Brain-Tools, LLC

Program to Develop and Commercialize MSF: A Superior Anti-dementia Drug for Alzheimer's Disease

BRIEF GUIDE to MSF

Why Methane Sulfonyl Fluoride (MSF) is a Superior Anti-dementia Drug for Alzheimer's Disease

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EXECUTIVE SUMMARY

Alzheimer's disease is one of the most compelling problems of modern health care. In spite of the clear and increasing burden of Alzheimer's, there is a severe unmet immediate need for an effective treatment for the millions of affected patients and their families.

The available drugs that are supposed to help Alzheimer's patients cause such negative side effects that the dosage is limited to how much persistent nausea, vomiting and diarrhea the patient can tolerate. At tolerable doses, the current drugs have proven ineffective.

MSF, on the other hand, is extremely effective in the brain and has no significant effect on the gastrointestinal system. MSF does NOT trigger nausea, vomiting, and diarrhea.

The current drugs (Aricept and Exelon) block acetylcholinesterase (AChE) in the brain, as needed to treat dementia, but they are miserably ineffective because their inferior **temporary** action also blocks AChE in the intestines and causes unbearable nausea, vomiting, and diarrhea.

Blocking the action of AChE holds enormous promise for the treatment of Alzheimer's, but the serious side effects of the old drugs have been an unsolved barrier to success. The perplexing problem of toxic side effects has stood in the way of effective treatment for Alzheimer's for the past twenty years.

Methane Sulfonyl Fluoride (MSF) is a superior anti-dementia drug that blocks AChE **permanently**, a fundamentally different action. Experiments in rats and monkeys prove that MSF can block 80% or more AChE in the brain (more than required to treat dementia) with only trivial effect in the intestines.

MSF has advanced far beyond animal experiments. Phase One clinical experiments in normal humans prove that MSF, with its permanent mechanism of action, successfully avoids the side effects that have condemned the old drugs to failure. In addition, a Phase Two study in Alzheimer's patients shows that MSF produces the promised unparalleled highly effective treatment – it produced *three to five times more improvement* in Alzheimer's patients than has been achieved with the old drugs with temporary mechanisms of action.

For the first time in the history of Alzheimer's disease, MSF has overcome what has been, until now, an insurmountable barrier to effective treatment. MSF is late in the development process, far beyond the early, high risk tests of safety and efficacy. Phase One and Phase Two human clinical trials prove its superiority. MSF is on the threshold of revolutionizing the treatment of Alzheimer's dementia. It is a rare opportunity for investors to take over a drug in this final stage of development, as near a sure thing as can be found in pharmaceuticals.

TECHNICAL SUMMARY OF MSF

Introduction:

Alzheimer's dementia is due, in large part, to the severe loss of midbrain neurons that provide critical acetylcholine in the brain (Whitehouse et al., 1981) [Whitehouse PJ, Price DL, Clarke AW, Coyle JT, and DeLong MR. Alzheimer's disease: Evidence for selective loss of cholinergic neurons in the nucleus basalis. *Annals of Neurology* 10: 122-126, 1981]. The only clinically validated strategy for treating dementia is to increase acetylcholine in the brain by blocking acetylcholinesterase (AChE), the enzyme that breaks it down. Stopping the enzymatic destruction of acetylcholine in the brain holds a tremendous but as yet unfulfilled promise to relieve Alzheimer's dementia and give the patients back their lives, living at home and enjoying life for precious additional years.

The current AChE blocking drugs (e.g. Aricept, Exelon, and Razadyne) have failed. They produce only marginal, almost nonexistent clinical improvement because these drugs cannot be tolerated at effective doses. Therefore, the present summary examines the reasons for the dismal failure of the currently available cholinesterase inhibitors – and offers **M**ethane **S**ulfonyl **F**luoride (MSF) as a solution.

Why MSF is Superior to Existing Drugs for Alzheimer's dementia:

The currently available anti-dementia drugs are excellent at blocking AChE. The reason they fail is simple. They are **temporary** blockers of AChE which are indiscriminate in their action, acting everywhere in the body equally. In order to treat a serious disease like Alzheimer's, the drugs must block the action of AChE to a much higher level than the patients can endure. Blocking any significant amount of AChE in the intestines causes intolerable nausea, vomiting, and diarrhea, and prevent patients from taking effective doses. Until now, it has been accepted that the toxic side effects in the intestines cannot be separated from therapeutic AChE blockade in the brain. This erroneous conclusion has led all current drugs to fail.

