Poster #24835

Exploratory Dose-Escalation Study of NFC-1 in ADHD Adolescents With Glutamatergic Gene Network Variants

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Conflict of Interest:
This study was sponsored by NeuroFix Therapeutics. Dr. Hakon Hakonarson serves on the Advisory Board and has stock or equity in NeuroFix Therapeutics LLC.

BACKGROUND:

Attention deficit/hyperactivity disorder (ADHD), one of the most common childhood psychiatric disorders, persists into adulthood, causing significant life-long impairments (1).

Growing evidence suggests that different neurotransmitter genes are involved in the pathophysiology of ADHD. In particular, the glutamatergic system has been shown to play direct and indirect roles in various animal models of ADHD (2) and human ADHD studies (3).

A recent large-scale, genome-wide study comparing copy number variants (CNVs) in children with ADHD (n=3,500) vs. healthy controls (n=13,000) reported rare, recurring CNVs affecting GRM/mGluR network genes at a significantly higher frequency in ADHD patients (4). The CNVs in these genes accounted for approximately 10% of ADHD cases. These findings warranted further research to study glutamatergic agents as targeted therapy in ADHD.

NFC-1 (fasoracetam monohydrate) is a small synthetic molecule that stimulates metabotropic glutamate receptors (GRM) that has been tested extensively in humans for stroke and vascular dementia. It may have the potential in certain ADHD patients with glutamatergic hypofunction.

SUBJECTS AND METHODS:

This is a single-site, phase 1 trial to evaluate the safety, tolerability, plasma concentration profile and targeted efficacy of orally administered NFC-1 in adolescents (12-17 years) ADHD patients exhibiting mutations in genes within the GRM network.

1. Primary objectives: Evaluate safety and tolerability of NFC-1 administered orally and characterize pharmacokinetic parameters of NFC-1.
2. Secondary objective: Explore the dose-response relationship of NFC-1 on ADHD severity and global measures and determine effect size of specific GRM-network genes on ADHD based on responsiveness of patients to NFC-1.

PARTICIPANTS: 30 patients with ADHD harboring disruptive copy number variants (CNVs) in one or more glutamatergic gene network genes were recruited from the Center of Applied Genomics at The Children's Hospital of Philadelphia. Consents were obtained from parents and assents from study subjects.

INCLUSIONARY CRITERIA: Male and female patients, ages 12-17 of any ancestry, ADHD defined by DSM-5 and Vanderbilt ADHD Rating Scale Score ≥ 16, genotyped to have disruptive CNVs in the glutamatergic gene networks.

EXCLUSIONARY CRITERIA: Inability to perform the study tasks; use of illicit drugs on a regular basis.

METHODS: Open-label 5-week dose-escalation study that proceeded after study subjects completed a 24-hour PK study. ADHD medications were discontinued with a wash-out phase up to 14 days. The 24 hour PK study included 5 groups with 6 subjects/group, where each group was given the following respective single doses: 50mg x1; 100mg x1; 200mg x1, 400mg x1, and 800mg x1. The patients subsequently received a placebo bid (Week 1) followed by NFC-1 50 mg bid in Week 2, 100 mg bid in Week 3, 200 mg bid in Week 4, and 400 mg bid in Week 5. Safety data was reviewed by the DSMB after each dose cohort before proceeding with each dose increase. Patients were blinded as to which week of the five weeks they received placebo.

MEASURES: CGI-I, CGI-S scales and Vanderbilt ratings

RESULTS:

Out of 30 participants, 29 completed all study time points. All 30 study subjects were included in the analysis.

- Subjects were further stratified by their mGluR variants which included 17 subjects with CNVs in the most significant mGluR genes (Tier 1); 7 subjects with variants in other mGluR primary network genes (Tier 2); and 6 subjects with variants in a more distal reciprocal mGluR network genes (Tier 3).

Of note:

- NFC1 was generally safe and well tolerated.
- Adverse events were generally mild, not related to study drug and not treatment limiting (See Table 1).
- The mean CGI-S score of all subjects at baseline was **4.83** (moderately to severely ill), decreasing to **3.86** (mildly to moderately ill) after receiving 400 mg bid of NFC-1 Week 5 (P<0.001). No subject demonstrated worsening of CGI-S during the study.
- CGI-I scores showed improvement during dose escalation (Figure 1).
- Most marked improvement was observed in the Tier-1/Tier-2 mGluR patients (Figure 4); (P<0.001).
- Mean Vanderbilt scores improved at each weekly assessment (Figures 2 and 3); (P <0.001)

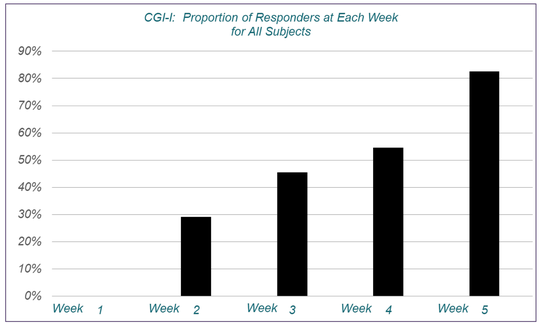

Fig. 1: CGI-I: Proportion of Responders at each Visit (all subjects) Responder defined as CGI-I of 1(very much improved) or 2 (much improved)

Further analysis of mean CGI-S and CGI-I scores comparing subjects after stratifying by mGluR variants was also performed.

