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RESEARCH ARTICLE

An international, randomized, placebo-controlled, phase 2b clinical trial of intepirdine for dementia with Lewy bodies (HEADWAY-DLB)

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Abstract

Introduction: A phase 2b clinical trial, HEADWAY-DLB, was performed to assess treatment with intepirdine, a serotonin receptor antagonist, in patients with dementia with Lewy bodies (DLB).

Methods: HEADWAY-DLB was a multinational, double-blind, randomized, placebo-controlled study. Two hundred sixty-nine DLB patients were randomized to receive placebo, 70 mg/day intepirdine, or 35 mg/day intepirdine over 24 weeks. The primary endpoint was change from baseline to week 24 on the Unified Parkinson's Disease Rating Scale–Part III (UPDRS-III).

Results: Both intepirdine groups did not demonstrate significant benefits over placebo at 24 weeks on the UPDRS-III (35 mg/day: $P = .1580$, 70 mg/day: $P = .6069$). All other endpoints were not significant. Intepirdine was well tolerated, with a slightly higher incidence of gastrointestinal adverse events observed in the intepirdine groups versus placebo.

Discussion: Intepirdine treatment did not lead to improvements over placebo in patients with DLB. As one of the largest DLB studies to date, HEADWAY-DLB demonstrates that international trials for DLB are feasible within a reasonable timeframe.

KEYWORDS
5-HT6, clinical trial, dementia with Lewy bodies, intepirdine, phase 2b

1 | INTRODUCTION

Dementia with Lewy bodies (DLB) is a progressive neurodegenerative disorder characterized by intracellular neuronal accumulation of pathological alpha-synuclein clusters. DLB is clinically defined by impairments in cognition and alertness, recurrent visual hallucinations, and REM sleep behavior disorder, with parkinsonian motor symptoms tending to occur later in the disease course.[1] Accounting for up to 25% of all dementia cases,[2] DLB is reported to be the second most common cause of neurodegenerative dementia after Alzheimer's disease (AD) and is associated with a more rapid decline than AD dementia.[3] DLB presents a large burden to caregivers and the broader health-care system, particularly as the worldwide number of dementia cases rises each year.[4,5] There are currently no medications approved to treat DLB in most areas, including the United States and Europe.[6]

Despite the lack of regulatory approvals, medications for AD and Parkinson's disease (PD) are widely used to treat patients with DLB.[6] Similar to AD, cholinergic deficits are a prominent feature in the pathophysiology underlying cognitive dysfunction in DLB. Acetyl-cholinesterase inhibitors (AChEIs), which boost acetylcholine neuro-transmission in the brain, have shown benefits across multiple ran-domized controlled DLB trials.[7–10] Cholinergic deficiency appears to be more pronounced in DLB compared to AD, and AChEIs have been reported to confer greater benefit in patients with DLB.[6] Never-theless, AChEIs can induce peripheral cholinergic stimulation, caus-ing side effects such as gastrointestinal (GI) disturbances, muscle cramps, bradycardia, and weight loss.[11] In addition, anti-parkinsonian dopaminergic therapy is commonly used to treat DLB motor symp-toms, although these agents are associated with an increased risk of psychosis.[3] Ultimately, the armamentarium of treatments for DLB is lacking, and current management of DLB is suboptimal as treating one symptom may exacerbate others.

In this context, intepirdine (also called RVT-101 or SB-742457) was deemed to have therapeutic potential for multiple aspects of DLB. As a potent antagonist of the serotonin (5-hydroxytryptamine) subtype 6 (5-HT6) receptor, intepirdine has been shown to boost synaptic acetylcholine transmission in preclinical models of cogni-tive impairment and could improve cholinergic deficiency in DLB patients.[12] Because the 5-HT6 receptor is found almost exclusively in the central nervous system, targeting this receptor may provide benefits over AChEIs by reducing the risk for adverse peripheral effects.[11] Equally important, intepirdine has been shown to have antagonist activity against the 5-HT2a receptor, which may be useful in the treatment of DLB parkinsonian symptoms given the observed benefit of 5-HT2a/c receptor antagonists in clinical studies for PD patients.[13–15] Preservation of the 5-HT2a receptor has also been impli-cated in the pathophysiology underlying visual hallucinations in DLB and PD.[16,17]