The key to unlocking the great therapeutic benefit for treating Alzheimer's is to find an AChE blocker that works with high efficiency in the brain, but without the toxic side effects. This is exactly how MSF works. MSF is different from the older drugs because MSF is a **permanent** AChE blocker. The only way to recover AChE activity after a permanent blocker is for the nerve cells to manufacture new, unblocked AChE. Thirty years ago, Dr. Moss made the key discovery that the brain makes new AChE very slowly while the intestines make new AChE more than ten times faster. The extremely slow new synthesis of AChE in the brain opens the door to accumulating extremely high AChE blockade in the brain (Moss et al., 1988). [Moss, D.E., Kobayashi, H., Pacheco, G., Palacios, R., and Perez, R.G. Methanesulfonyl fluoride: A CNS selective cholinesterase inhibitor. In: *Current Research in Alzheimer Therapy: Cholinesterase Inhibitors*, E. Giacobini and R. Becker (Eds.), Taylor and Francis, New York, 1988. pp. 305-314]. http://academics.utep.edu/LinkClick.aspx?link=Moss+et+al.%2c+1988.pdf&tabid=73107&mid=167024

Figure One illustrates the clear side-by-side difference between temporary and permanent mechanisms of action. The left side of Figure One [side A] shows Aricept (donepezil) AChE blockade in the brain and intestines during 21 days of treatment. This

is based on Aricept's real-life temporary (competitive) mechanism of action that has a half-life of 3 days and strong brain selectivity.

The right side of Figure One [side B] shows MSF-induced AChE blockade in the brain and intestines, also during 21 days of treatment. This is based on MSF's irreversible, permanent mechanism of action and the real half-times for new synthesis of AChE of 12 days for brain and 1 day for intestines. In this example, MSF produces an equal 10% blockade of AChE in both brain and intestine with each daily dose.

FIGURE ONE

Accumulated AChE Blocking in the Brain and Intestines with Temporary (Aricept) versus Irreversible (MSF) Blockers

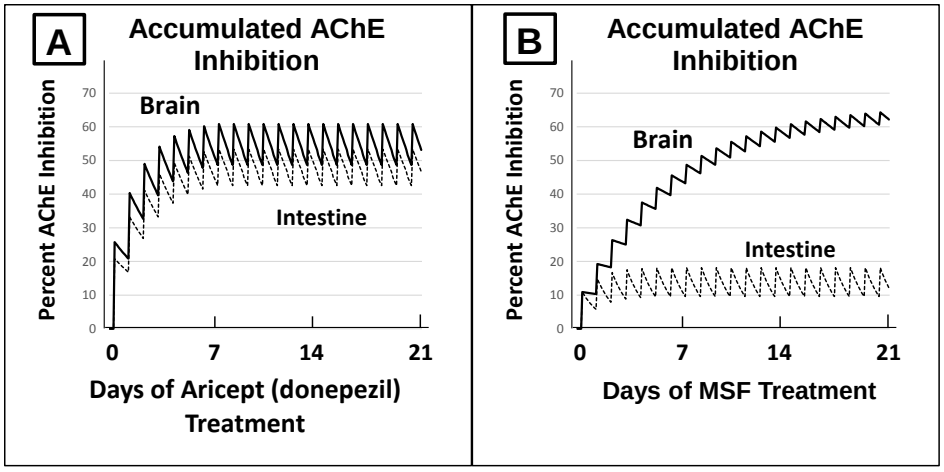


Figure One. Comparison of AChE blockade in brain (solid lines) and intestines (dashed lines) with a temporary inhibitor (Aricept, left side [A], a competitive inhibitor) as compared to a permanent inhibitor (MSF, right side [B]) accumulated over 21 days of treatment. The saw-tooth appearance of the lines shows an abrupt upward *increase* in inhibition with each daily dose. The downward slope shows the natural *decrease* in inhibition between doses. The left panel [A] assumes the real characteristics of Aricept (donepezil) with a half-time of 3 days and strong selectivity for the brain (1.25 times more inhibition in the brain than in the intestines). The right panel [B] assumes the real characteristics of MSF with half-times of 12 days and 1 day for the new synthesis of uninhibited AChE in brain and intestines, respectively. MSF produces highly effective AChE in the brain with very little effect in the intestines.

