



MITHRIDION, INC

Building a High Value CNS drug company

Executive Summary – 11/2009

At A Glance

- Wisconsin C-corporation
- Start of operations: Feb 2006
- Equity funding to date: \$7.4m
- Grants/contracts to date: ~\$4.5m
- Current \$1.2m/3 year SBIR grant
- WI State TDF Loan: \$0.2m
- Core team: 11
- Certified QNBV in Wisconsin

Unmet Clinical Need

- 26 million Alzheimer's disease sufferers worldwide, growing fast
- Drugs poorly effective

Market Opportunity

- Current market >\$4.1 billion
- Potential market \$10 billion

Intellectual Property

- 9 issued US patents
- 9 patent applications
- Worldwide exclusive license

Management Team

- Trevor M Twose, CEO
- Bruce G McCarthy, MD, VP Drug Development and CMO
- Alex M Kasper, CPA, CFO
- Richard R Copp PhD, VP Chemistry
- Wayne P Hoss, Director, Toledo
- Prof William S Messer, Jr, CSO
- Patti A Twose, Operations Director

Board of Directors

- Trevor M Twose (CEO/Chair)
- Paul M Weiss PhD MBA
- Wayne P Hoss PhD
- John Neis MBA

Scientific/Clinical Advisers

- Prof Daniel A Rich
- Franklin P Bymaster

Professional Advisers

- Biopons, Inc (Business)
- Foley & Lardner (Legal)
- Grant Thornton (Financial)

Investors

- Venture Investors LLC (Madison, WI)
- State of Wisconsin Investment Board
- Wisconsin Investment Partners
- Rocket Venture Fund (Toledo, OH)
- WARF (Madison, WI)
- Rosetta Partners (Lake Forest, IL)
- Biopons, Inc (Fitchburg, WI)

Funding

- Cash in hand to complete phase I
- Currently seeking final closing of Series B

Mission

Mithridion is a biopharmaceutical company that discovers and develops drugs for central nervous system disorders, with an initial focus on Alzheimer's disease and schizophrenia.

History

In Feb 2006, Mithridion raised its first equity funding, and commenced operations, building a strong Central Nervous System drug research and development team. In February 2007, Mithridion installed powerful triple-quad mass spec capability for evaluating brain penetration, metabolism and pharmacokinetics of its drug candidates. In June 2008, Mithridion acquired Cognitive Pharmaceuticals Ltd (Toledo, OH), which brought an exciting clinical-stage drug candidate and a platform technology, and expanded the management team. In June 2008 and January 2009, Mithridion closed \$5.2m of Series B funding. The company is headquartered in laboratories and offices at the University Research Park in Madison, WI. Clinical drug development is managed out of Toledo (OH) and Ann Arbor (MI).

The Opportunity

Alzheimer's disease (AD) is a devastating condition affecting 5 million Americans and 26 million people worldwide. The five drugs approved by FDA provide only modest symptomatic relief of limited duration for a proportion of patients. Mithridion aims to develop drugs for AD that halt or slow down the inexorable loss of neurons that is the ultimate cause of memory loss and cognitive decline in AD (disease modifying drugs) and improve memory and cognitive function. No such drugs are available today. MCD-386 is its first such clinical-stage drug candidate. The unmet clinical need and market opportunity are immense. The potential world market is expected to grow to \$10 billion over the next decade, fuelled by demographics - an aging population and the 'baby boom' generation. Mithridion's drug candidate are also designed to treat cognitive impairment in schizophrenia – a major unmet clinical need.

Product Pipeline

- MCD-386CR is in Phase I clinical trials as a potential first-in-class disease-modifying drug for AD, and for cognitive impairment in AD and schizophrenia.
- A back-up drug compound for MCD-386 has been identified ***NEW***.
- Series 09-018 drug leads are in preclinical development as next-generation disease-modifying drugs for AD (preclinical proof-of-concept established), and for treating cognitive impairment in AD and schizophrenia; they have extremely potent potential anti-psychotic activity in lab animal models ***NEW***.
- Forte (high dose), Transderm (skin patch) and Forte/Transderm product options are available for MCD-386, backups, and Series 09-018 drug leads (preclinical proofs-of-concept established) ***NEW***.

Business Model

Mithridion's strategy is to develop drug candidates in house, then project-manage pre-IND studies and Phase I and II clinical trials, contracted out to specialist service providers (CROs). By this strategy, Mithridion seeks to create and add great value, then to realize it in the form of licensing fees and royalties, by licensing its drug candidates to pharmaceutical company partners at latest for Phase III clinical development, regulatory approval and marketing. The company aims to provide liquidity for investors through an IPO or a trade sale.

Management Team

The management team is led by an entrepreneur with extensive large and small pharmaceutical company experience, including start ups and IPOs, Mithridion has a strong group of scientific, industry and professional advisors.