Prior to HEADWAY-DLB, intepirdine had been studied in 21 com-pleted clinical trials involving more than 2000 subjects. In a 48-week placebo-controlled study of 684 patients with mild-to-moderate AD dementia, 35 mg/day intepirdine added to stable donepezil demon-strated statistically significant benefits on cognition and activities of daily living, although a subsequent phase 3 study with a similar design (MINDSET) was negative.[18,19] Thirty-five mg/day intepirdine had also demonstrated statistical improvement over placebo on AD global func-tion when administered as monotherapy in a 24-week phase 2 study for mild-to-moderate AD dementia.[20] Intepirdine was generally well tol-erated and demonstrated no dose-limiting toxicities across any clinical study, including at repeated doses of 70 mg.

The mechanistic rationale for antagonizing the 5-HT6 and 5-HT2a receptors, as well as the benefits previously observed in AD demen-tia clinical studies, led us to assess the use of intepirdine in a 24-week phase 2b study of DLB patients (HEADWAY-DLB). A pharma-cokinetic study of intepirdine demonstrated that the 35 mg/day dose achieved near-complete occupancy of the 5-HT6 receptor but only ≈60% occupancy of the 5-HT2a receptor.[21] We therefore also stud-ied a dose of 70 mg/day to attain greater antagonism of the 5-HT2a

RESEARCH IN CONTEXT

1. **Systematic review:** We searched PubMed with terms "dementia with Lewy bodies" (DLB) AND "randomized controlled trial" (RCT). We identified several success-ful trials of acetylcholinesterase inhibitors and antipsy-chotics. Prior to HEADWAY-DLB, no RCTs had assessed a 5-HT6 receptor antagonist in DLB patients.

2. **Interpretation:** HEADWAY-DLB failed to demonstrate improvement with 35 or 70 mg/day intepirdine ver-sus placebo on the Unified Parkinson's Disease Rating Scale–Part III and all other endpoints over 24 weeks. Both intepirdine doses were generally well tolerated, although an increase in gastrointestinal adverse events was observed in the intepirdine arms.

3. **Future directions:** Intepirdine did not benefit DLB patients in this study, corroborating the previous neg-ative results of the 5-HT6 receptor antagonist class in dementia studies. Encouragingly, HEADWAY-DLB was completed within 2 years, enrolled the most patients ever for a DLB-specific study at the time, and did not show apparent rater variability across sites. This study demon-strates that large-scale trials in this patient population are feasible.

receptor and potentially achieve greater therapeutic benefit, particu-larly with respect to parkinsonian symptoms. The primary objective of HEADWAY-DLB was to assess the effect of intepirdine on motor func-tion in DLB patients. The secondary objectives were to assess intepir-dine's effects on cognition and global function.

2 | METHODS

2.1 | Trial design

HEADWAY-DLB was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study in patients with DLB. The efficacy and safety of intepirdine at doses of 70 and 35 mg adminis-tered daily as an oral tablet were evaluated over a 24-week treatment period. Sixty-one clinical sites were activated across seven countries (Canada, France, Netherlands, Italy, Spain, United Kingdom, United States). The trial protocol, statistical analysis plan, and a list of site investigators are provided in supporting information. The study was reviewed and approved by an independent ethics committee (IEC) or institutional review board (IRB) for each clinical site. An independent safety monitoring committee was established to review interim safety data (supporting information). The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The study's ClinicalTrials.gov number is NCT02669433.

2.2 | Patients

HEADWAY-DLB included patients who (1) were between 50 and 85 years of age, inclusive; (2) met the third DLB Consortium Consensus criteria for probable DLB[22] for ≥2 months; (3) had a Mini-Mental State Examination (MMSE) score of 14 to 26, inclusive, across screening and baseline visits (range 0 to 30, higher score indicates lower impairment)[23]; (4) had a regular caregiver who would guide and monitor the patient during the study; and (5) if applicable, was on a treatment regimen that had been stable during the 30 days prior to screening, with no intent to change during the study. Treatment with AChEIs, anti-parkinsonian medications, memantine, and atypical antipsychotics was allowed. Patients were excluded if they (1) showed clinical evidence of a non-DLB dementia diagnosis; (2) had a computed tomography (CT) or magnetic resonance imaging (MRI) scan within the past 12 months or at screening that was indicative of a non-DLB dementia diagnosis; (3) had a history of significant neurological or psychiatric illness other than DLB; or (4) exhibited unacceptable laboratory values. Before participation in the study, all patients and caregivers provided written informed consent or assent.

