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Treatment of Alzheimer's Disease with Benfotiamine and Novel Analogues and Prodrugs of Thiamine

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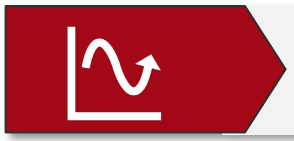
There is a need for therapeutics targeting alternative pathways in Alzheimer's Disease

Alzheimer's disease (AD) treatments which target amyloid-β **are often ineffective**, suggesting the need for novel therapeutics

Reduction of cerebral glucose metabolism correlates highly with cognitive decline, suggesting a role of metabolic dysregulation in AD pathogenesis

Thiamine-dependent enzymes regulate cerebral glucose metabolism, and a decline in their activities is apparent in AD patients

Toxic protein modifications called **Advanced glycation end products (AGE)** are indicative of abnormal glucose metabolism.



AGE are sensitive to thiamine and provide **a readily measured target of engagement**

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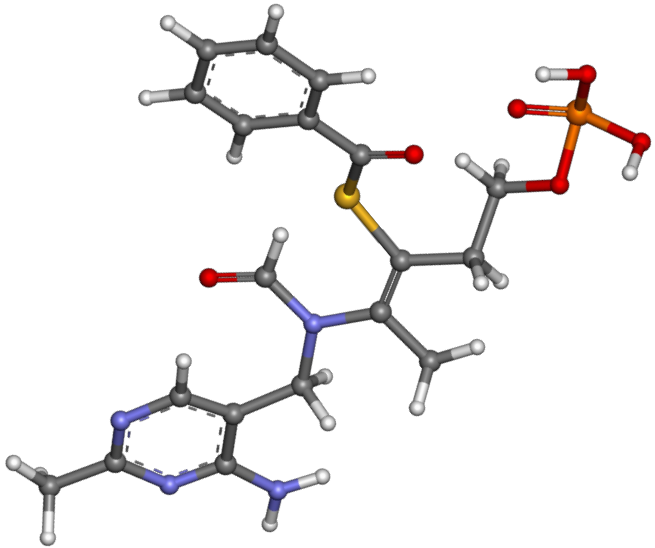
Gibson et al. *J Alzheimers Dis*. 2020.

Benfotiamine is a synthetic thiamine prodrug which acts on metabolism, oxidative stress and inflammatory pathways



Chemical structure of Benfotiamine

BFT is a synthetic **Vitamin B1 (thiamine) prodrug** which raises blood thiamine to levels not possible by administering thiamine

Elevated thiamine has many functions, acting on metabolism as well as both an **anti-oxidant and anti-inflammatory**

BFT reduces the production of **Advanced Glycation Products (AGE)** by activating transketolase, improving glucose metabolism

BFT has been **demonstrated to be safe in clinical trials** for peripheral diabetic neuropathy with no significant toxicity[1]

BFT is available as **an OTC supplement**. However, the BFT we use is a **unique preparation approved by the FDA** for use in our trials for treating mild Alzheimer's disease

AD: Alzheimer's Disease; BFT: Benfotiamine

[1] Stracke et al. *Exp Clin Endocrinol Diabetes*. 2008., Stirban et al. *Diabetes Care*. 2006.

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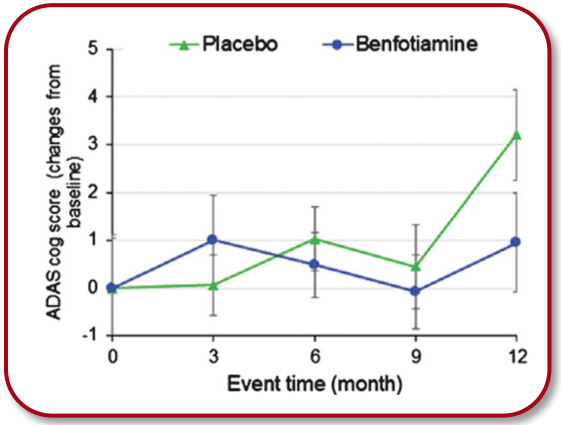
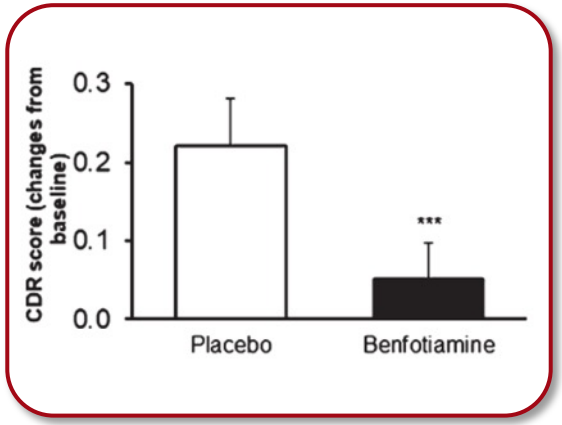
BFT was shown in a Phase 2a trial to improve patient outcomes based on clinical and biological markers of AD

