Conflicts of Interest: The study was sponsored by NLS-1 Pharma AG. All coauthors are paid consultants of NLS-1 Pharma AG. EK is the inventor of the patent for the use of mazindol in ADHD and VS is the inventor of the patent for mazindol CR. Other COIs including as Consultant, Advisory Board, Research Support: Akili Interactive (TW JN), Alcobra (JN), Arbor (JN), Cingulate (JN), Enzymotec (JN), Ironshore (TW SW JN), KemPharm (JN), Lundbeck (JN), Medice (JN), Neos (JN SW), Neurovance (TW SW), Nextwave (SW), NFL (JN), Pfizer (SW) Purdue (TW SW), Quintiles (SW), Rho (SW), Rhodes (TW SW JN), Shire (TW SW JN), Sunovion (TW SW JN), Supernus (JN), Tris Pharma (TW SW).

Efficacy, Safety, Tolerability and PK of Mazindol Controlled Release (CR) in Adults with ADHD

Wigal T[1], Newcorn J[2], Wigal S[1], Handal N[3], Mulligan I[4], Schmith V[5], Konofal E[6]

[1] AVIDA Inc, 1600 Dove Street, Suite 305, Newport Beach, CA; [2] Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, New York, NY; [3] Dothan Behavioral Medicine Clinic, Harmonex Neuroscience Research, 408 Healthwest Drive, Dothan, AL; [4] Worldwide Clinical Trials, Waterfront House, Beeston Business Park, Beeston, Nottingham, NG9 1LA, UK; [5] Nuventra Pharma Sciences, 2525 Meridian Parkway Suite 280, Durham, NC; [6] Pediatric Sleep Disorders Center, 48 Boulevard Serurier Hôpital Robert Debré, Assistance Publique – Hôpitaux de Paris, Paris, France

Mazindol was originally developed as an appetite suppressant in 1973, but was withdrawn from US/European markets by 2002 for commercial reasons (unrelated to efficacy or safety). Mazindol CR is a new formulation with a lower Cmax than the IR tablet and an equivalent AUC. The primary objective of this study was to evaluate the efficacy of Mazindol CR in adult patients with ADHD. Additionally, the safety, tolerability and PK were assessed. **Methods:** This was a randomized, double-blind, placebo-controlled, flexible dose trial of Mazindol CR vs. placebo (1:1) for 6 weeks in 85 participants with ADHD. The Mazindol CR dose was titrated (1 mg QD x 7 days, then 2 mg QD x 7 days, then 3 mg QD x 7 days) based on clinical response and tolerability. Dose reductions in the final 4 weeks of the study were allowed due to lack of tolerability. The primary endpoint was the reduction from baseline in ADHD-RS-DSM5 clinician- rated scale score at the end of treatment (Day 42). Secondary endpoints were responders as measured by a 30% and 50% reduction in rating scores and by Clinical Global Impressions Improvement (CGI-I) at end of treatment. Safety and tolerability were assessed through adverse event reporting (AEs), vital signs, physical examination, laboratory parameters, and assessment of suicide risk at each weekly visit. **Results:** Using a repeated-measures mixed-effect model, mazindol was different from placebo for each weekly measurement beginning at Day 7 (p<0.005), with a LS Mean difference (Mazindol CR-Placebo) of -13.2 (p<0.001) at Day 42 (ITT population) with an effect size of 1.09. There were significantly more responders for Mazindol CR compared to placebo (p<0.001) as defined by both a 30% and a 50% reduction ADHD-RS-DSM5 rating scale scores and by CGI-I (1 or 2). AEs were reported in 31 and 21 participants from the Mazindol CR and placebo group, respectively. The primary AEs were dry mouth (23% vs 4.8%), decreased appetite (9.3 vs 7.1%) and heart rate increased/tachycardia (16% vs 0%). Overall, mazindol CR had a moderate effect on heart rate and a small effect on blood pressure. No serious AEs were reported and the only participant discontinued due to an AE was in the placebo group. **Conclusions:** This study demonstrated that Mazindol CR was efficacious in the treatment of adults with ADHD, with a large effect size of 1.09, and was well-tolerated, supporting the progression to Phase 3 studies.

