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RESEARCH ARTICLE

A phase 1b/2a multicenter study of the safety and preliminary pharmacodynamic effects of selective muscarinic M_1 receptor agonist HTL0018318 in patients with mild-to-moderate Alzheimer's disease

Pradeep J. Nathan[1,2] | **S. Babli Millais**[1] | **Alex Godwood**[1] | **Odile Dewit**[1] | **David M. Cross**[3] | **Janet Liptrot**[1] | **Bharat Ruparelia**[1] | **Stephen Paul Jones**[4] | **Geor Bakker**[1] | **Paul T. Maruff**[5] | **Gregory A. Light**[6] | **Alastair J.H. Brown**[1] | **Malcolm Peter Weir**[1] | **Miles Congreve**[1] | **Tim Tasker**[1]

[1] Heptares Therapeutics Ltd, Cambridge, UK

[2] Department of Psychiatry, University of Cambridge, Cambridge, UK

[3] Cross Pharma Consulting Limited, Cambridge, UK

[4] tranScrip Partners LLP, Wokingham, UK

[5] Cogstate Ltd, New Haven, Connecticut, USA

[6] Department, of Psychiatry, University of San Diego, San Diego, California, USA

Correspondence
S. Babli Millais, Heptares Therapeutics Ltd, CB21 6GP, Cambridge, UK.
E-mail: babli.millais@soseiheptares.com

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Abstract

Introduction: This study examined the safety and pharmacodynamic effects of selective muscarinic M_1 receptor orthosteric agonist HTL0018318 in 60 patients with mild-to-moderate Alzheimer's disease (AD) on background donepezil 10 mg/day.

Methods: A randomized, double-blind, placebo-controlled 4-week safety study of HTL0018318 with up-titration and maintenance phases, observing exploratory effects on electrophysiological biomarkers and cognition.

Results: Treatment-emergent adverse events (TEAEs) were mild and less frequently reported during maintenance versus titration. Headache was most commonly reported (7–21%); 0 to 13% reported cholinergic TEAEs (abdominal pain, diarrhea, fatigue, nausea) and two patients discontinued due to TEAEs. At 1 to 2 hours post-dose, HTL0018318-related mean maximum elevations in systolic and diastolic blood pressure of 5 to 10 mmHg above placebo were observed during up-titration but not maintenance. Postive effects of HTL0018318 were found on specific attention and memory endpoints.

Discussion: HTL0018318 was well tolerated in mild-to-moderate AD patients and showed positive effects on attention and episodic memory on top of therapeutic doses of donepezil.

KEYWORDS
Alzheimer's disease, attention, cholinergic, clinical trial, cognition, Cogstate neuropsychological test battery, electrophysiology, event related potential, HTL0018318, memory, muscarinic M_1 receptor, pharmacodynamic, safety, symptomatic, tolerability

1 | INTRODUCTION

Over the last two decades, many of the drug discovery strategies for Alzheimer's disease (AD) have focused on disease-modifying treatments targeting amyloid beta (Aβ) pathology. Despite extensive research and large numbers of clinical trials, these, as well as other targeted approaches, have generally failed to show clinical benefit.[1] In the future, it seems probable that multiple therapeutic approaches will be necessary to successfully treat AD. While newer mechanisms and potential targets for disease-modifying treatments are being explored,[2–7] there remains an urgent need for novel symptomatic drugs that can reinstate damaged or dysfunctional neurotransmission to provide sustained and clinically meaningful benefits for patients, regardless of the outcome of the disease modification strategies.

The cholinergic system remains an important target for symptomatic treatments in AD, as cholinergic neurons in the early stages of the disease are particularly susceptible to AD pathology. Cholinergic neurons in the basal forebrain are among the first to degenerate due to neurofibrillary tangles and Aβ-containing plaques.[8–11] Acetylcholinesterase inhibitors (AChEIs) are a symptomatic treatment that remain the first-line standard of care for AD, despite yielding only modest improvements in cognition, behavior, and general clinical outcome.[12,13] More recently, drugs targeting both cholinergic and non-cholinergic receptors on pre-synaptic cholinergic neurons have been explored and tested in clinical trials, including agonists targeting nicotinic $\alpha_4\beta_2$ and α_7 receptors[14–16] and antagonists targeting H_3 and 5-HT_6 receptors.[17,18] However, to date, none of these drugs have shown clinical benefits either as a monotherapy or combined with AChEIs. One possible reason for this consistent lack of clinical benefit is that these compounds rely on intact cholinergic neuronal integrity for maximal efficacy, which shows progressive atrophy in AD.[8–12,19–21]

An alternative treatment strategy is to target post-synaptic muscarinic M_1 receptors with selective agonists, as post-synaptic M_1 receptors remain relatively well preserved in AD.[22–27] Preclinical studies have reported improvements in learning and memory after treatment with selective M_1 receptor agonists.[28–32] Furthermore, improvements in episodic memory were observed with selective M_1 receptor agonist GSK1034702 in a model of cognitive impairment in healthy volunteers.[33] In contrast, the M_1 positive allosteric modulator (PAM) MK-7622 failed to show improvements in cognitive function when used as an adjunct treatment with AChEI in mild-to-moderate AD.[34] The lack of efficacy with MK-7622 may have been due to the effectiveness of the PAM being similarly reliant on the integrity of cholinergic neurons, which are severely compromised in AD. Support for this hypothesis can be found from findings that M_1/M_4 agonist xanomeline improves cognition and neuropsychiatric symptoms in patients with mild-to-moderate AD,[35] suggesting that targeting post-synaptic M_1 receptors may be a better pharmacological strategy.

HTL0018318 is an M_1 receptor orthosteric partial agonist with moderate selectivity for M_1 over M_4 receptors and no detectable functional agonist activity at human M_2 and M_3 receptors.[36] In rats, HTL0018318 reversed scopolamine-induced deficits in passive avoidance learning, and demonstrated statistically significant changes in pre-clinical quantitative electroencephalogram (EEG) measurements, consistent with prior studies of M_1 agonists.[36] Single and multiple ascending dose studies in healthy young and elderly participants showed that HTL0018318 was well tolerated at doses up to 35 mg.[37,38] In addition, 10 days of treatment with HTL0018318 improved short-term learning and memory in both young and elderly participants, with moderate to large effect sizes (ESs).[37] The current study examined the safety, tolerability, and pharmacodynamic (PD) effects of HTL0018318 over 4 weeks of treatment in patients with mild-to-moderate AD on a stable dose of standard of care donepezil.

