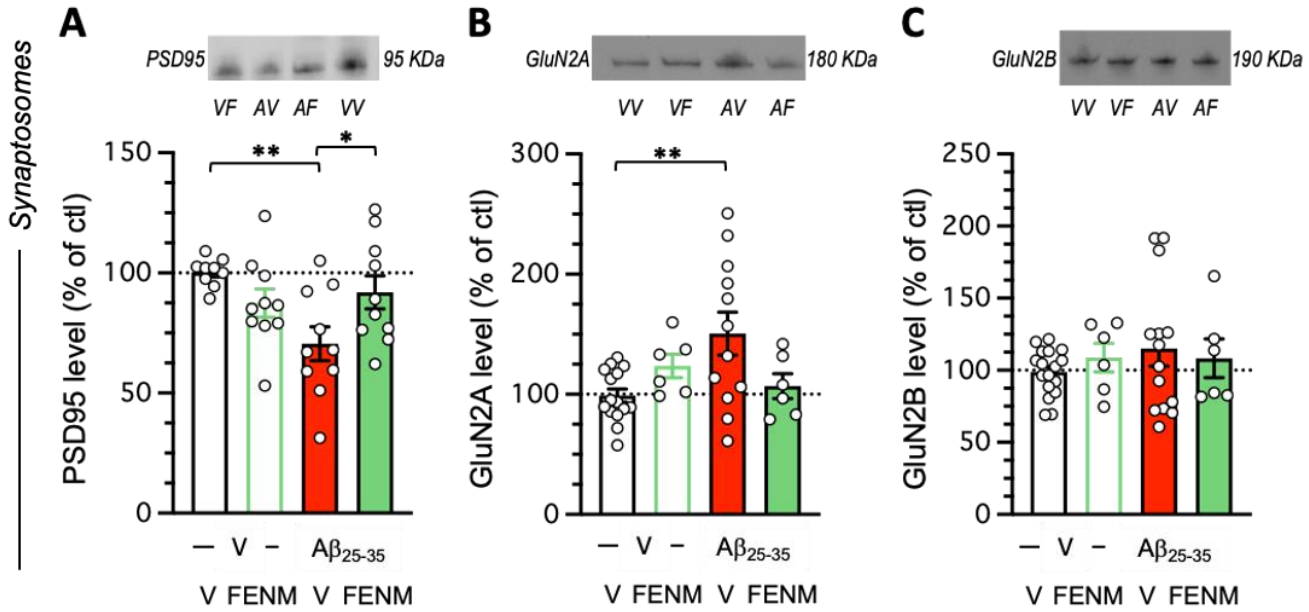




IP and Publications

2013 - 2023

FENM has a strong IP base

Exclusivity 2042 on PTSD and 2045 on AD with CTT

ReST Therapeutics **fully owns 2 patent families (FENM and its application for treating PTSD) which have been granted in several counties (US, EU, …):**

- **2013 -** EP3003399 - NOVEL CHEMICAL COMPOUNDS DERIVED FROM NORMEMANTINE AND USE OF SAME IN THE MEDICAL FIELD
- **2017 -** EP3723742 - USE OF FLUOROETHYLNORMEMANTINE FOR THE PREVENTION AND TREATMENT OF ANXIETY

ReST Therapeutics **co-owns and has exclusive rights to two other 2 patent applications (FENM application to Neurodegeneratives diseases),** one having been published :

- **2020 -** WO2021234324 - COMPOUND AND COMPOSITION FOR INDUCING NEUROPROTECTION
- **2021 -** WO2023079187 - NEW SYNERGISTIC COMBINATIONS BASED ON FENM AND AN ACETYLCHOLINESTERASE INHIBITOR

ReST Therapeutics has **an Option for exclusive license on a Patent of Columbia (FENM for primary protection against Stress)** :

- **2020 -** EP3968977 - COMPOSITIONS AND METHODS AGAINST STRESS-INDUCED AFFECTIVE DISORDERS AND THEIR ASSOCIATED SYMPTOMS

FENM IP Portfolio status as of Feb 27 2023 (I)