Introduction

History

Mazindol IR is an imidazo-isoindole agent, originally developed as an appetite suppressant in 1973, and classified at that time as a C4 controlled substance (low probability for misuse/abuse). It was withdrawn from US markets by 2002 due to commercial reasons unrelated to efficacy or safety. A recent open label study **(1)** of mazindol IR (1 mg/day, 7 days) in 24 children (aged 9-12) with ADHD found a 90% improvement in symptoms with a change from baseline in total ADHD-RS score of -24.6 (P<0.0001).

Mechanism of Action

Mazindol CR is a novel investigational agent with a lower Cmax than the IR formulation and an equivalent AUC, with a Tmax of ~4 hr and a t½ of ~10 hr. *In vitro* studies at 10 μM (>600x Cmax at 16.5 nM after mazindol CR 3 mg) showed that mazindol has 39% binding at orexin-1 receptors. Orexin has been recently implicated as part of a dual transmitter system regulating not only wakefulness but also attentional/cognitive processes from cell bodies in the hypothalamic neural hub **(2)**. Orexin is classified as a neuromodulator due to involvement in the regulation of energy metabolism, emotionality, arousal and attentional functioning **(3)**.

In addition, mazindol is a dopamine-, noradrenaline- and serotonin-reuptake inhibitor, with >50% binding at the 5-HT1A and 5HT7 receptor, muscarinic receptors, histamine H1 receptor, and μ-opioid receptor. The pharmacological profile of mazindol and the results of the pilot study of mazindol IR in children with ADHD suggest that mazindol CR has considerable potential as a "non-C2 stimulant" treatment for ADHD.

Objectives

- To evaluate the efficacy of mazindol CR given QD in adult patients with ADHD.
- To characterize the safety and tolerability of mazindol CR.

Methods

Design: Randomized, double-blind, placebo-controlled, flexible dose trial of mazindol CR vs. placebo (1:1) for 6 weeks in 85 participants with ADHD (see Figure 1).

Inclusion criteria:

- 18-65 years with primary diagnosis of ADHD as established by score of >28 on ADHD-RS-DSM5 and score ≥4 (moderate) on the Clinical Global Impressions Severity scale (CGI-S), when not taking ADHD medications for ≥14 days

Exclusion criteria

- Any comorbid DSM5 disorder requiring treatment, life-time history of DSM5 bipolar disorder, or prohibited meds (e.g., potent inhibitors of CYP2D6 or CYP3A4)

Assessment Measures (Response to Treatment): Measures were clinician rated and taken at baseline and each of the six weekly, clinic visits.

Primary Outcome: Attention Deficit Hyperactivity Disorder Rating Scale (ADHD-RS-DSM5) total score. This is the sum of all 18 symptoms presented in the checklist format and scored 0-3, utilizing the exact descriptors found in DSM-5. Total ADHD-RS-DSM5 score on Day 42 was the primary endpoint.

Secondary Outcomes: Responder status (See Table 2) as measured by the ADHD-RS-DSM5 (30% [minimal response threshold] or 50% [optimal response threshold] reduction from Baseline) for mazindol CR versus placebo; responder status as measured by the dichotomized CGI-I (score of 1 or 2) for mazindol CR versus placebo.

Exploratory Outcome:

Target Rating Scale scores. This clinical assessment tool was used as an exploratory endpoint. It establishes targets (i.e., individualized functional treatment goals) in at least 2 of the following contexts (Work, Home, School, Social or Personal) and quantifies target level of impairment in daily activities. (See Figure 3). Pre-treatment target scores were assessed at each visit, prior to obtaining the ADHD-RS-DSM5 and CGI-I ratings.