Figure One [A] shows that temporary Aricept-induced AChE blockade in the brain (solid line) and intestines (dashed line) overlap even with strong CNS-selectivity. At this level of AChE blockade, there would be minimal therapeutic effect in the brain and strong nausea, vomiting, and diarrhea would be common. This is also the problem with Exelon(rivastigmine) which also has a temporary mechanism of action (pseudo-irreversible, half-time of 6 – 8 hours).

The temporary AChE blockers (e.g., Aricept and Exelon) cannot achieve an effective level of AChE blockade in the brain (above 50%) with adequate separation from AChE blockade in the intestines. To avoid nausea, vomiting, and diarrhea, AChE blockade must not exceed a maximum of 40%, a standard that cannot, and has not, been achieved with any approved Alzheimer's drugs (Imbimbo, 2001) [Imbimbo BP.

Pharmacodynamic tolerability relationships of cholinesterase inhibitors for Alzheimer's disease. *CNS Drugs* 15(6): 375-390, 2001].

Figure One [B] shows that MSF with a superior permanent mechanism of action produces highly significant AChE blockade in the brain (solid line, well over 60%) with clinically insignificant blockade in the intestines (dashed line, less than 20%). By producing minimal AChE blockage in the intestines, MSF avoids gastrointestinal toxicity. The MSF-induced separation between AChE blockade in brain and intestines shown in Figure One [B] is far superior to Aricept, Exelon, and any other drugs with a temporary mechanism of action.

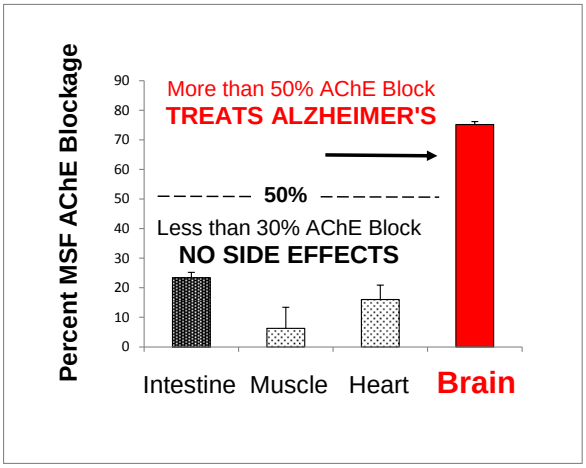
Actual MSF-Induced Permanent AChE Blocking *in vivo*:

Calculations shown in Figure One are instructive in terms of illustrating the superior underlying dynamics of MSF, a permanent inhibitor. However, do these calculations predict actual results obtained *in vivo*? To answer this, rats were treated with MSF for three weeks and then the amount of AChE blockage was measured in the brain, intestines, heart, and skeletal muscle. The results are shown in Figure Two.

FIGURE TWO

Actual CNS-Selectivity Produced by MSF Treatment

Figure Two. Actual MSF-induced AChE blockade in rat intestine, skeletal muscle, heart and **brain** after MSF treatment for three weeks (Moss et al., 2013). [Moss, D.E., Fariello, R.G., Sahlmann, J., Sumaya, I., Pericle, F., and Braglia, E. A randomized Phase I study of methanesulfonyl fluoride, an irreversible acetylcholinesterse inhibitor, for the treatment of Alzheimer's disease. *British Journal of Clinical Pharmacology*, 75: 1231-1239, 2013]. http://academics.utep.edu/LinkClick.aspx?link=Moss+et+al.%2c+2013.pdf&tabid=73107&mid=167024



The results shown in Figure Two confirm the expectation that repeated doses of MSF, with its superior permanent mechanism of AChE blockade, can produce 75% AChE inhibition in the brain, a level *more than required* to be highly effective in treating Alzheimer's, with less than 25% inhibition in peripheral tissues, especially in the intestines. This low level of inhibition is tolerated without toxicity such as nausea, vomiting, and diarrhea. The finding of exceptionally low levels of accumulated AChE inhibition in heart and skeletal muscle also avoids the risk of side effects in these critical tissues during Alzheimer's treatment (Imbimbo, 2001, cited above).

Overall, MSF given in regular small doses over time, as it will be used in treating Alzheimer's dementia, produces exceptionally potent CNS-selective AChE blockade, far beyond the reach of temporary AChE drugs. MSF is unique in opening the door to testing the full therapeutic potential of cholinesterase inhibitor therapy in Alzheimer's

disease without dose-limiting side effects, especially those related to gastrointestinal system, that have made all previous drugs failures.

Is MSF effective in treating Alzheimer's patients?