RESEARCH IN CONTEXT

1. **Systematic review**: Novel symptomatic drugs for Alzheimer's disease (AD) are needed. Acetylcholinesterase inhibitors are first-line standard of care treatment for AD, despite only yielding modest improvements in cognition, behavior, and clinical global outcome. This is the first published clinical study of an alternative strategy of targeting post-synaptic muscarinic M_1 receptors with a selective orthosteric agonist,HTL0018318. Previously, HTL0018318 has shown positive effects on cognition in preclinical and early healthy volunteer studies.
2. **Interpretation**: In this randomized, double-blind, phase 1b/2a 4-week study of HTL0018318 versus placebo in 60 patients with mild-to-moderate AD receiving therapeutic doses of donepezil, HTL0018318 was well tolerated and showed positive effects on tests of attention and episodic memory that justify further exploration.
3. **Future directions**: These findings support further development of HTL0018318 as a symptomatic treatment of dementias including AD. Future studies should use a wider dose range and include a higher proportion of patients receiving memantine.

HIGHLIGHTS

- A phase 1b/2a 4-week study of HTL0018318 versus placebo in mild-to-moderate AD.
- HTL0018318 was well tolerated; most treatment-associated adverse events were mild with higher occurrence during the titration phase.
- Maximum mean increases in blood pressure of 5 to 10 mmHg with HTL0018318 were observed at T_{max}.
- HTL0018318 showed positive effects on tests of attention and episodic memory.

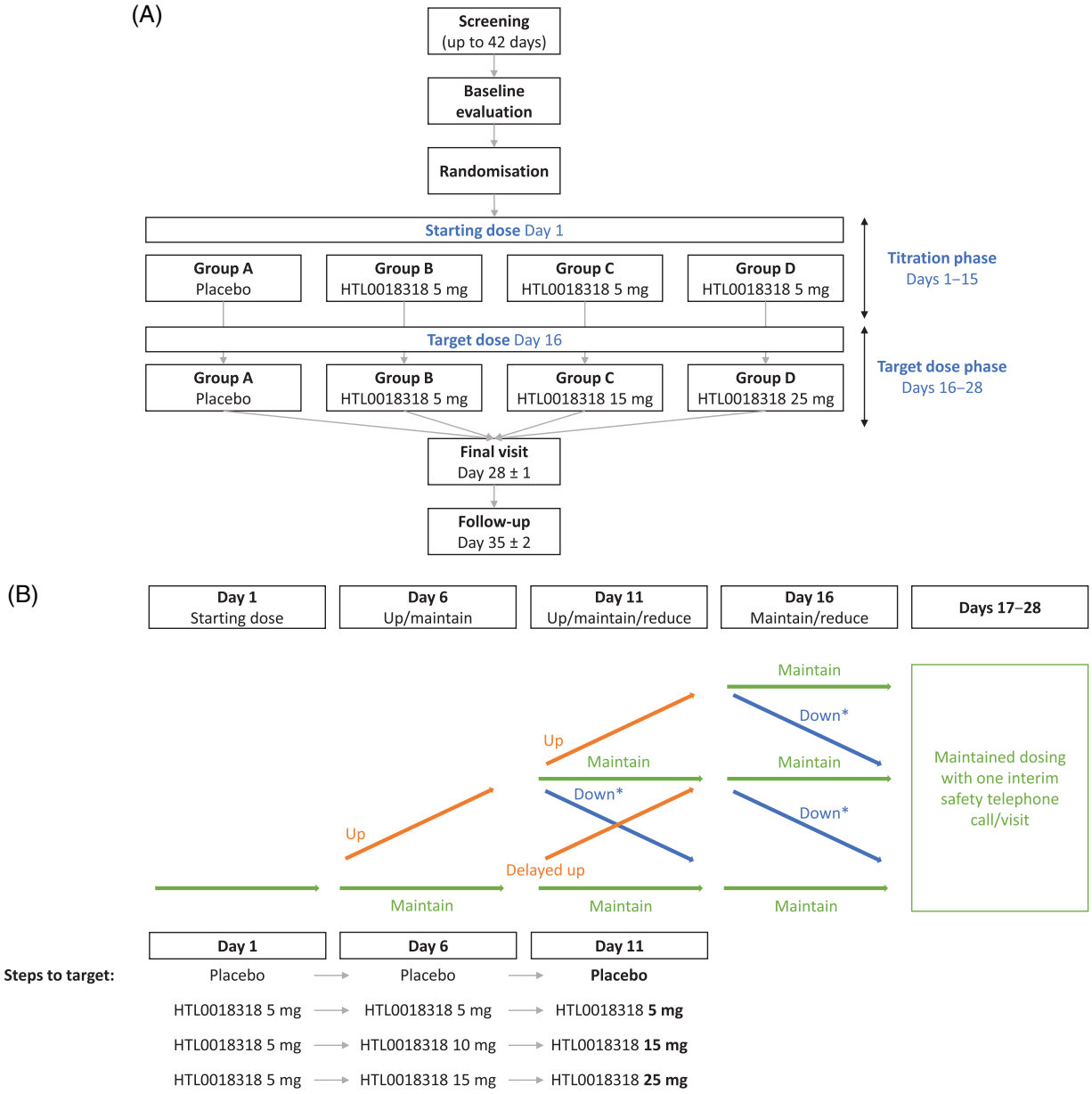

FIGURE 1 A, Study design. B, Titration schedule. *down = 5 mg dose reduction

2 | METHODS

2.1 | Study design

This was a randomized, double-blind, parallel-group, placebo-controlled study in which patients with mild-to-moderate AD received placebo or one of three doses of HTL0018318 over a 4-week period as an adjunctive treatment to standard of care donepezil (10 mg per day) with or without memantine. The study was an outpatient study conducted across 18 centers in Poland, Czech Republic, Spain, and Slovakia (NCT03456349, registered at clinicaltrials.gov). All appropriate regulatory and ethical approvals were obtained, and all participants provided informed consent. Patients were assessed for eligibility during a 42-day screening period and randomized equally to either placebo or a HTL0018318 target dose of 5, 15, or 25 mg per day (Figure 1A). HTL0018318 was titrated to the target dose during a 2-week titration period (Figure 1B); investigators could maintain or reduce the dose to limit tolerability/safety issues throughout this period.