Scientific Rationale

- Muscarinic cholinergic receptors are vital for memory and cognitive function
- Target: restore cholinergic function with muscarinic drug
- Selectively activate M1 subtype or M1 and M4
- Avoid activating M2 and M3 subtypes to avoid side effects
- Activate multiple modes of disease-modifying actions, including α -secretase to reduce A- β production

First Generation Muscarinic Drugs

- Several first generation drugs improved memory in laboratory animals
- AF267b demonstrated disease-modifying activity in a transgenic mouse model of AD
- Xanomeline and talsaclidine reduced A- β in the CSF of AD patients
- Xanomeline (Lilly) demonstrated clinical effects in AD and schizophrenia, validating the therapeutic approach
- First generation drugs had unwanted muscarinic activity in humans, leading to unacceptable side effects

MCD-386 Pharmacology

- Thought to be one of the most active and M1 selective muscarinic agonists described to date
- A second generation M1 selective muscarinic agonist drug
- Selective for M1 receptor in in vitro functional tests ('functionally selective')
- Improves memory function in three models, including a rat model of the AD cholinergic defect
- Multiple modes of potential disease-modifying actions in cell lines
- Engages key signaling pathways in lab animal models in vivo ***NEW***
- Free of muscarinic side effects at a dose that improves memory/cognition in lab animals

Initial Clinical Proof-of-Principle

- Seeking to establish quickly whether MCD-386 is free of unwanted side effects at predicted therapeutic doses

MCD-386 Clinical Development Status

- US FDA IND cleared July 2009
- Completed Phase I single ascending dose study
- Completed development of controlled release tablets (MCD-386CR)
- Clinical supplies of MCD-386CR have been manufactured
- Further Phase I studies of MCD-386CR are planned to begin Q4/2009 for completion in Q1/2010

Scientific Background and MCD-386

Cholinergic Function and Cognition

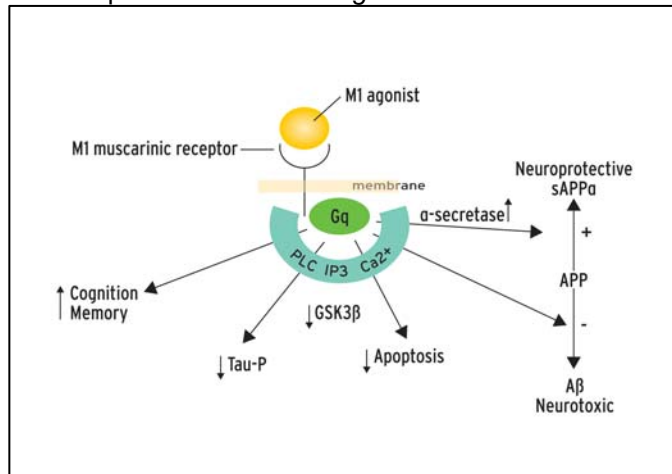
Many neurons in the brain (known as 'cholinergic' neurons), including those vital for memory and cognition, communicate via the neurotransmitter, acetylcholine, (ACh). ACh is released from neuron endings, crosses to other neurons, binds to receptors ("muscarinic receptors"), and activates internal mechanisms. In laboratory animal models, drugs that mimic ACh ("muscarinic agonists") enhance memory and cognition, and drugs that block acetylcholine ("muscarinic antagonists") impair memory and cognition. In AD, cholinergic neuron function is deficient, most likely due to neuron death caused by the neurotoxic peptide, amyloid A β .

Five Muscarinic Receptor Subtypes

The M1 muscarinic receptor sub-type is vital for memory and cognition. The other four subtypes (M2-M5) are responsible for other actions of acetylcholine. For examples, activation of M2 receptors slows down the heart; and activation of M3 receptors causes sweating, salivation, tear production, and gastrointestinal tract effects, including diarrhea. Mithridion has designed and developed small-molecule drugs that selectively activate individual sub-types of muscarinic receptors. Replacing lost ACh function using an M1-selective muscarinic agonist should improve memory in AD patients and cognition in AD and schizophrenia patients, while avoiding side effects caused by activation of M2-M5 receptor subtypes.

Potential Disease-Modifying Action

Muscarinic M1 agonists activate several pathways that potentially will slow or halt the disease process in AD: see figure.



Previous Clinical Experience with Selective Muscarinic Agonist Drugs

In Phase II clinical trials, Lilly's xanomeline had beneficial effects on disease symptoms in both AD and schizophrenia. However, unacceptable muscarinic effects were seen, including diarrhea, fainting, sweating, and salivation. This first generation drug validated

this therapeutic approach, and defined the key challenges: to improve agonist activity, but above all, to achieve better selectivity to avoid side effects.

MCD-386 Pharmacology

In preclinical tests of cholinergic function, MCD-386 strongly activated M1 receptors, only weakly activated M3 and possibly M5 receptors, and had negligible activity on M2 and M4 receptors. MCD-386 improved memory function in three different animal models, including a model of the cholinergic defect of AD, at doses that did not cause untoward muscarinic effects. MCD-386 activated α -secretase in cultured cells in preclinical laboratory models, decreased A β , reduced Tau phosphorylation and decreased apoptosis, thereby potentially reducing the production of A β and preventing neuron death in AD. Key aspects of these actions of MCD-386 have been confirmed in laboratory animal models *in vivo* ***NEW***.

MCD-386/MCD-386CR Clinical Trials

MCD-386 successfully passed the safety and toxicology studies, and batches of GMP MCD-386 were successfully manufactured for Phase I clinical trials. The development work up to the IND was principally funded by the NIH. A controlled release formulation has been developed and Phase I trials should be completed by Q1/2010 ***NEW***. See column to the left.