2.3 | Randomization and blinding

Patients were randomized in a 1:1:1 ratio to receive 35 mg/day intepirdine, 70 mg/day intepirdine, or placebo. Randomization was performed using a validated interactive voice/web response system. Randomization was stratified by patients' baseline MMSE scores (point groupings of 14–17, 18–21, and 22–26) and according to whether patients were or were not taking an AChEI. The randomization sequence was generated by an independent statistician. All site staff and patients were blinded to treatment group assignment. Intepirdine and placebo tablets were indistinguishable in appearance, smell, and taste.

2.4 | Procedures

The study consisted of a 4-week screening period, a 2-week single-blind placebo run-in period, and a 24-week randomized double-blind treatment period. During the run-in period, patients were administered blinded placebo to evaluate baseline variability. Patients then received 35 mg/day intepirdine, 70 mg/day intepirdine, or placebo during the double-blind treatment period. Patients who completed the last on-treatment visit of HEADWAY-DLB could enroll in a double-blind 24-week extension safety study (NCT02928445). Patients who did not enter the extension study had a follow-up safety visit at 26 weeks.

Scheduled visits were at weeks 1, 2, 4, 6, 8, 10, 12, 18, and 24 during the double-blind treatment period. All investigators and site staff obtained training and certification to administer efficacy assessments. The primary outcome measure Unified Parkinson's Disease Rating Scale–Part III (UPDRS-III)[24] was measured at baseline and at weeks 1, 4, and 24. The secondary outcome measure 11-item Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog)[25] was performed at baseline and at weeks 12 and 24. The secondary outcome measure Clinician Interview-Based Impression of Change plus caregiver interview (CIBIC+)[26] was performed at weeks 4, 8, 12, 18, and 24 and was rated relative to a Clinician Interview-Based Impression of Severity (CIBIS) assessment administered at baseline. The CIBIC+ and CIBIS were assessed by independent raters who did not administer other efficacy measures. Tertiary endpoints were assessed at baseline and week 24. Compliance was assessed by tracking pill count.

2.5 | Outcomes

The primary endpoint was the change from baseline to week 24 on the UPDRS-III total score (range 0–108, higher score indicates greater severity of motor features). The UPDRS-III is the gold standard for capturing pharmacological effects on parkinsonian motor features. The secondary endpoints were (1) ADAS-Cog score change from baseline to week 24 (range 0–70, higher score indicates more severe cognitive impairment) and (2) CIBIC+ score at week 24 (range 0–7, score above 4 indicates worse function relative to baseline). Tertiary endpoints included changes from baseline to week 24 on outcome measures such as UPDRS-5 (5-item subscale of UPDRS-III); ADAS-Cog-13 (ADAS-Cog plus delayed word recall and total digit cancellation score);[27] Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL);[28] Controlled Oral Word Association Test (COWAT);[29] Neuropsychiatric Inventory (NPI) Parts A (hallucinations), B (delusions), D (depression/dysphoria), and E (anxiety);[30] Cognitive Drug Research (CDR) computerized assessment system;[31] North-East Visual Hallucinations Interview (NEVHI);[32] Clinician Assessment of Fluctuation (CAF);[33] and Dependence Scale (DS).[34]

Safety endpoints included analyses of adverse events (AEs), physical examinations, vital signs, electrocardiograms, clinical analytes, a questionnaire assessing orthostasis, and the Columbia Suicide Severity Rating Scale. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

2.6 | Statistical analysis

Sample size estimates were based on treatment benefits that were deemed clinically relevant for the primary and secondary endpoints at a two-sided alpha level of 0.05. We calculated that a sample size of 240 patients would provide ≈90% power to detect differences of 4 points on UPDRS-III, 3 points on ADAS-Cog, and 0.5 points on CIBIC+.