2.2 | Patients

Eligible patients were aged 55 to 85 years, with diagnostic evidence of probable AD according to the 2011 National Institute of Aging–Alzheimer's Association criteria,[39] mild-to-moderate dementia according to a Mini-Mental State Examination (MMSE) score of 12 to 24, and taking donepezil at a stable dose of 10 mg daily (with or without

TABLE 1 Baseline demographics and clinical characteristics (SAF, randomized)

	Placebo (n = 15)	HTL0018318 5 mg (n = 15)	HTL0018318 15 mg (n = 14)	HTL0018318 25 mg (n = 16)
Age, mean (SD)	72.1 (8.5)	72.2 (6.4)	71.1 (4.3)	73.5 (8.9)
Female, n (%)	10 (66.7)	9 (60.0)	11 (78.6)	11 (68.8)
White race, n (%)	15 (100)	15 (100)	14 (100)	16 (100)
BMI (kg/m^2), mean (SD)	27.0 (3.3)	27.1 (3.8)	26.6 (3.4)	25.9 (4.6)
Years since AD diagnosis, mean (SD)	2.9 (2.5)	3.6 (2.4)	2.4 (2.1)	2.9 (1.5)
MMSE, mean (SD)	20.5 (3.5)	21.5 (1.8)	20.6 (3.1)	20.8 (2.5)
Donepezil use, n (%)	15 (100)	14 (100)	14 (100)	16 (100)
Memantine use[a], n (%)	1 (6.7)	1 (6.7)	1 (7.1)	1 (6.3)
Country, n (%)				
Czech Republic	3 (20.0)	3 (20.0)	2 (14.3)	4 (25.0)
Poland	1 (6.7)	2 (13.3)	3 (21.4)	4 (25.0)
Slovakia	6 (40.0)	7 (46.7)	6 (42.9)	6 (37.5)
Spain	5 (33.3)	3 (20.0)	3 (21.4)	2 (12.5)

Abbreviations: AD, Alzheimer's disease; BMI, body mass index; MMSE, Mini-Mental State Examination; SAF, safety set; SD, standard deviation.
[a]In Poland, use of memantine was exclusionary.

memantine), for at least 6 weeks prior to screening. Full inclusion and exclusion criteria are reported in Appendix S1.2.1 and S1.2.2 in supporting information.

2.3 | Endpoints

The primary endpoint of this study was to evaluate the safety and tolerability of HTL0018318. Safety and tolerability were assessed via the incidence and severity of treatment-emergent adverse events (TEAEs), and via evaluation during study visits of vital signs (including blood pressure [BP] and heart rate [HR]), electrocardiogram [ECG] measurements, physical and neurological examinations, laboratory hematology, clinical chemistry, and urine analysis.

Exploratory PD effects of HTL0018318 were examined via both behavioral (Cogstate neuropsychological test battery [NTB]) tests of cognitive function and electrophysiological (EEG and evoked response potentials [ERPs]) biomarkers. Further details of each biomarker/test and outcome variables are provided in Appendix S1.3.2 and S1.3.3 in supporting information. Twelve-item neuropsychiatric inventory (NPI-12) scores were used to evaluate neuropsychiatric symptoms.

Selected plasma pharmacokinetics (PK) parameters for HTL0018318 were estimated during the period over which PD assessments were made.

Details of assessment times for all endpoints are described in Appendix S1.3.

2.4 | Statistical analyses

Statistical evaluation was performed using SAS (SAS Institute). Changes from baseline in vital signs were analyzed using a mixed model for repeated measures with fixed effects for baseline, treatment, timepoint, and treatment by timepoint interaction. The exploratory PD endpoints were analyzed using an analysis of covariance with change from baseline as the dependent variable, and baseline and treatment as covariates. The least square means (LSM) for each dose (and difference from placebo) are presented with the 90% confidence interval (CI), *P*-value, and ES.

It was estimated that a sample size of 60 patients (15 per treatment group, with a discontinuation rate of up to 10%) would provide ≥80% power, assuming a true standardized ES of at least 0.97 in each active group versus placebo in mean change from baseline in EEG-ERP paradigms or cognition endpoints. Testing used a two-sided significance level of 0.10, without adjustment for multiple comparisons. PD endpoints with $P < .10$ were identified as potential signals that justify further exploration and comment.

3 | RESULTS

3.1 | Patients

Eighty-seven patients were screened, and 60 were randomized and received at least one dose of the study drug (placebo, n = 15; HTL0018318 5 mg, n = 15; 15 mg, n = 14; 25 mg, n = 16; safety set [SAF, randomized dose], PK set [PKS]; Figure S1 in supporting information). The full analysis set (FAS) comprised 59 patients, with 1 patient excluded from the 5 mg group. All patients receiving placebo and 93.5% of patients (43/45) receiving HTL0018318 completed the study. Median treatment compliance was 100% in all arms. Baseline demographics and clinical characteristics were generally comparable across treatment groups (Table 1).

TABLE 2 (A) Incidences of TEAEs, SAEs, and TEAEs leading to discontinuation (SAF, randomized); (B) timing of TEAEs (SAF, day 16 dose received)[a]

A				
	Placebo (n = 15)	**HTL0018318 5 mg (n = 15)**	**HTL0018318 15 mg (n = 14)**	**HTL0018318 25 mg (n = 16)**
Number of TEAEs, n	12	18	16	26
TEAE incidence, n (%)	6 (40.0)	8 (53.3)	8 (57.1)	11 (68.8)
Severity: mild	6 (40.0)	7 (46.7)	8 (57.1)	9 (56.3)
Severity: moderate	0	1 (6.7)	1 (7.1)	4 (25.0)
Severity: severe	0	1 (6.7)	0	0
Individual TEAE incidences,[b] n (%)				
Abdominal pain	**0**	**1 (6.7)**	**0**	**0**
Accidental overdose	0	1 (6.7)	1 (7.1)	0
Decreased lymphocyte count	0	0	1 (7.1)	1 (6.3)
Decreased white blood cell count	0	0	1 (7.1)	1 (6.3)
Diarrhea	**1 (6.7)**	**1 (6.7)**	**0**	**1 (6.3)**
Fatigue	**0**	**0**	**0**	**2 (12.5)**
Headache	3 (20.0)	1 (6.7)	3 (21.4)	3 (18.8)
Hyperhidrosis	0	0	2 (14.3)	0
Lymphopenia	0	0	1 (7.1)	1 (6.3)
Nausea	**0**	**1 (6.7)**	**1 (7.1)**	**0**
Urinary tract infection	1 (6.7)	1 (6.7)	0	1 (6.3)
Viral upper respiratory tract infection	0	1 (6.7)	0	1 (6.3)
Treatment-related[c] TEAE incidence, n (%)	2 (13.3)	4 (26.7)	7 (50.0)	5 (31.3)
TEAE leading to discontinuation incidence, n (%)	0	1 (6.7)[d]	1 (7.1)[e]	0
SAE incidence, n (%)	0	0	0	0