Patents own or co owned by REST THERAPEUTICS : state on 26/02/2023

Rest Invention	Owner	Title	Country	Status	Application #	Date Filed	Patent #	Expiry date*	Comment
FENM NCE	REST THERAPEUTICS	NEW CHEMICAL COMPOUNDS DERIVED FROM MEMANTINE AND ABLE TO BIND TO N-METHYL-D-ASPARTATE (NMDA) RECEPTORS	**France**	**Granted ; substituted by European patent where same object is claimed**	FR1301216	29-May-2013	**FR3006193**	29-May-2033	priority filing
		NOVEL CHEMICAL COMPOUNDS DERIVED FROM NORMEMANTINE AND USE OF SAME IN THE MEDICAL FIELD	PCT	Published ; expired	PCT/EP2014/060981	27-May-2014	na	na	-
			European Patent Office	**Granted ; in force**	EP14732508.8	27-May-2014	EP3003399	27-May-2034	-
			Germany				**60 2014 006 634.8**		-
			France				**EP3003399**		-
			UK				**EP3003399**		-
			United States of America	**Granted ; in force**	US14894822	27-May-2014	**US9714212**	27-May-2034	-
FENM ANXIETY	REST THERAPEUTICS	USE OF FLUOROETHYLNORMEMANTINE FOR THE PREVENTION AND TREATMENT OF ANXIETY	**France**	**Granted ; in force**	FR1762290	15-Dec-2017	**FR3075038**	15-Dec-2037	priority filing
			PCT	Published ; expired	PCT/EP2018/85333	17-Dec-2018	na	na	LO1 to be responded
			Canada	Under examination	CA3085585	17-Dec-2018	-	-	Examination requested
			China	Under examination	CN2018800894975	17-Dec-2018	-	-	-
			European Patent Office	Under examination	EP18815771.3	17-Dec-2018	-	-	LO awaited on March 2023
			Japan	Under examination	JP2020-552138	17-Dec-2018	-	-	LO1 to be responded
			United States of America	**Granted ; in force**	US16772582	17-Dec-2018	**US11464751**	24-Dec-2038	-
FENM NEUROPROTECTION	REST THERAPEUTICS INSERM EPHE UNIVERSITE DE MONTPELLIER	COMPOUND AND COMPOSITION FOR INDUCING NEUROPROTECTION	**France**	**Granted ; in force**	FR2005138	20-May-2020	**FR3110393**	20-May-2040	priority filing
			PCT	Published ; expired	PCT/FR2021/050929	20-May-2021	na	na	Found patentable during international preliminary examination
			Canada	Filed	CA3,178,633	20-May-2021	-	-	-
			China	Filed	to be assigned	20-May-2021	-	-	Request for examination to be filed on May 20,2023
			European Patent Office	Under examination	EP4142703	20-May-2021	-	-	-
			Japan	Filed	JP2022-571216	20-May-2021	-	-	Request for examination on to be filed May 20,2024
			Republic of Korea	Filed	KR10-2022-7044712	20-May-2021	-	-	Request for examination to be filed on May 20,2024
			United States of America	Filed	US17924420	20-May-2021	-	-	-
FENM AChEi combinations	REST THERAPEUTICS INSERM EPHE UNIVERSITE DE MONTPELLIER	NOVEL SYNERGISTIC COMBINATIONS COMPRISING FENM	France	Under examination	FR2111841	08-Nov-2021	-	-	-
			PCT	Filed	PCT/EP2022/081184	08-Nov-2022	-	-	-

* subjected to payment of maintenance fees

FENM IP Portfolio status as of Feb 27 2023 (II)

Patents under license agreement : state on 26/02/2023

Title	Country	Status	Application #	Date Filed	Patent #	Comments	Owner
PROPHYLACTIC EFFICACY OF FENM AGAINST STRESS-INDUCED DEPRESSION	United States of America	expired	US62/848,406	15- May-2019	na	Priority filing US Provisionnal application	The Trustees of Columbia University in the City of New York
PROPHYLACTIC EFFICACY OF FLUOROETHYLNORMEMANTINE (FENM) AGAINST STRESS INDUCED DEPRESSION	United States of America	expired	US62/861,765	14- June-2019	na	Priority filing US Provisionnal application	
COMPOSITIONS AND METHODS AGAINST STRESS-INDUCED AFFECTIVE DISORDERS AND THEIR ASSOCIATED SYMPTOMS	PCT	Published ; expired	PCT/US2020/032886	14-May-2020	na	-	The Research Foundation For Mental Hygiene, Inc.
	European Patent Office	Under examination	EP20806905.4	14-May-2020	-	Response to ESR to be filed in July 2023	
	United States of America	Under examination	US17526716	14-May-2020	-	-	

… and high-impact scientific publications

FENM as a Radiotracer

- Anne-Sophie Salabert et al.; Radiolabeling of [18F]-fluoroethylnormemantine and initial *in vivo* evaluation of this innovative PET tracer for imaging the PCP sites of NMDA receptors; **Nuclear Medicine and Biology (2015)**
- Anne-Sophie Salabert et al.; Evaluation of [18F]FNM biodistribution and dosimetry based on whole-body PET imaging of rats; **Nuclear Medicine and Biology (2018)**