MSF Human Clinical Studies

Phase One Studies – Safety in Humans:

The safety and tolerability of MSF in normal aged human volunteers has been tested in two different Phase One clinical studies. The therapeutic dose of 180 µg/kg MSF was exceptionally well tolerated – no troublesome side effects (Moss et al., 1999; 2013). [Moss DE, Berlanga P, Hagan MM, Sandoval H, and Ishida C. Methanesulfonyl fluoride (MSF): A double-blind, placebo-controlled study of the safety and efficacy in the treatment of senile dementia of the Alzheimer type. *Alzheimer Disease and Associated Disorders* 13: 20-25, 1999; and Moss DE, Fariello RG, Sahlmann J, Sumaya I, Pericle F, and Braglia E. A randomized Phase I study of methanesulfonyl fluoride, an irreversible acetylcholinesterse inhibitor, for the treatment of Alzheimer's disease. *British Journal of Clinical Pharmacology* 75: 1231-1239, 2013). http://academics.utep.edu/LinkClick.aspx?link=Moss+et+al.%2c+1999.pdf&tabid=73107&mid=167024 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3635594/pdf/bcp0075-1231.pdf

The reports of nausea were, as expected, rare and trivial (5 reports of nausea out of 56 administrations of the highest dose) and they were brief and mild, far from the persistent, severe, dose-limiting intensity that plagues conventional AChE inhibitors. Diarrhea and vomiting were even more infrequent and inconsequential. MSF fulfills the promise of being extraordinarily well tolerated at clinically effective doses, with no dose-limiting gastrointestinal side effects (Moss et al., 2013), cited above).

Phase Two Study – MSF Improves Patients:

To determine if MSF might fulfill the very favorable expectations in treating Alzheimer's, it was administered three times per week for 8 weeks in a double-blind, placebo-controlled Phase Two study of mild to moderately demented patients. The same patients also received placebo during another 8 weeks in this 16 week cross-over protocol (Moss et al., 1999, cited above).

This first-ever trial of MSF in Alzheimer's patients presented a unique problem. Because of the absence of gastrointestinal side-effects, the dosage could not be determined by simply increasing the drug until the patients began to suffer intolerable nausea, vomiting and diarrhea as with the older AChE inhibitors. Therefore, the therapeutic dose of MSF had to be selected solely on the basis of experiments in rats and monkeys and calculations like those shown in Figure One.

A conservative dose of 180 µg/kg MSF was selected for three-times-per- week dosing because it was expected to produce and maintain a mean of 65% AChE blockade in the brains of the patients. This would put the patients well into the therapeutic window (above the needed minimum of 50% CNS AChE blockade) for the duration of the MSF clinical trial (Moss et al., 1999, cited above).

The results showed that MSF given at 180 µg/kg three times per week produced 90% blockade of the patients' RBC AChE. This corresponds to an estimated 66% AChE blockade in the brain, in remarkably good agreement with the target of 65% blockade expected from the pretrial dose calculations.

The Alzheimer's patients in this clinical experiment (Figure Three) tolerated the 8 weeks of MSF treatment without troublesome side effects. The patients also showed

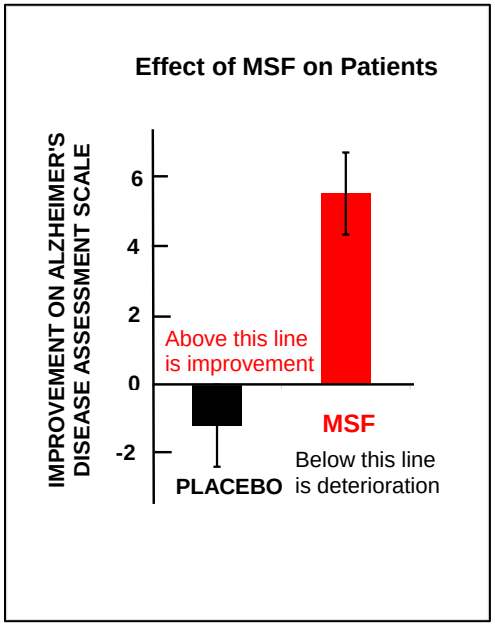
remarkable clinically-significant improvement, an average of 6 points on the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog). The success of MSF was ***three to five times*** the meager 1 to 2 points improvement over baseline reported for Aricept and Exelon (Moss et al., 1999, cited above). It is expected that even better results can be obtained at higher doses which have not been tested.