B					
	Placebo (n = 15)	**HTL0018318 5 mg (n = 17)**	**HTL0018318 10 mg (n = 1)**	**HTL0018318 15 mg (n = 16)**	**HTL0018318 25 mg (n = 11)**
TEAE incidence during titration(days 1–15), n (%)	6 (40.0)	8 (47.1)	1 (100)	8 (50.0)	6 (54.5)
TEAE incidence during maintenance(days 16–28), n (%)	1 (6.7)	4 (23.5)	0	2 (12.5)	2 (18.2)

Note: Bold text highlights TEAEs potentially related to cholinergic stimulation.
Abbreviations: BP, blood pressure; SAE, serious adverse event; SAF, safety set; TEAE, treatment-emergent adverse event.
[a]Patients grouped according to the dose that they were taking at the Week 16 visit.
[b]TEAEs potentially related to cholinergic stimulation or occurring in ≥2 patients receiving HTL0018318 and/or in ≥2 patients in any HTL0018318 dose group.
[c]TEAEs considered by the investigator to be definitely or possibly related to the study drug at the time of the event.
[d]Patient experienced a severe drug-related increase in BP and met stopping criteria on Day 1.
[e]Patient experienced mild drug-related nausea leading to study drug discontinuation on Day 24.

3.2 | Safety and tolerability

TEAEs reported in ≥2 patients receiving placebo or HTL0018318 are shown in Table 2; headache was the most commonly reported TEAE across all treatment groups. The majority of TEAEs were mild in severity and occurred during the titration phase (TEAE incidence was ≈30% lower during the dose maintenance phase). There were no serious TEAEs or deaths. Two patients discontinued treatment due to TEAEs (increased BP in one patient randomized to 5 mg, on day 1 of dosing; nausea in one patient randomized to 15 mg, on day 24 of dosing). TEAE incidence (but not treatment-related TEAE incidence) increased with increasing dose of HTL0018318. Cholinergic TEAEs included abdominal pain, diarrhea, fatigue, and nausea, with incidences of 0 to 13% at the two highest HTL0018318 doses (15 and 25 mg).

Post-dose increases in systolic BP (SBP) and diastolic BP (DBP) were observed in patients receiving HTL0018318 (all doses, without a dose relationship), generally returning to pre-dose levels after a few hours (Figure S2 in supporting information); pre-dose BP did not increase progressively with continued dosing. Post-dose decreases in SBP and DBP were observed in patients receiving placebo. Mixed model statistical analysis showed that the maximum mean elevations in SBP and DBP in patients receiving HTL0018318 were 5 to 10 mmHg above mean values in patients receiving placebo and occurred at time of maximum concentration (T_{max}; 1–2 hours post-dose; Figure 2). The drug effect appeared similar across all HTL0018318 doses, and was only observed on days 1, 6, and 11, with no differences between patients receiving placebo and HTL0018318 on days 16 and 28. There were no significant changes in orthostatic BP or HR with HTL0018318 (across doses) or placebo (Figure 2, Figure S2).

There were no significant or consistent patterns of change in ECG profiles or other vital signs across treatment groups or study days. There were no clinically significant physical or neurological examination findings, or laboratory abnormalities, including liver function and hematology, and no increased risk of suicide.

3.3 | Exploratory pharmacodynamic endpoints: Cogstate neuropsychological test battery

Improvements in attention performance (reaction time; on the Identification task IDN) were observed at the HTL0018318 15 mg dose (LSM difference 0.11; 90% CI: 0.02, 0.21; $P = 0.0455$; ES 0.62; Figure 3). Smaller magnitude of improvements was observed at the 5 and 25 mg doses (ES 0.21 and 0.37).

Consistent improvements in learning and memory were observed with HTL0018318 25 mg (International shopping list (ISL)-immediate recall: LSM difference 1.11 words; 90% CI: −1.04, 3.25; $P = .39$; ES 0.34; ISL-delayed recall: LSM difference 0.65; 90% CI: −0.25, 1.56; $P = .2330$; ES 0.49; composite [ISL-immediate and -delayed recall]: LSM difference 0.21, 90% CI: −0.09, 0.51; $P = .2421$; ES 0.48; Figure 3). However, the magnitude of these positive effects was too small to reach the significance level of $P < .10$ and these effects were not observed at the 5 or 15 mg doses.

There were no noteworthy differences in One Back (ONB) reaction time or accuracy, or Groton Maze Learning (GML) task (forward or reverse) performance, at any HTL0018318 dose (Figure 3).

3.4 | Exploratory pharmacodynamic endpoints: EEG and ERP

3.4.1 | Resting state paradigm

An increase in delta power at the central (Cz) electrode in the eyes open condition was observed with the 5 and 15 mg doses of HTL0018318, with a small effect in the same direction observed with the 25 mg dose; the largest ES was observed with the 15 mg dose (LSM difference 3.8; 90% CI: 0.6, 7.0; $P = .053$; ES 0.75). There were no other noteworthy effects on EEG power across the different frequency bands in the eyes open or closed conditions at any dose.

3.4.2 | Passive auditory oddball paradigm

An improvement in mismatch negativity (MMN) amplitude (i.e., more negative) at the frontal (Fz) electrode was observed with the 5 and 15 mg doses of HTL0018318, with a small effect in the same direction observed with 25 mg (Figure 4A). The ES was large with the 5 mg dose (LSM difference −0.82 uV; 90% CI: −1.43, −0.20); $P = .030$; ES −0.84), and moderate with the 15 mg dose (LSM difference −0.63uV; $P = .105$; ES −0.64). Improvements in MMN amplitude and peak MMN amplitude using the frontal central composite (FCComp) electrode were consistent with those observed at the Fz electrode. No improvements were observed in peak MMN latency.