FENM as a Drug candidate in AD

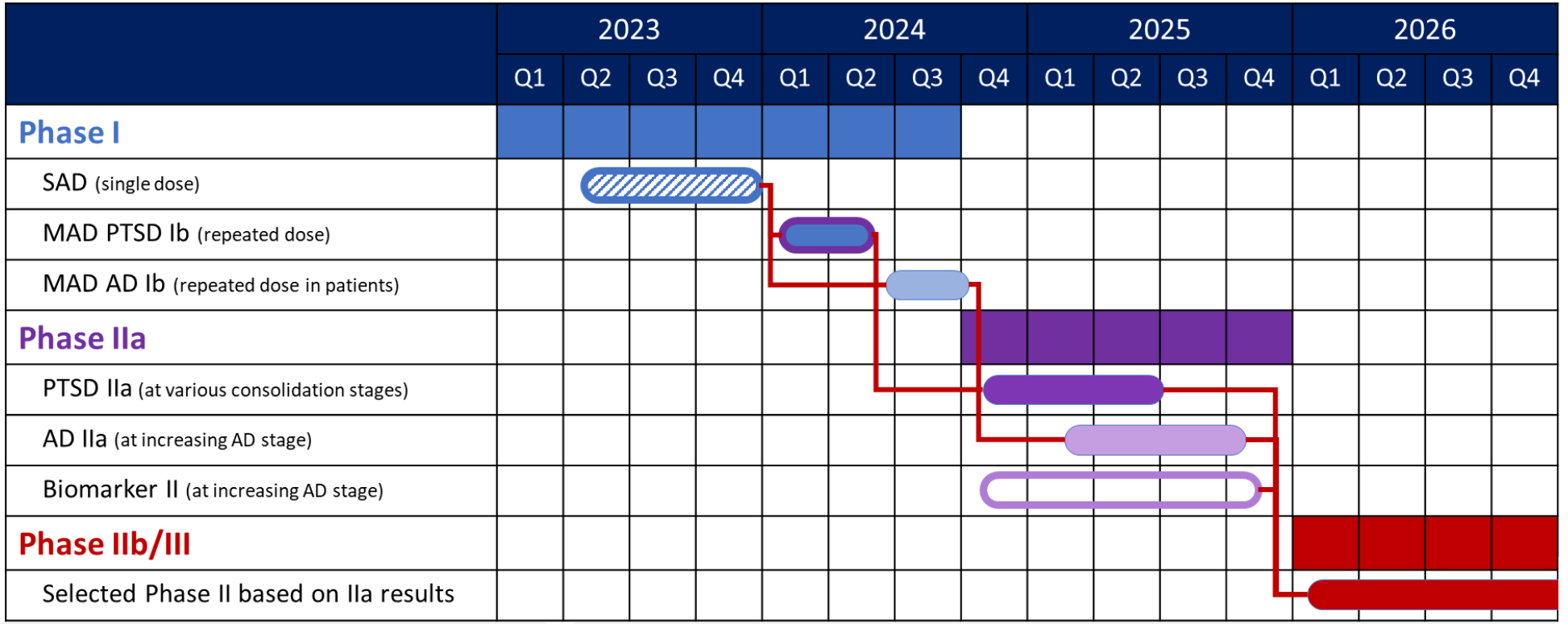
- Simon Couly et al.; Anti-amnesic and neuroprotective effects of Fluoroethylnormemantine in a pharmacological mouse model of Alzheimer's disease; **International Journal of Neuropsychopharmacology (2020)**
- Allison Carles et al.; Neuroprotective effects of Fluoroethylnormemantine (FENM) in the Aß25-35 mouse model of Alzheimer's disease: chronic infusion by Alzet pumps and long-term efficacy; **Neurosciences (2022)**

FENM as a Drug candidate in PTSD

- Briana K. Chen et al.; Fluoroethylnormemantine, A novel derivative of memantine, facilitates extinction learning without sensorimotor deficits **International Journal of Neuropsychopharmacology (2021)**
- Briana K.Chen et al.; Fluoroethylnormemantine, a Novel NMDA Receptor Antagonist, for the Prevention and Treatment of Stress-Induced Maladaptive Behavior**. Biological Psychiatry (2021)**

Clinical development strategy

FENM clinical pathway until PIIb



Phase I

~80 Healthy volunteers, primary to demonstrate:

- The safety of the drug and notably (Lack of off-target effects and psychotropic activity)
- Proper pharmacokinetic properties of the drug

Phase IIa

150-200 Patients, primary to demonstrate:

- PTSD Phase IIa: patients at various stages of PTSD consolidation (3 months, 6 months, 12 months, 24 months + 30 days administration)
- AD Phase IIa: patients at increasing AD 4 stages (30 days administration)
- Biomarker Phase II: [18F]FENM PET scan at the inclusion, after 30 days treatments, and at 6 months on the patients from AD Phase IIa

Strategy for early Pharmacodynamics demonstration (I)

Biomarkers selection

There is no “unequivocal biomarker” of specific inhibition of GluN2D-containing-NMDA-R in human and specific GluN2D-linked activity. So there is a need for early demonstration of FENM pharmacodynamics.