BFT or a placebo was administered orally for 12 months to 70 patients with mild cognitive impairment (MCI) or mild AD

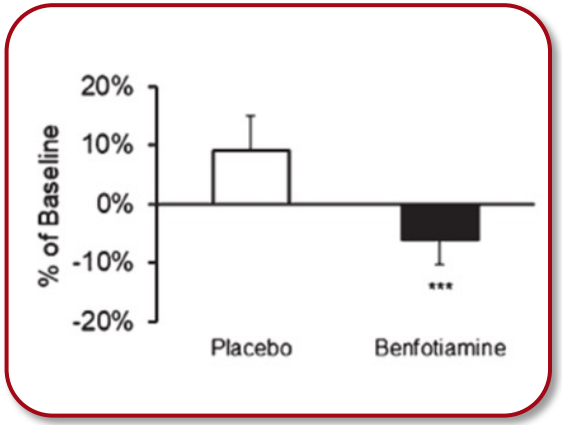
The decline in ADAS-Cog Score was 43% lower in treatment group (P=0.125)



The decline in Clinical Dementia Ratio (CDR) was 77% lower (P=0.034)



Advanced Glycation Products (AGE) were significantly reduced (P=0.044)



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BFT: Benfotiamine

Gibson et al. *J Alzheimers Dis*. 2021.

The Burke Neurological Institute has received a $45M NIH grant for a larger, multi-center trial with increased dosage

	Phase 2a Study of BFT for AD (NCT02292238)[1]	Multi-center Phase 2a/b Study of BFT for AD[2]
Study Size	71	400
Treatment	**600 mg** BFT/day	600 or **1200 mg** BFT/day
Study Duration	12 months	18 months
Number of Study Sites	1	50
Status	Completed	First patients to be treated in July 2023
Results	BFT was well tolerated, has encouraging PK and PD, and demonstrated improvement of clinical dementia scores	TBD

*This larger clinical trial is appropriately powered to demonstrate if BFT has a significant effect in lowering ADAS-Cog Scores for AD patients and will use **double the dose** of the initial study*