No consistent effects were observed on P3a amplitude or latency at the Fz electrode or FCComp across the three HTL0018318 doses. However, a decrease in P3a amplitude at the Fz electrode was observed with the 15 mg dose (LSM difference −0.84 uV; 90% CI: −1.59, −0.09; $P = .065$; ES −0.73); the effects with 5 and 25 mg were not consistent with this.

3.4.3 | Active auditory oddball paradigm

There were no differences in P3b mean amplitude at the central parietal composite (CPComp) electrodes with any HTL0018318 dose. However, consistent increases in P3b mean amplitude were observed across all three doses (ESs: 0.22–0.44; Figure 4B).

There were decreases in peak P3b latency of moderate to large magnitude at the CPComp electrodes with the 5 and 25 mg doses of HTL0018318 (Figure 4B). The largest effect was with 5 mg (LSM difference −38 ms; 90% CI: −70, −6.1; $P = .052$; ES −0.81). No decrease in peak P3b latency was observed with the 15 mg dose.

3.4.4 | Hz auditory steady-state response paradigm

There were no effects with any HTL0018318 dose in amplitude of gamma-band evoked power or phase locking at the Fz electrode across all time bands/window (i.e., 1–500 ms).

3.5 | Exploratory pharmacodynamic endpoints: neuropsychiatric inventory

There was a reduction in NPI-12 symptoms (total score) at the 5 mg HTL0018318 dose (LSM difference −1.79; 90% CI: −3.31, −0.26; $P = .055$; ES −0.73) compared to placebo, with consistent results observed at the 15 and 25 mg doses (ES −0.54 and −0.53, respectively). Overall, the incidence of symptoms was low across patients (mean scores 2–2.5 [range 0–26]).

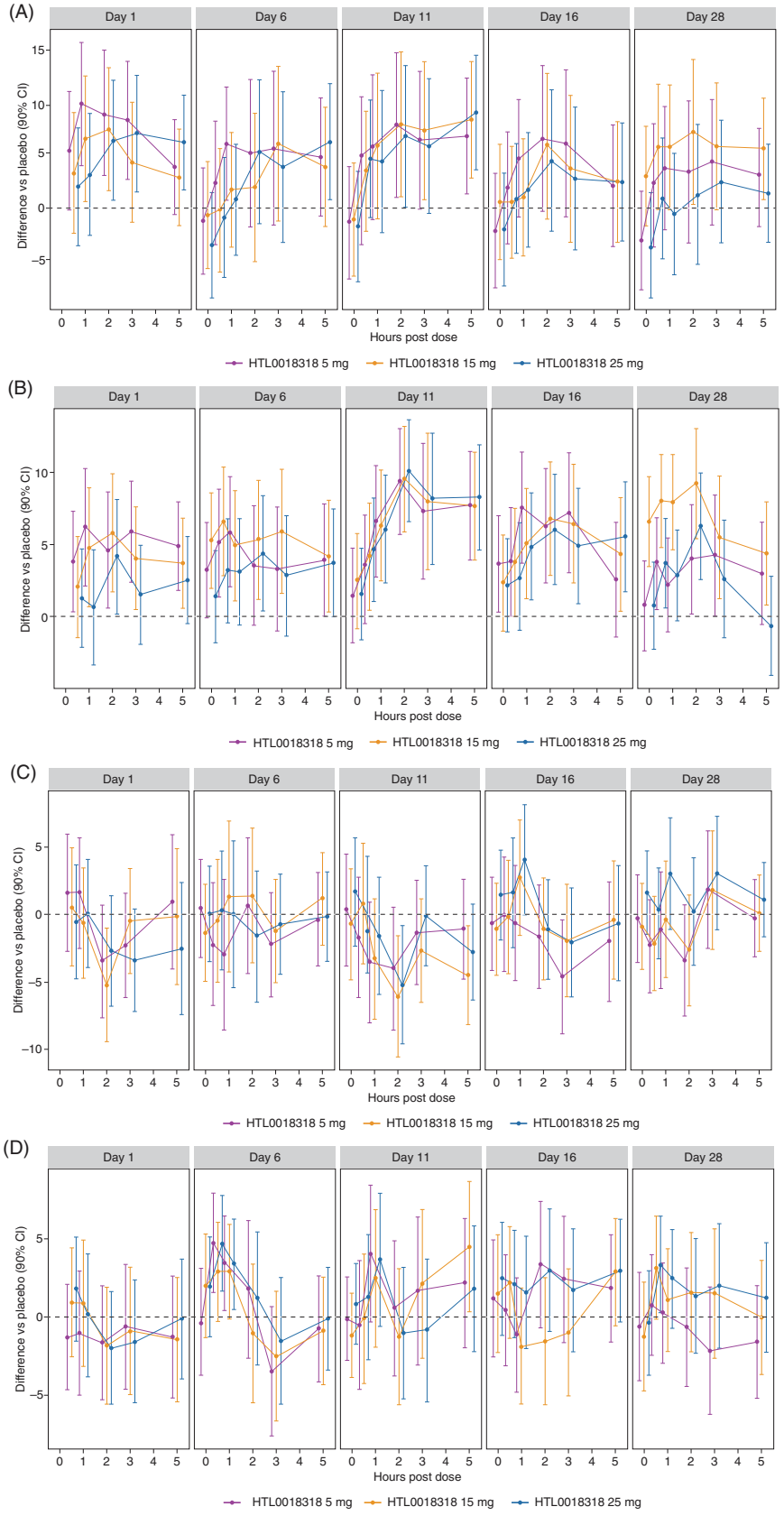

FIGURE 2 Difference in vital signs between patients randomized to HTL0018318 versus placebo. A, Supine systolic blood pressure. B, Supine diastolic blood pressure. C, Orthostatic difference in systolic blood pressure. D, Supine heart rate (SAF, randomized)