FENM Clinical pathway makes use of both PTSD and AD developments to successfully show, that during the phase 1a (SAD) and the two 1b (MAD) studies:

1. FENM does cross the Blood-Brain-Barrier;
2. FENM does interact with (at least one member of) the NMDA-R family;
3. FENM does not exert clinical activities know to be related to GluN2A- & GluN2B- NMDA-R, which would prove the specificity of FENM

Due to safety and ethical considerations regarding human subjects involved in clinical trial we would be able to deploy this demonstration on 3 clinical trials:

- SAD – Single ascending dose of oral administrated FENM
- MAD PTSD – 28 days Multiple Ascending dose of oral AFENM in Young Healthy Volunteers. It is very unlikely that we would be in position to do this study on PTSD patients, given the variables still pending at the end of the FIH considering repeated administration. Additionally, in 2024, ReST would not have acquired the preliminary repro-tox safety results allowing to include non-menopaused women in the study.
- MAD AD – 28 days Multiple Ascending dose of oral AFENM in Elderly patients with AD. Conversely, once, the P1b phase results show the good tolerance on Young Healthy Volunteers of an FENM 28 days treatment, it will make sense, given the problematic definition of “healthy” in elderly volunteers (and the associated risk to participate into any P1 trial) and the importance to address some key biomarkers for further clinical development in AD, to apply for a CTA in AD patients for this study.

Strategy for early Pharmacodynamics demonstration (II)

	Single ascending dose of oral administrated FENM	28 days Multiple Ascending dose of oral FENM in Young Healthy Volunteers	28 days Multiple Ascending dose of oral FENM in Elderly patients with AD

FENM does cross the Blood-Brain-Barrier	• NA	• PET-Scan/MRI with 18-FENM at the inclusion (primary baseline)
		  ○ good crossing of the Blood-Brain-Barrier in Human;
		  ○ low non-specific binding/noise, with strong labelling of cerebral cortex, cerebellar cortex, brain stem and central nuclei (grey matter)
		• PET-Scan/MRI with 18-FENM also at :
		  ○ 4 weeks of administration, at equilibrium of measured FENM plasma concentration (assuming equilibrium also within the brain) : competition between steady state cold-FENM and 18-FENM;
		  ○ 2 weeks after treatment discontinuation, with no more FENM in plasma (measured and controlled) : secondary baseline
			• At D0 and D28:
			  ○ dosage of FENM level in CSF (CerebroSpinal Fluid) obtained by lumbar
			  ○ additional CSF biomarkers : Amyloid-β42, total Tau, phospho-Tau;
			• this will also allow a simultaneous pharmacokinetic analysis of plasma and CSF concentrations of FENM, at a stationary level and quasi equilibrium of plasma concentration; thus, we will confirm brain & CSF penetration of FENM, and we will be able to quantify this penetration through the clinical measure of the ratio “CSF/plasma concentrations”.

FENM does interact with (at least one member of) the NMDA-R family	• Optional measurement of plasma level BDNF at higher doses	• PET-Scan/MRI with 18-FENM 4 weeks after the discontinuation of the treatment to show :
		  ○ competition between ketamine-IV at 0.5mg/kg (a dose that affect all NMDA-R subtypes) and 18-FENM
		  ○ We anticipate that ketamine will strongly decrease (maybe even will almost abolish) 18-FENM radiolabelling (i.e. like that has already been observed and published in rats)
		• Optional measurement of plasma level BDNF at higher doses
			• NA

FENM does not exert clinical activities know to be related to GluN2A- & GluN2B- NMDA-R, which would prove the specificity of FENM	• at plasma FENM pic concentration (6-8h after oral intake), for the 3 higher doses :
	  ○ canonical scales used for assessment of sedation (Ramsay scales)
	  ○ dissociation (CADSS-6, full CADSS, typically found in publications with ketamine),
	  ○ to ensure that no classic clinical effects of non-specific NMDA antagonist (Ketamine, Memantine) are observed
		• at D7, D14, D21, D28, D42 :
		  ○ canonical scales used for assessment of sedation (Ramsay scales)
		  ○ dissociation (CADSS-6, full CADSS, typically found in publications with ketamine),
		  ○ to ensure that no classic clinical effects of non-specific NMDA antagonist (Ketamine, Memantine) are observed
			• NA