Category

Best Startup

Product/Solution Name

FENM, a cure for PTSD and AD

Date of Approval

N/A

Indications

PTSD, AD

Therapeutic Categories

Central Nervous System Diseases

Attached Files:

- 230522 ReST Therapeutics short deck .pdf

Background information and need for solution/product

Post-Traumatic Stress Disorder (PTSD) is a severe disease following a psychic trauma. Victims or even witnesses of warfare, physical or sexual assault, natural disasters, traffic accident, would develop this condition that affects over 18 million people in Europe & US.

If its cause is simple, PTSD is complex and borrows symptoms from almost all other psychiatric diseases. Untreatable life-long depression, phobia and recurrent panic attacks, multiple addictions, lead to social withdrawal, disruption of family and professional life, extracerebral heavy comorbidities. Over 20% of PTSD patients will try and end their own life.

Thanks to the Veteran's Associations and remarkable movies and testimonies on the suffering of soldiers, PTSD received social recognition in the 90's, not only the "military PTSD" but also the "civilian traumatisms" which account for 80% of the patients, awfully mostly women victims of sexual assault. Depending to the nature of the trauma, 1/4 to 1/2 of the victims develop life-long PTSD. A recent pharmacoeconomic survey estimated that, in US only, the economical burdens of PTSD reach $232Bn yearly.

Classical psychiatric managements of PTSD, whether based on drug or on cognitive and psychotherapies, have very limited efficacy. They are mostly symptomatic and do not address the root cause of PTSD, the pathological dreadful memory becoming unforgettable, encysted, distorted and deforming, invasive. Therefore, there is an urgent need for effective, safe and disease-specific medicines, particularly ones that could be given at the earlier stages of PTSD consolidation (3-6 months after the trauma), act as secondary prophylactics and would be a real cure to PTSD.

Less know is that PTSD is linked to another plague, Alzheimer (AD) that affect 35 million people worldwide today and expectedly 113 million by 2050. Victims who suffer from PTSD see their risk to

develop AD doubling, which is daunting knowing that elderly people over 85 already have a basal 25% risk to develop AD. Underlying this epidemiological connection, NMDA receptors are both critical in the pathophysiology of PTSD and a key step in the excitotoxicity and neuronal death in AD.

In that context the actual lack of disease modifying solutions and the economical un-sustainability of the recently developed amyloid targeting monoclonal antibodies make AD look like a “slow rising pandemic emergency”, calling for efficient but also economically realistic therapeutic solutions.

At the crossroad of several brain diseases, NMDA receptors have been the target of drug developments for many years. Among the “limited” successes, one can cite Memantine, one approved treatments for AD and Ketamine which has recently revolutionized psychiatry, creating the new class of “fast acting antidepressant”. But Memantine only temporarily alleviates AD symptoms and the condition flares when the treatment ends and Ketamine is only able to treat the Depression associated with PTSD. The reason for this lack of efficacy appears to be a lack of precision in targeting the desired NMDA sub-type resulting in a too narrow (or even negative) therapeutic index. On the other hand they are the right benchmarks to use to design and validate the right solution.

History of the development of the solution/product

FluoroEthylNorMemantine (FENM) was invented in 2013, designed to be a PET scan radiotracer specific of NMDA Receptors (NMDA-R). It rapidly fulfilled all the requirements to be a good radiotracer : safe and well tolerated, high crossing of the blood-brain-barrier, but mainly a distribution within the brain perfectly correlated with the localization of NMDA-R. [18F] FENM also proved to be a functional radiotracer as its specific colocalization with NMDA-R is abolished when Ketamine is used as anesthetic. [18F] FENM PET-scan imaging in models of traumatic brain injury follows NMDA-R disturbances. These results were of even more interest because the previously designed fluorinated Memantine, when administrated does not accumulate in the relevant NMDA-R rich cerebral substructures.

Based on these results, preclinical experiments were conducted between 2015 and 2021 on PTSD and AD.

Our murine preclinical PTSD development has been performed with Dr Christine Denny (Columbia University, NY, USA). FENM allows a complete release from fear conditioning, is efficient on depression & despair induced by several stress paradigms, being even better than Ketamine. Furthermore, FENM notably reduces anxious behaviors of stressed mouse, while Ketamine elicits anxiety (an effect that is present in clinico). This side-effect of Ketamine can explain its failure in the latest clinical trial on PTSD and is known to hamper its efficacy in depression. Based on these results, we believe FENM has the potential to be a first-in-class drug on PTSD.