The safety population was made up of all patients who received at least one dose of double-blind study medication. The population for analysis of all efficacy endpoints except the UPDRS-III and UPDRS-5 consisted of all randomized patients who took at least one treatment dose and had a baseline and at least one post-baseline efficacy assessment for the UPDRS-III or ADAS-Cog (modified intent-to-treat [mITT] population). The population for the UPDRS-III primary efficacy analysis was comprised of all mITT patients, excluding those with no change or a worsening in UPDRS-III total score prior to a dose increase in

anti-parkinsonian medications followed by a subsequent improvement or stabilization of UPDRS-III total score (UPDRS primary analysis population).

Primary treatment comparisons were performed on the change from baseline to week 24 using a mixed model for repeated measures (MMRM) with restricted maximum likelihood estimation, an unstructured covariance matrix, and the Kenward-Roger approximation for denominator degrees of freedom. Countries were pooled into three regions for analysis. The statistical model included terms for treatment group, visit, treatment by visit interaction, baseline value for the respective outcome, baseline MMSE score, baseline score by visit interaction, and pooled region. The interaction term of region by treatment was evaluated at the 10% level of significance. If the interaction term were found to be significant, it was included in the MMRM model. Primary inferences were drawn from treatment differences for the

changes from baseline derived from the MMRM models at week 24. No imputation of missing values was performed for the primary analyses.

All hypothesis tests and confidence intervals (CI) were two-sided at an alpha level of 0.05 with a pre-specified hierarchical testing plan. Adjusted means, 95% confidence intervals (CIs), and nominal *P*-values are reported for each analysis. All analyses were performed using SAS software, version 9.4. The statistical analysis plan was finalized prior to unblinding the treatment allocation codes.

3 | RESULTS

HEADWAY-DLB randomized patients between March 9, 2016, and June 15, 2017, completing enrollment in about 15 months. Four hundred eighty-four patients were screened, 306 patients entered the
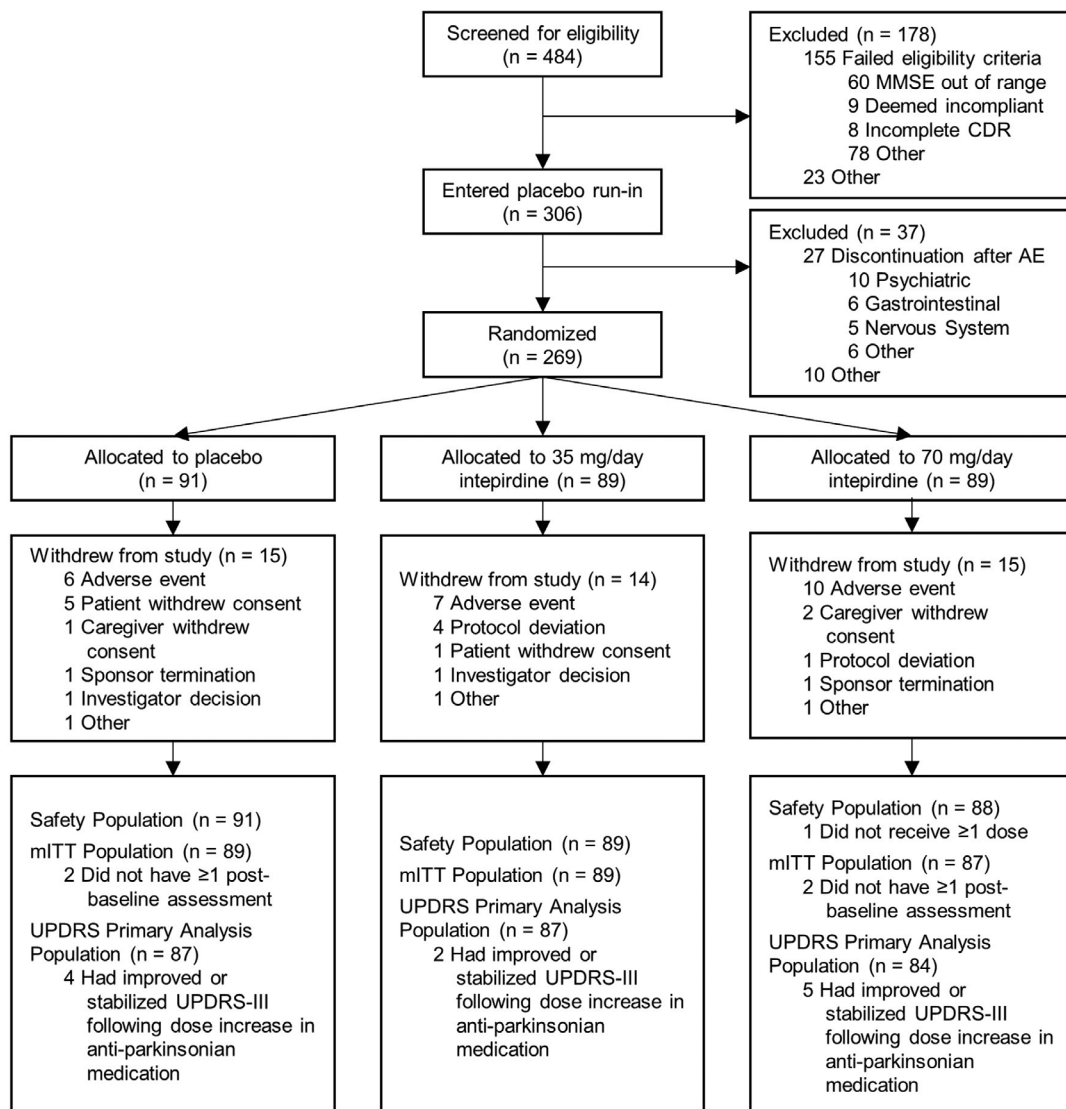