FIGURE THREE

MSF-Induced Cognitive Improvement in a Double-Blind, Placebo-Controlled, Crossover Phase Two study in Patients.

Figure Three. Alzheimer Disease Assessment Scale-Cognitive Scores throughout the 16 weeks double-blind, placebo-controlled, crossover trial of MSF in Alzheimer's patients. The difference between MSF and Placebo was highly significant ($p<0.005$) (Moss et al., 1999). [Moss DE, Berlanga P, Hagan MM, Sandoval H, and Ishida C. Methanesulfonyl fluoride (MSF): A double-blind, placebo-controlled study of the safety and efficacy in the treatment of senile dementia of the Alzheimer type. *Alzheimer Disease and Associated Disorders* 13: 20-25, 1999].

http://academics.utep.edu/LinkClick.aspx?link=Moss+et+al.%2c+1999.pdf&tabid=73107&mid=167024



The unparalleled improvement shown in Figure Three demonstrates the immense promise of MSF as a treatment for Alzheimer's – that the powerful CNS AChE blocking, produced by MSF, free of side effects, can unleash the as yet unrealized full and effective therapeutic potential of cholinesterase inhibitor therapy in treating Alzheimer's dementia.

Conclusions:

A myriad of *in vitro* and *in vivo* proof-of-concept experiments in animals demonstrate that MSF can produce and maintain exceptionally high levels of CNS inhibition without dose-limiting toxicity from unwanted AChE inhibition in peripheral tissues. The results from animal experiments were confirmed in humans. MSF is unique among AChE blockers in that it alone exploits the special property of the brain, the exceptionally slow new synthesis of AChE in the brain, to treat the brain itself. Through its unique permanent mechanism of action, MSF has the power to open the door, for the first time in the history of Alzheimer's, to the full highly-effective therapeutic potential of CNS cholinesterase inhibitor therapy in Alzheimer's patients. MSF is the only irreversible blocker available for the treatment of Alzheimer's disease.*****

MSF is far into the development process. It has been through three successful human clinical trials that provide real-world proof-of-concept for the power of its unique mechanism of action. MSF lives up to its full unparalleled potential for being a safe and

highly effective treatment for Alzheimer's dementia. It stands on the threshold of imminent success. It is a rare opportunity for investors to step in and assist with the final approval of a proven, highly effective drug that will revolutionize the treatment of Alzheimer's dementia with minimal, low risk investment.

MARKET EXCLUSIVITY STRATEGY

Moss, D.E. U.S. Patent Serial No. 5,798,392; "Sulfonyl Fluorides for the Treatment of Alzheimer's Disease", Issued August 25, 1998, will expire in August, 2016. The related European patents (EPO 0 921 790) have lapsed. With the termination of these patent rights, market exclusivity can now be aggressively pursued for MSF as a "New Chemical Entity" under both US law (21 CFR 314.108) and the European Union Data Exclusivity Directive (Directive 2004/27/EC (Hathaway C, Manthei J, and Scherer C. Exclusivity strategies in the United States and European Union. *FDLI UPDATE* May/June 2009, 34-39). These regulations allow for 5 years in US (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=314.108) and up to 11 years in Europe (http://www.biosafety.be/PDF/2004_27.pdf) of market exclusivity **after market approval** for products without patent protection. Similar protective regulations exist in other important world markets (e.g., China). At its late stage of development, MSF is an excellent candidate for market exclusivity afforded by these non-patent based strategies. This is the avenue forward now that the patent protection has expired.

***** DO NOT CONFUSE MSF with Metrifonate, an *organophosphate* often described as an "irreversible" or permanent AChE blocker. Metrifonate was withdrawn from drug development because it caused severe, life-threatening muscle weakness and respiratory paralysis in patients in clinical trials [Lopez-Arreita J and Schneider L. Metrifonate for Alzheimer's Disease (Review), *The Cochrane Collaboration*, J Wiley, 2008]. MSF, a sulfonyl fluoride – *not being an organophosphate* – **does not share the risk** of these exceptionally dangerous "organophosphate-induced delayed neuropathy" side effects. MSF specifically does *not* interact with the neuropathy target enzyme, the origin of these toxic effects [Osman KA, Moretto A, and Lotti M. Sulfonyl fluorides and the promotion of diisopropyl fluorophosphate neuropathy. *Fundamentals of Applied Toxicology* 33; 294-297, 1996, Table 1, p. 295].