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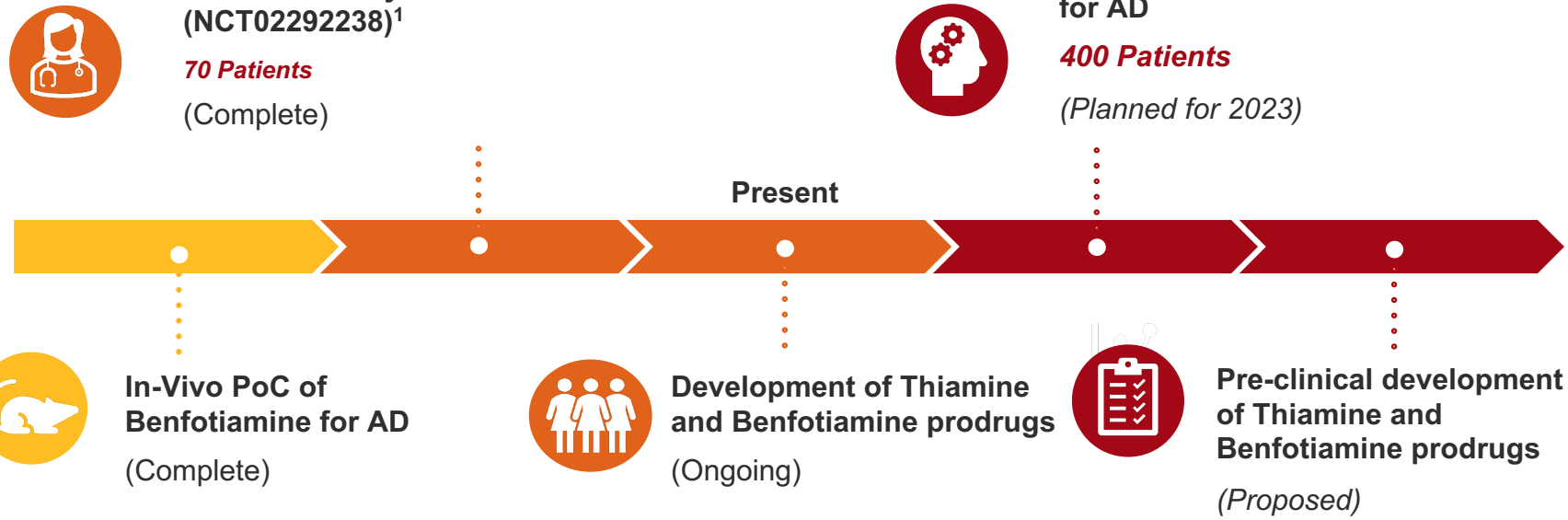
AD: Alzheimer's Disease, BFT: Benfotiamine

[1] Benfotiamine in Alzheimer's Disease: A Pilot Study (Benfotiamine)

[2] NIH grant R01AG076634

In parallel to BFT clinical trials, the team is developing novel thiamine and BFT analogs and prodrugs for additional testing

Commercialization Plan



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AD: Alzheimer's Disease, BFT: Benfotiamine

[1] Benfotiamine in Alzheimer's Disease: A Pilot Study (Benfotiamine)

The BFT program is supported by national patent filings and several peer reviewed publications

IP Status & Publications

- **Intellectual Property:**
  - WO2022026696A1: “Method for treating neurodegenerative diseases by administering benfotiamine or derivative thereof” (Priority Date July 30, 2020)
    - National stage applications have been filed in: US, EP, and CA
  - Cornell Dockets: D-6462
- **Publications:**
  - Gibson et al. “Pharmacological thiamine levels as a therapeutic approach in Alzheimer's disease.” *Front Med (Lausanne)*. 2022.
  - Bhawal et al. “Serum Metabolomic and Lipidomic Profiling Reveals Novel Biomarkers of Efficacy for Benfotiamine in Alzheimer's Disease.” *Int J Mol Sci*. 2021.
  - Gibson et al. “Benfotiamine and Cognitive Decline in Alzheimer's Disease: Results of a Randomized Placebo-Controlled Phase IIa Clinical Trial.” *J Alzheimers Dis*. 2020.
  - Tapias et al. “Benfotiamine treatment activates the Nrf2/ARE pathway and is neuroprotective in a transgenic mouse model of tauopathy.” *Hum Mol Genet*. 2018.
- **Press Releases:**
  - “Burke Neurological Institute Receives a $45 Million NIH Grant to Study a Vitamin B1 Precursor for Treatment of Alzheimer’s Disease in Multi-center Clinical Trial” (July 7, 2022)

WCM is seeking an industry partner to assist with medicinal chemistry for novel analogs and prodrugs of Benfotiamine

Development Status & Next Steps

Development Achievements

- ☑ Benfotiamine has demonstrated safety in clinical trials for diabetic neuropathy and AD
- ☑ Phase 2a clinical trial of Benfotiamine for AD has shown clinical improvements for patients
- ☑ Multi-center clinical trial for use of Benfotiamine for AD treatment is planned to start in 2023

Next Steps

Collaborate with an industry partner with medicinal chemistry expertise to advance the development of novel analogues and prodrugs of thiamine and Benfotiamine.

AD: Alzheimer's Disease

Lead Inventor

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Lab Director, Laboratory for Mitochondrial Biology and Metabolic Dysfunction in Neurodegeneration, Burke Neurological Institute

Ph.D., Cornell University, 1973

Research interest: Age-related neurodegenerative disease

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