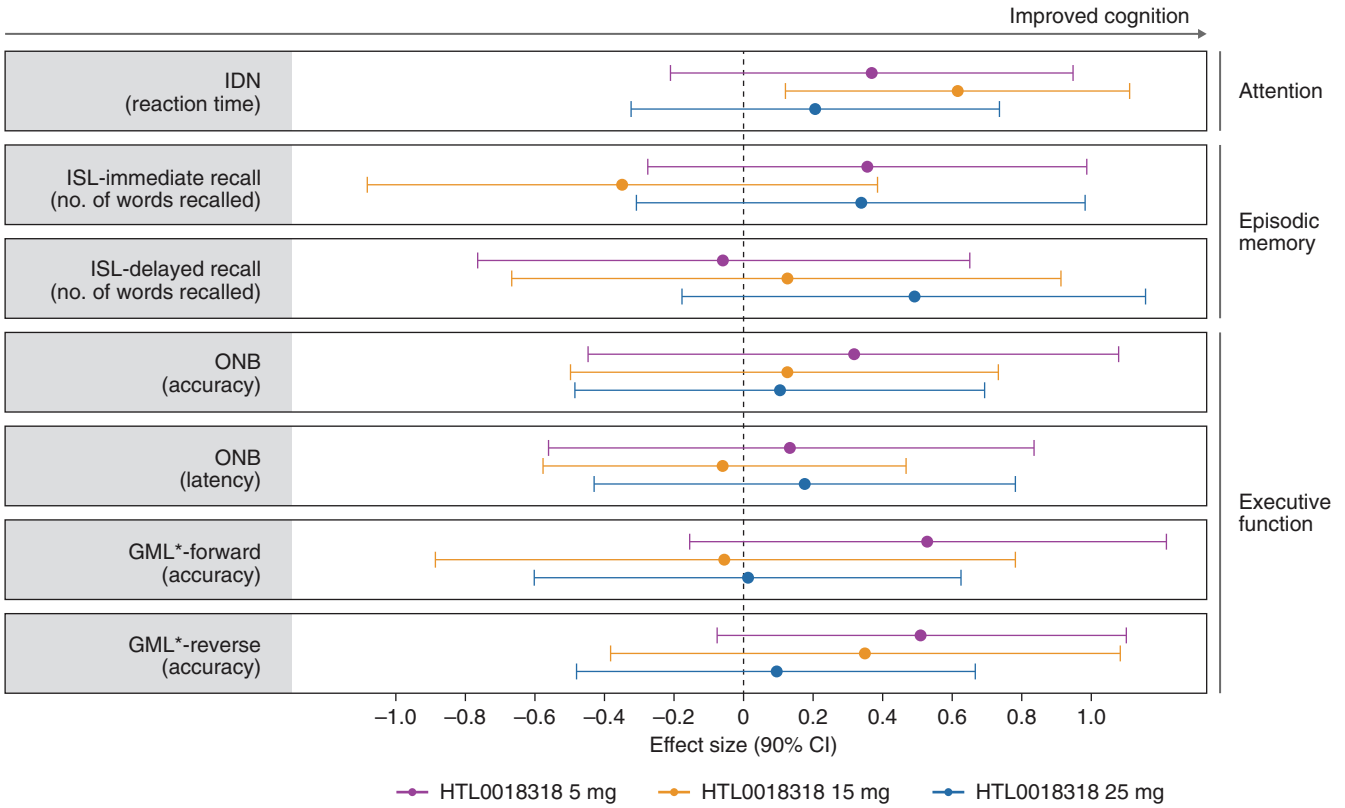

FIGURE 3 Cogstate NTB ES in patients receiving HTL0018318 compared to placebo (FAS). *The effect in the 5 mg HTL0018318 group was driven by a single patient, who made a very large number of errors during the baseline assessment, and substantially fewer at day 28. ES, effect size; NTB, neuropsychological test battery; IDN, Identification; ISL, International Shopping List; ONB, One Back; GML, Groton Maze Learning.

3.6 | Exploratory endpoints: pharmacokinetics

Plasma PK of HTL0018318 was used to establish the dose–exposure relationship as patients progressed through the up-titration scheme (Table S1 in supporting information). Once established on any given dose level, PK did not change on subsequent PK sampling days, showing that steady-state was achieved with 5 days of daily dosing. Predose concentrations, reflecting trough concentrations at steady-state, showed the mean minimum concentration above which HTL0018318 was sustained throughout the dosing interval. Dose-exposure proportionality was confirmed on day 28. On day 28, HTL0018318 mean maximum concentration (C_{max}) was 51.8 ng/mL in patients receiving 5 mg, 89.0 ng/mL for 10 mg, 123 ng/mL for 15 mg, and 224 ng/mL for 25 mg. Likewise, on day 28, mean area under the curve (AUC) from time 0 to 4 hours post-dose ($AUC_{0\text{-}4h}$) was 144 h.ng/mL with 5 mg, 222 h.ng/mL with 10 mg, 368 h.ng/mL with 15 mg, and 668 h.ng/mL with 25 mg. Median T_{max} ranged from 1 to 2 hours for all doses.

There was no clear dose–response relationship on the safety or PD endpoints. The dose response relationship was partially confounded by the titration schedule with 11/16 (69%) receiving the maximum dose of 25 mg (see Figure S1). However, the seven subjects with the highest exposure observed improvement on at least three of four Cogstate endpoints related to attention and episodic memory.

4 | DISCUSSION

This phase 1b/2a study is the first investigation of the safety, tolerability, PK, and exploratory PD effects (cognition and neuropsychiatric symptoms) of the selective muscarinic M_1 receptor orthosteric agonist HTL0018318, in patients with mild-to-moderate AD. HTL0018318 was up-titrated over a 2-week period adjunctive to a stable dose of donepezil during a 4-week study.