Methods

At Baseline, subjects were asked to identify three functional impairments and their frequency in at least two different settings. A clinician translated each impairment description into a distinct, DSM-5 ADHD symptom. This resulted in the majority of targets being based on inattentive symptoms (83%), and all 18 symptoms except "Can't be quiet in leisure activities" were utilized as a functional target at least once. The functional impairment settings were Home (38%), followed by Workplace (29%), Personal (19%), School (8%) and Social (6%).

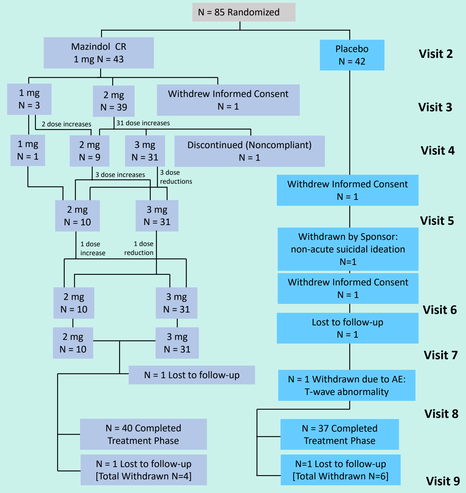
Procedure

Mazindol CR dose was titrated (1 mg QD x 7 days, then 2 mg QD x 7 days, then 3 mg QD x 7 days) based on clinical response and tolerability as assessed at each of the 6 weekly visits after baseline. Participants were to remain on a fixed dose for the final 4 weeks, with dose reductions allowed due to lack of tolerability.

Safety and tolerability were assessed through adverse event reporting, vital signs, physical examination, laboratory parameters, and assessment of suicide risk (C-SSRS).

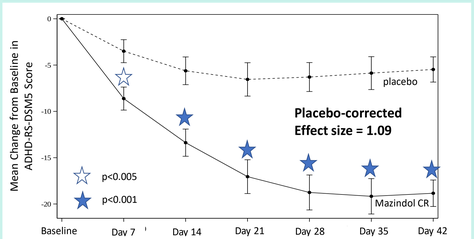
Results

Figure 1: Subject Disposition



Results: Efficacy

Figure 2: Mean ADHD-RS-DSM5 Score Over Time by Treatment (ITT Population)



- **ADHD – RS – DSM5 scores:** The ES favoring mazindol CR over placebo was 1.09. Onset of efficacy was prompt, with a significant number of subjects with a 30% reduction from Baseline in the ADHD-RS-DSM5 score favoring mazindol CR by 7 days (the first post-treatment visit), and with a 50% reduction in ADHD RS DSM5 score favoring mazindol CR by 14 days (see Table 2).
- **CGI-I Scores:** More subjects were responders on the CGI-I on mazindol CR compared to placebo from Visit 4 (Day 14) and at each subsequent visit (p≤0.003).
- **Target Scores:** A treatment group by study visit univariate analysis found a significant Treatment by Visit (F=6.55, p<.001) interaction. As Figure 3 illustrates, the mazindol CR group improved more rapidly and to a greater degree than the placebo group. The proportion reporting at least a 50% reduction in target scores by Visit 8 (Day 42) were 42.9% on Mazindol CR compared to 11.9% of subjects on placebo; the difference between treatments was statistically significant (p=0.002).

Safety/Tolerability Results

- 42%, 38%, and 57% of subjects receiving mazindol CR 1 mg, 2 mg, and 3 mg, respectively, had TEAEs, while 21%, 12%, and 36% of patients receiving placebo during identical time periods, respectively, had TEAEs
- There were only 4 dose adjustments (n=3 mazindol CR ; n=1 placebo) due to lack of tolerability; tolerability improved in those subjects who had dose reductions.
- The following TEAEs were more prevalent (>5% than placebo) for mazindol CR vs placebo: dry mouth, headache, nausea, fatigue, HR increased, decreased appetite, somnolence, middle insomnia, and constipation.
- There were minimal increases in systolic and diastolic BP, a small increase in HR, and no significant changes in QTcF interval.
- One mazindol CR subject withdrew 4 days after baseline, one Placebo Subject withdrew after a positive drug screen and another placebo subject took an excluded medication; 3 subjects who were not compliant with study treatment (n=2 on mazindol CR and n=1 on placebo) also withdrew.