FIGURE 1 CONSORT flow diagram for HEADWAY-DLB. Two hundred sixty-nine patients were randomized across seven countries. Two hundred sixty-eight patients were included in the safety population, 265 patients in the mITT population, and 258 in the UPDRS primary analysis population. AE, adverse event; CDR, Cognitive Drug Research; mITT, modified intent to treat; MMSE, Mini-Mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale

TABLE 1 Demographics and baseline characteristics of the mITT population (n = 265)

	Placebo (n = 89)	Intepirdine 35 mg (n = 89)	Intepirdine 70 mg (n = 87)
Age (y), mean (SD)	73.7 (6.41)	73.0 (5.70)	73.1 (6.79)
Age (y) at diagnosis, mean (SD)	72.2 (6.81)	71.5 (6.08)	71.6 (6.80)
Time (y) since diagnosis, mean (SD)	1.89 (1.91)	1.86 (1.76)	1.93 (1.82)
Female sex, n (%)	20 (22.5)	22 (24.7)	15 (17.2)
White race, n (%)	88 (98.9)	81 (91.0)	84 (96.6)
Non-Hispanic ethnicity, n (%)	84 (94.4)	83 (93.3)	85 (97.7)
Region			
US, n (%)	50 (56.2)	42 (47.2)	51 (58.6)
UK and Canada, n (%)	12 (13.5)	12 (13.5)	9 (10.3)
All other Europe (non-English), n (%)	27 (30.3)	35 (39.3)	27 (31.0)
MMSE score			
Mean (SD)	20.9 (3.27)	21.2 (3.18)	21.1 (3.15)
Stratification	27 (30.3)	23 (25.8)	24 (27.6)
14–19, n (%)	62 (69.7)	66 (74.2)	63 (72.4)
20–26, n (%)			
Concomitant medications			
AChEIs, n (%)	77 (86.5)	75 (84.3)	74 (85.1)
Donepezil, n (%)	31 (34.8)	29 (32.6)	33 (37.9)
Rivastigmine, n (%)	45 (50.6)	43 (48.3)	38 (43.7)
Anti-parkinsonian medication, n (%)	42 (47.2)	40 (44.9)	38 (43.7)
Memantine, n (%)	16 (18.0)	15 (16.9)	16 (18.4)
Atypical antipsychotics, n (%)	1 (1.12)	3 (3.37)	1 (1.15)
Risperidone, n (%)	1 (1.12)	1 (1.12)	0 (0)
UPDRS-III, mean (SD)	25.8 (13.0)	27.7 (14.2)	27.2 (14.3)
UPDRS-5, mean (SD)	10.7 (6.77)	11.8 (7.03)	11.8 (7.12)
ADAS-Cog, mean (SD)	20.2 (8.71)	21.4 (8.64)	20.3 (8.03)
ADAS-Cog-13, mean (SD)	32.3 (9.99)	33.6 (10.1)	32.2 (9.52)
CIBIS, mean (SD)	3.8 (0.81)	3.9 (0.74)	3.8 (0.74)
ADCS-ADL, mean (SD)	53.8 (13.6)	53.4 (14.2)	55.7 (14.3)
COWAT, mean (SD)	22.8 (9.99)	19.6 (10.5)	22.7 (12.7)
NPI			
Parts A+B subscore, mean (SD)	2.60 (3.95)	2.77 (4.98)	2.95 (5.18)
Parts D+E subscore, mean (SD)	3.60 (4.66)	3.61 (4.91)	3.64 (4.51)
CDR, mean (SD)	0.68 (2.29)	-0.73 (2.57)	0.37 (2.20)
NEVHI			
Total severity score, mean (SD)	2.73 (8.44)	1.85 (6.05)	3.01 (8.81)
Total distress score, mean (SD)	2.47 (3.06)	3.01 (4.14)	2.75 (3.74)
Total presence score, mean (SD)	1.80 (1.58)	1.95 (1.86)	1.79 (1.54)
CAF			
Cognition severity score, mean (SD)	5.43 (3.90)	4.50 (3.14)	4.06 (3.38)
Confusion severity score, mean (SD)	5.62 (3.46)	4.97 (3.17)	5.10 (3.81)
DS, mean (SD)	5.64 (2.58)	6.11 (3.12)	5.85 (2.66)