Tier 1 subjects had the greatest mean reduction in CGI-S scores most evident in their dosage increase from 200 mg bid to 400 mg bid. Mean CGI-S scores at baseline was **4.8** compared to **3.6** at Week 5 (P<0.001).

Tier 2 subjects also showed statistically significant improvement in CGI-S scores after receiving 200 mg bid (P=0.0306) and 400 mg bid (P=0.0124) of NFC-1.

Tier 3 subjects showed minimal improvement in mean CGI-S scores from baseline (5.0) compared to Week 5 (4.57), and this difference was not statistically significant.

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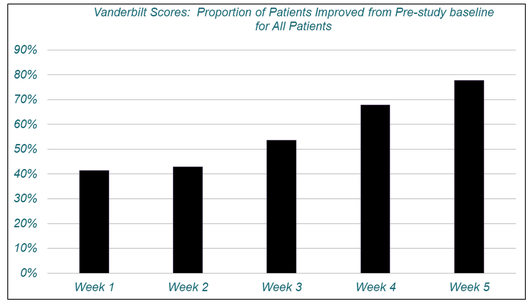

Fig. 2: Vanderbilt Scores: Proportion of Patients Improved by 25% or more in hyperactivity/inattention domains from baseline

	Week 1	Week 2	Week 3	Week 4	Week 5
Mean	29.1	26.4	24.0	23.3	22.5

P < 0.001

Fig 3: Average Vanderbilt score at each week – all patients

TEAE Preferred Term	Number of Subjects		Mild		Moderate	
	N	%	N	%	N	%
Headache	19	63.3	18	60.0	1	3.3
Fatigue	11	36.7	9	30.0	2	6.7
Abdominal Pain Upper	8	26.7	7	23.3	1	3.3
Diarrhoea	7	23.3	7	23.3	0	0.0
Irritability	6	20.0	5	16.7	1	3.3
Dizziness	4	13.3	4	13.3	0	0.0
Pyrexia	4	13.3	4	13.3	0	0.0
Anxiety	3	10.0	2	6.7	1	3.3
Somnolence	3	10.0	2	6.7	1	3.3
Onychophagia	3	10.0	2	6.7	1	3.3
Tearfulness	3	10.0	3	10.0	0	0.0
Depressed Mood	3	10.0	3	10.0	0	0.0
Cough	3	10.0	3	10.0	0	0.0
Oropharyngeal Pain	3	10.0	3	10.0	0	0.0
Vomiting	2	6.7	2	6.7	0	0.0
Memory Impairment	2	6.7	2	6.7	0	0.0
Social Avoidant Beha	2	6.7	2	6.7	0	0.0
Visual Impairment	2	6.7	2	6.7	0	0.0
Nausea	2	6.7	2	6.7	0	0.0
Contusion	2	6.7	1	3.3	1	3.3

Table 1: Number and percent of subjects reporting TEAE's occurring in more than 5% of the study population.

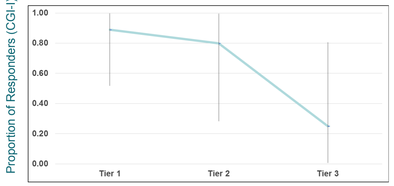

Fig 4: Proportion of Responders at Week 5 with 95% confidence intervals by Genetic Tier

CONCLUSIONS:

- Adolescents with ADHD and disruptive mutations in mGluR network genes showed clinical improvement in symptoms using global rating scales in response to escalating doses of NFC-1, a glutamate receptor activator.
- At baseline most subjects were rated as moderately to severely impaired (mean CGI-S 4.83), indicating that their ADHD symptoms were causing functional impairment.
- At week 5 most subjects showed clinically significant reduction in ADHD symptoms with mean CGI-S score of 3.86 (mildly to moderately impaired). (P<0.001).
- Significant improvement was also observed in CGI-I scores and this was most marked in Tier-1/Tier-2 mGluR mutation positive subjects (P<0.001)
- Subjects in mutation Tier 1 have been identified to have the most impactful CNV enrichment in mGluR network genes.
- These results suggest that the subset of individuals who have the most disruptive mGluR network CNV (Tier-1/Tier-2), have greater response to NFC-1.
- NFC-1 was generally safe and well tolerated.
- This study supports the continued investigation of NFC-1 in the treatment of ADHD.

LIMITATIONS:

Limitations of this study include small sample size and no comparison group of patients without ADHD or disruptive mutations in the glutamatergic gene network. This study was an open trial. With the exception of patient blinding as to which week they received placebo, patients were aware of the medication given and dose escalation during the study.

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