HTL0018318 exhibited reproducible PK, consistent with previous studies in healthy young and elderly participants.[37,38] Systemic exposure to HTL0018318 (as indexed by C_{max} and $AUC_{0\text{-}4h}$) increased proportionally across 5 mg to 25 mg doses and did not change on repeat dosing. HTL0018318 was generally well tolerated, with only two patients discontinuing treatment and the majority of TEAEs being mild and infrequent; the safety profile was generally consistent with that reported in previous studies.[37,38] The most common TEAEs were dose related and included abdominal pain, diarrhea, fatigue, headache, hyperhidrosis, and nausea; only headache occurred in > 2 patients taking HTL0018318. Of note, incidences of cholinergic TEAEs were a maximum of 7% or 13% at the two highest doses (15 and 25 mg). It has previously been suggested that M_1 PAMs may have a better cholinergic TEAE profile than M_1 receptor agonists.[40] However, the incidence of cholinergic adverse events was 21% in a recent clinical study of

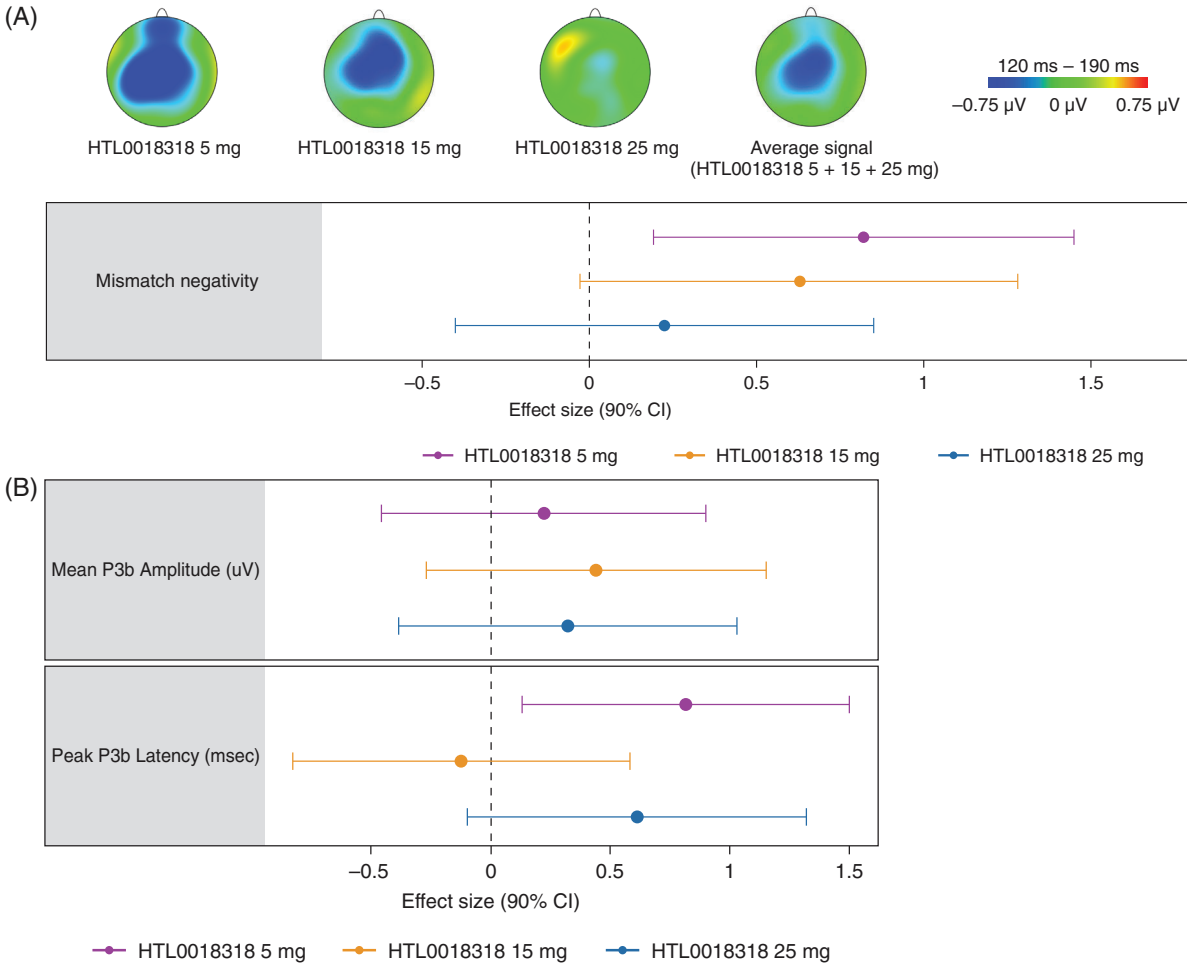

FIGURE 4 EEG and ERP differences between patients receiving HTL0018318 and placebo during a passive and active auditory oddball paradigm. A, Passive auditory oddball paradigm: head maps show drug–placebo differences in MMN amplitude. Cooler colors show greater drug related increases in MMN amplitude. The chart below shows effect size of change in MMN amplitude in patients receiving HTL0018318 compared to placebo at the Fz electrode. B, Active auditory oddball paradigm: charts show effect sizes on mean P3b amplitude and peak latency changes* in patients receiving HTL0018318 compared to placebo at the CPComp electrode. *Shortening of peak latency represents a positive treatment effect and is thus shown as a positive effect size in the chart. CPComp, central parietal composite electrode; EEG, electroencephalogram; ERP, evoked response potential; Fz, frontal (electrode); MMN, mismatch negativity

the M_1 PAM MK-7622 in patients with mild-to-moderate AD,[34] higher than the 7% to 13% incidences reported with the two highest doses of HTL0018318 in the current study. Interestingly, the incidence of TEAEs appeared to be approximately 30% less during the dose maintenance (days 16–28) versus up-titration (days 1–15) period. While previous clinical experience did not indicate that an up-titration regimen was necessary to manage TEAEs, this approach may have contributed to the low TEAE incidence and mild TEAE profile (overall and cholinergic TEAEs specifically) in the current study.

HTL0018318 was associated with transient increases in BP, with the maximum mean increase of 5 to 10 mmHg in SBP and DBP observed around the estimated time of highest systemic drug exposure, without a clear dose–response relationship and with some evidence for tolerance with continued dosing. While the exact mechanism associated with the transient increase in BP is not known, it is likely that it is mediated through central activation of M_1 receptors.[41–44] No significant treatment effects were observed on other cardiovascular endpoints (including orthostatic BP, HR, and ECG) or clinical laboratory safety parameters. The increase in BP with no significant effects on orthostatic BP or HR contrasts with other muscarinic agonists, including the M_1/M_4 agonist xanomeline, which caused significant increases in BP and HR, as well as a decrease in orthostatic BP.[43] Our data suggest that the cardiovascular effects of muscarinic agonists in AD may be less pronounced with a partial agonist and when dosed using a titration regimen within the dose range tested here.