Notes: The treatment groups were comparable with respect to the distributions of each parameter. Three regions were pre-specified for statistical analysis as follows: US = United States; UK and Canada = United Kingdom, Canada; All other Europe (non-English) = Spain, Italy, France, Netherlands.

Abbreviations: AChEIs, acetylcholinesterase inhibitors; ADAS-COG, Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADAS-COG-13, ADAS-Cog 13-Item Scale; ADCS-ADL, Alzheimer's Disease Cooperative Study–Activities of Daily Living; CAF, Clinician Assessment of Fluctuation; CDR, Cognitive Drug Research; CIBIS, Clinician Interview-Based Impression of Severity; COWAT, Controlled Word Association Test; DS, Dependence Scale; mITT, modified intent to treat; MMSE = Mini-Mental State Examination; NEVHI, North-East Visual Hallucinations Interview; NPI, Neuropsychiatric Inventory; UPDRS, Unified Parkinson's Disease Rating Scale; UPDRS-5, UPDRS – Part 5; UPDRS-III, UPDRS – Part III.

placebo run-in, 269 patients were randomized, and 268 received at least one double-blinded dose (safety population). Twenty-seven patients were screened twice. Seventy-six (84%) placebo-treated patients, 75 (84%) 35 mg/day-treated patients, and 74 (83%) 70-mg/day-treated patients completed the study through week 24. The most common reason for screen failure was an out-of-range MMSE score, and the most common reason for withdrawal during the double-blind period was AE. Two hundred sixty-five patients were included in the mITT population, and 258 patients were included in the UPDRS primary analysis population (Figure 1).

The demographics and baseline characteristics of the mITT population were generally similar across treatment groups (Table 1). All patients were on at least one concomitant medication: 85.3% of patients were taking an AChEI, 45.3% were taking at least one anti-parkinsonian medication, 17.7% were taking memantine, and 1.9% were taking atypical antipsychotics. The mean age of participants was 73.2 years, with an average of 1.89 years between DLB diagnosis and study screening; 10.6% of patients had a UPDRS-III ≤10, indicating little motor impairment. UPDRS-III scores were slightly lower in the placebo group (25.8) compared to the intepirdine groups (35 mg/day: 27.7; 70 mg/day: 27.2). The average baseline MMSE score was 21.1, with 72.1% of patients having a score between 20 and 26 (consistent with mild dementia) and 27.9% between 14 and 19 (consistent with moderate dementia). Most patients (87.3%) were considered compliant with study drug (i.e., took between 80% and 120% of the expected pill count).