In several murine AD models, our collaboration with Pr Tangui Maurice (Montpellier University, France) demonstrated that FENM provides efficient neuroprotection and largely surpasses Memantine. Particularly, we were able to establish a amyloid peptide based model that shows the decay of Memantine’s efficacy over time, in the same manner to what is observed in AD patients, thereby establishing one of the first translational models for the pathology management. In this model, not only does FENM induce a sustainable cognitive protection during the entire course of the 2 months treatment, but its efficacy does not vanish after discontinuation of the administration. Furthermore, in mice first treated with Memantine, with the initial efficacy lost over time, switching treatment to FENM

allowed to restore the cognitive functions, proving that FENM could be a disease-modifying drug in AD.

The Preclinical superiorities of FENM on both Memantine/AD and Ketamine/PTSD can be related to its unique pharmacological properties and mode of action : coupling specificity on NMDA-GluN2C&D receptors and PK/PD profile. At pharmacological dose FENM does not affects main pyramidal neurons (containing GluN2A&B) and does not induce anterograde amnesia, sedation/anaesthesia, delusion, as Ketamine and Memantine do (which ws confirmed in several preclinical experiments). Hence FENM would be able to inhibit parvalbumin inhibitory interneurons (expressing GluN2D), and probably operate on the Cerebellum (expressing GluN2C) based fear extinction, inducing efficient neuroprotection (AD) and suppression of dreadful memory (PTSD) without side effects.

ReST Therapeutics has entered the Clinical stage of its development in 2023, with a positive Scientific Advice received from EMA and the application for FIH Clinical Trial Authorization in May.

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- 20230522 ReST Therapeutics Science Deck form Galien.pdf

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

The unique mode of action of FENM allows for a rapid development, first in PTSD and then slightly time-shifted in AD.

In PTSD FENM can be a 1st in class, applied at preventing the consolidation of PTSD, basically allowing for a normal healing of the memory of a nevertheless traumatic event. This would work by allowing re-balancing memories to form a prevent the encysting of the trauma and would be facilitated by a particularly good tolerance of the product (anticipated by the preclinical results) but also by the fact that the lack of psychedelic component in its action make it particularly fit for vulnerable people, that the victims of trauma definitely are. This situation would facilitate the pivotal clinical proof of concept, and allow a rapid access for a first subset of patients (women victims of sexual assault) before extending to other indications and trauma in subsequent phase3 trials.

In the case of AD, FENM is “the Memantine that should have been” when it was designed almost 40 yeas ago. Indeed it is probably the poorer bioavailability of Memantine at the desired NMDA concentrated sites within the Brain that explains its lack of efficacy and induce its side effects, vertigo, falling, sedation, particularly problematic in elderly patients. FENM being a targeted NMDA antagonist would inhibiting excitotoxicity and death of interneurons, disrupting the neuroinflammatory cascade and vicious circle, preventing the progression of the disease.

Since we also demonstrated a synergistic action with Acetylcholinesterase Inhibitors (AChEIs) already marketed, FENM can be given at all stages of AD (and not only late stage, contrary to Memantine), in combination with standard of care AChEIs (typically Donepezil/Aricept) at early stage of AD. The clinical development will then be thus further accelerated.

A clear pitfall of many drug developments today is that their market cost is too high. It sometime looks like every development is treated though a rare disease economic model point of view. Even if often justified from an industrial point of view (many developments are based on hard to make biological

products) these costs are not sustainable for healthcare systems for disorders affecting millions of patients. In PTSD and AD, cures will thus need to be not only efficient but also affordable, with administration related costs compatible with the large number of prescriptions. FENM is a small molecule, fit for easy daily oral tablet administration at home and despite an original route of synthesis, ReST Therapeutics succeeded in keeping its cost reasonable. A price of $15-10.000 for a complete cure of PTSD and the golden target of $1000 yearly treatment for AD seem perfectly achievable with FENM !

Attached Files:

- Denny REST Letter.pdf
- 230524 Lett ReST Galien.pdf
- ReSTLetter of Support Pr GaillardGalien_2023.pdf

Please provide appropriate references (ie Pubmed links)

FENM as a Radiotracer and related references

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Patents and Patent application covering FENM

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WO2021234324A1 COMPOUND AND COMPOSITION FOR INDUCING NEUROPROTECTION https://worldwide.espacenet.com/patent/search/family/073013493/publication/WO2021234324A1?q=pn%3DWO2021234324A1

WO2023079187A1 NEW SYNERGISTIC COMBINATIONS BASED ON FENM AND AN ACETYLCHOLINESTERASE INHIBITOR https://worldwide.espacenet.com/patent/search/family/080595290/publication/WO2023079187A1?q=pn%3DWO2023079187

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Attached Files:

- Chen Int J NPP 2021.pdf
- Couly Int J NPP 2020.pdf
- Chen Biological Psychiatry 2021.pdf