Exploratory PD effects were measured using both behavioral and electrophysiological biomarkers of cognitive function. The behavioral tests within the Cogstate NTB are sensitive to cholinergic modulation[45] and are able to detect cognitive impairment in patients with AD[46,47], and it has also been shown to be more sensitive in detecting pro-cognitive signals after short durations of treatment compared to other measures, such as the Alzheimer's Disease Assessment Scale–Cognitive subscale (ADAS-Cog).[17] The EEG and ERP tasks evaluated very early sensory processing related to resting state brain

activity (EEG power in various frequency bands), attention and memory (MMN), network activity and synchrony in the gamma frequency range (40 Hz ASSR), attention (P3a), and attention/working memory (P3b). These biomarkers have been shown to detect cognitive deficits in patients with AD.[48–50]

HTL0018318 showed positive PD effects on several cognitive biomarkers, providing preliminary support that HTL0018318 is brain penetrant and may be modulating processes relevant to cognitive function. On the Cogstate NTB, an improvement in attention was observed, along with some evidence of improved episodic memory (HTL0018318 25 mg: ISL-delayed recall, ES 0.49; ISL composite, ES 0.48). While the improvement in episodic memory did not reach statistical significance, the effects observed are consistent with pre-clinical evidence across multiple muscarinic M_1 receptor agonists, as well as previous findings in humans using the same test with the M_1 agonist GSK1034702.[33] The improvement seen with HTL0018318 specifically on the tests of attention and episodic memory are relevant in the context of these cognitive domains being prominently affected in mild cognitive impairment (MCI) and AD (ES 0.5–2.5, respectively).[46,47] Moreover, the improvements seen with HTL0018318 on attention across doses (ES 0.4) and episodic memory (0.48–0.49) were comparable to those reported with xanomeline (estimated ES of 0.28–0.35 for tests of attention; estimated ES of 0.2–0.35 for episodic memory).[51] Although study designs and treatment durations of the studies were different, these data do support further investigation of HTL0018318 in a larger powered phase 2 study.

Consistent with the effects of HTL0018318 on behavioral tests of attention and episodic memory, physiologically relevant effects were also observed in electrophysiological biomarkers of attention and memory. Positive effects were observed for MMN and eyes open delta power; mean ESs (all HTL0018318 doses) were moderate (0.6 and 0.52, respectively). MMN is a biomarker of early sensory attention and memory and change detection. Impairments in MMN (both amplitude and latency) have been reported in MCI and AD,[52,53] with impairments correlated with episodic memory.[54] While the effects of cholinesterase inhibitors (such as donepezil) on MMN are not known, the magnitude of effects observed in this study in AD are comparable to the magnitude of effects reported with the cognitive enhancer memantine in various clinical populations.[55,56] Similarly, positive effects were observed on the P3b biomarker of attention and memory with moderate improvements in P3b amplitude and latency (ESs 0.33 and 0.42). Changes in P3b reflect the amount (and speed) of attentional resources allocated when working memory is updated.[57] Consistent impairments in P3b of moderate to large magnitudes have been reported in MCI and AD for both amplitude and latency, with positive associations found between P3b latency changes and various cognitive processes.[58,59] The positive effects of HTL0018318 on P3b amplitude and latency are similar or larger in magnitude than those reported for cholinesterase inhibitors such as donepezil and rivastigmine (ES of 0.08–0.21).[59] The significance of delta power changes is unknown, although slow oscillations in the delta and theta band are thought to be effective in activating long-range network states associated with cognitive function, including memory.[60] In this context, the observed increases in delta power are consistent with the effects observed on MMN and P3b, as well as the behavioral tasks that measured attention and episodic memory.

The PD effects of HTL0018318 on biomarkers of attention and episodic memory provide preliminary evidence for brain penetration and modulation of specific domains of cognition at a physiological and behavioral level in patients with AD maintained on therapeutic doses of donepezil. Specific effects on domains of cognition of moderate to large magnitude were observed in early sensory attentional and memory processing (MMN), attention (P3b and IDN), and episodic memory (ISL), but not in executive function (ONB and GML). It is possible that higher doses may be required to improve executive function, which requires more complex and effortful cognitive resources. Overall, these findings are encouraging for several reasons. The duration of treatment was only 4 weeks; larger effects may be observed over a longer treatment duration, when symptomatic effects may be more apparent against normal cognitive decline. Furthermore, the moderate to large ESs observed across a number of biomarkers of attention and memory reflect benefits that occurred on top of therapeutic doses of donepezil, which adds further significance to the findings. Interestingly, HTL0018318 also showed some positive effects of moderate magnitude on neuropsychiatric symptoms as measured by the NPI-12. These data, while preliminary, are encouraging and support findings previously reported with the M_1/M_4 receptor agonist xanomeline in AD.[35]

Similar increases in blood pressure were observed across all HTL0018318 doses, and there was no clear differentiation between doses in PD effects. Positive effects on biomarkers of attention and memory including MMN, P3b, and the Cogstate Identification task were found across all HTL0018318 doses with no clear evidence for response. The optimal dose for AD and other indications requires further exploration in future studies. As HTL0018318 was well tolerated at the top dose and given the subjects with highest exposure observed most improvement in the Cogstate endpoints related to attention and episodic memory, it would be feasible and informative to assess safety and PD effects using a wider dose range than 5 to 25 mg. A limitation of this study was that due to the small number of patients receiving concomitant memantine (n = 4), we could not draw conclusions on the tolerability or PD effects of the combination of HTL0018318 with memantine and this also requires further investigation.

In summary, this 4-week, phase 1b/2a study demonstrated that the M_1 receptor orthosteric agonist HTL0018318 was well tolerated in patients with mild-to-moderate AD when administered as an adjunctive treatment to stable doses of donepezil using a 2-week titration regimen. HTL0018318 showed positive effects on biomarkers of attention and episodic memory providing preliminary evidence for modulation of specific domains of cognition at a physiological and behavioral level. These findings provide encouraging data in support for further evaluation and development of HTL0018318 as a symptomatic treatment of dementias including AD.

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CONFLICTS OF INTEREST

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ORCID

Pradeep J. Nathan https://orcid.org/0000-0003-0943-5329
S. Babli Millais https://orcid.org/0000-0002-1824-3444

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SUPPORTING INFORMATION

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