Intepirdine failed to demonstrate significant differences from placebo on the UPDRS-III at week 24 in both the 35 mg/day group (adjusted mean difference = 2.01 vs. placebo, 95% CI [−0.79, 4.80], $P = .1580$) and 70 mg/day group (adjusted mean difference = −0.74 vs. placebo, 95% CI [−3.55, 2.08], $P = .6069$). All three groups demon-strated an initial trend toward improvement followed by a decline (Figure 2). Both intepirdine groups failed to demonstrate a statistical benefit over placebo on the secondary endpoint ADAS-Cog at week 24 (35 mg/day: adjusted mean difference = 0.47 vs. placebo, 95% CI [−1.60, 2.55=, $P = .6531$; 70 mg/day: adjusted mean difference = −0.67 vs. placebo, 95% CI [−2.75, 1.41], $P = .5274$), with an overall slow but stable decline in all three groups (Figure 3A). There were no statistical benefits in either intepirdine group over placebo on the secondary end-point CIBIC+ at week 24 (35 mg/day: adjusted mean difference = −0.15 vs. placebo, 95% CI [−0.50, 0.20], $P = .3953$; 70 mg/day: adjusted mean difference = −0.07 vs. placebo, 95% CI [−0.42, 0.28], $P = .7008$; Figure 3B). Finally, both intepirdine groups failed to demonstrate a statistical benefit over placebo on any of the tertiary endpoints at week 24, although there was a trend toward significance favoring the 70 mg/day group on the COWAT score and the NPI Parts A+B subscore (Table 2).

The incidence of treatment emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), and TEAEs leading to withdrawal were generally low and similar across treatment groups (Table 3). However, the intepirdine groups demonstrated a higher overall incidence of GI TEAEs versus the placebo group. There was a potential trend of increasing intepirdine dose associated with increasing incidence of study withdrawal due to TEAE, a finding which appeared to be driven by GI TEAEs. Back pain was also reported with higher incidence in the intepirdine groups (5–8%) compared to the placebo group (0%). The most common TEAEs across all groups were fall, urinary tract infection, constipation, orthostatic hypotension, and nasopharyngitis. No meaningful differences among treatment groups were observed across clinical laboratory parameters, vital signs, and electrocardiograms. No patients reported suicidal behavior, and the site investigators did not consider any death to be related to study treatment.
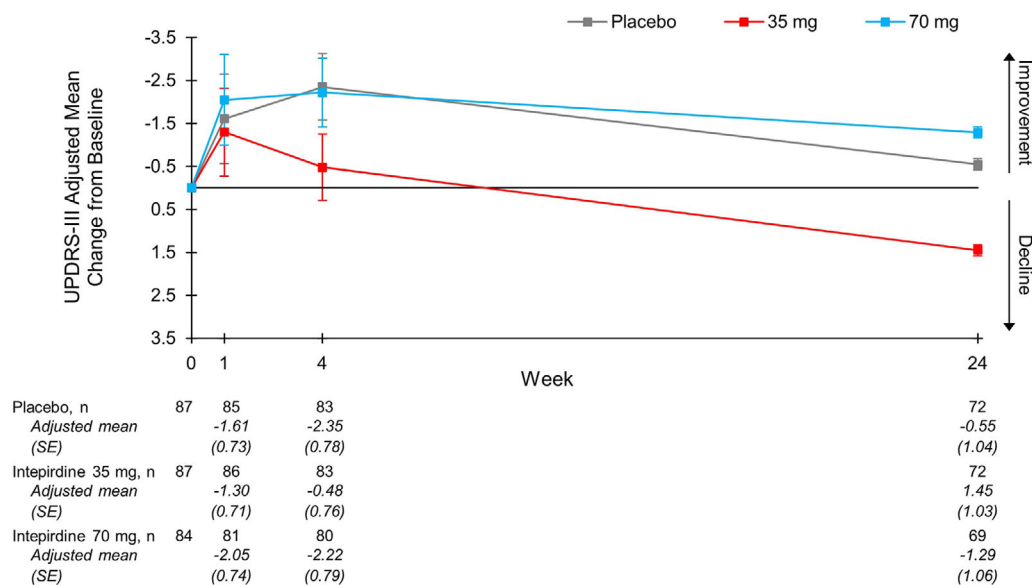