Figure 3: Target Score by Weekly Visit

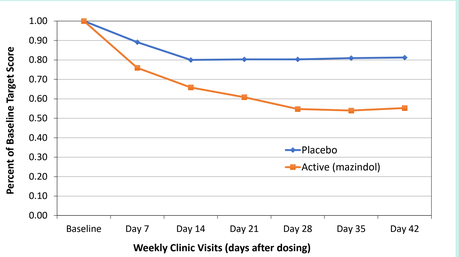


Table 1: Demographics

Parameter	Mazindol CR 1-3 mg, N=43	Placebo N=42
Sex (% Male/% Female)	42/58	43/57
Race (% White/% Black or African American/ % Asian/% Other)	81.4/14/2.4/0	81/11.9/2.4/2.4
Age in years (mean±SD (min,max))	32.6 ± 8.62 (18,52)	34.7 ± 11.87 (18,63)
ADHD Clinical Presentation (% Combined/% Inattention)	79/21	88/12
ADHD-RS-DSM5 at Baseline (mean±SD (min,max))	38.2 ± 5.96 (28,52)	40.2 ± 4.69 (32,49)

- A total of 85 subjects with 71 (83.5%) diagnosed with ADHD Combined presentation and 14 (16.5%) diagnosed with the ADHD Inattentive presentation.
- More female than male; 49 (57.6%) vs 36 (44.4%) subjects, respectively.
- A slightly greater percentage of subjects with ADHD-combined presentation were randomized to the mazindol CR 1-3 mg group compared with the placebo group (88.1% versus 79.1%, respectively).

Table 2: Summary of the Proportion of Responders

Visit	Reduction of ≥30% in ADHD-RS-DSM5 Score (Mazindol CR vs Placebo)	Reduction of ≥50% in ADHD-RS-DSM5 Score (Mazindol CR vs Placebo)	CGI-I =1 or 2 (Mazindol CR vs Placebo)
Day 7	33.3% vs 11.9%[a]	14.3% vs 4.8%	21.4% vs 11.9%
Day 14	54.8% vs 11.9%[b]	33.3% vs 9.5%[c]	45.2% vs 11.9%[e]
Day 21	65.9% vs 26.2%[b]	53.7% vs 9.5%[b]	58.5% vs 11.9%[b]
Day 28	68.3% vs 26.8%[b]	58.5% vs 9.8%[b]	63.4% vs 14.6%[b]
Day 35	70.7% vs 18.4%[b]	53.7% vs 13.2%[d]	61.0% vs 18.4%[b]
Day 42	70.0% vs 21.1%[b]	55.0% vs 15.8%[d]	62.5% vs 21.1%[b]

[a] p=0.034; [b] p<0.001; [c] p=0.018; [d] p=0.002; [e]p=0.003

Pharmacokinetics

- Trough levels of the metabolite following mazindol CR administration were equal to or higher than mazindol trough concentrations at steady-state.

Conclusions

- Mazindol CR has a robust effect on symptoms of ADHD with a placebo-adjusted effect size of 1.09. This effect size is similar to what is seen with C2 stimulants in the treatment for ADHD in other studies.
- Patients receiving mazindol CR responded quickly with a mean 30% reduction from Baseline in ADHD-RS-DSM5 score at 7 days (i.e., first assessment point) and a mean 50% reduction in the ADHD-RS-DSM5 score at 14 days.
- Mazindol CR was well tolerated, with mild to moderate GI TEAEs and CNS TEAEs, no effect on QTcF, and minimal to small effect on BP and HR.

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