	Week			
	0	1	4	24
Placebo, n	87	85	83	72
Adjusted mean		*-1.61*	*-2.35*	*-0.55*
(SE)		*(0.73)*	*(0.78)*	*(1.04)*
Intepirdine 35 mg, n	87	86	83	72
Adjusted mean		*-1.30*	*-0.48*	*1.45*
(SE)		*(0.71)*	*(0.76)*	*(1.03)*
Intepirdine 70 mg, n	84	81	80	69
Adjusted mean		*-2.05*	*-2.22*	*-1.29*
(SE)		*(0.74)*	*(0.79)*	*(1.06)*

FIGURE 2 Adjusted mean changes from baseline on the primary endpoint, UPDRS-III, over the 24-week treatment period in the UPDRS primary analysis population ($n = 258$). Treatment comparisons were based on a mixed model for repeated measures. Error bars are 95% CI. CI, confidence interval; UPDRS-III, Unified Parkinson's Disease Rating Scale-Part III; SE, standard error
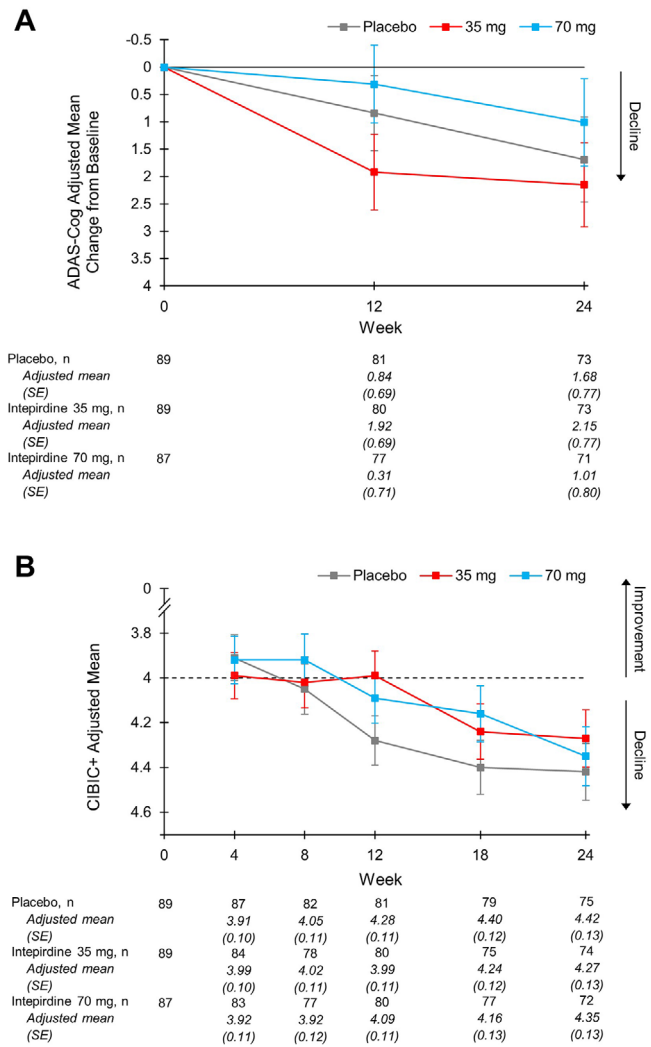
A

Placebo, n	89	81	73
Adjusted mean		*0.84*	*1.68*
(SE)		*(0.69)*	*(0.77)*
Intepirdine 35 mg, n	89	80	73
Adjusted mean		*1.92*	*2.15*
(SE)		*(0.69)*	*(0.77)*
Intepirdine 70 mg, n	87	77	71
Adjusted mean		*0.31*	*1.01*
(SE)		*(0.71)*	*(0.80)*

B

Placebo, n	89	87	82	81	79	75
Adjusted mean		*3.91*	*4.05*	*4.28*	*4.40*	*4.42*
(SE)		*(0.10)*	*(0.11)*	*(0.11)*	*(0.12)*	*(0.13)*
Intepirdine 35 mg, n	89	84	78	80	75	74
Adjusted mean		*3.99*	*4.02*	*3.99*	*4.24*	*4.27*
(SE)		*(0.10)*	*(0.11)*	*(0.11)*	*(0.12)*	*(0.13)*
Intepirdine 70 mg, n	87	83	77	80	77	72
Adjusted mean		*3.92*	*3.92*	*4.09*	*4.16*	*4.35*
(SE)		*(0.11)*	*(0.12)*	*(0.11)*	*(0.13)*	*(0.13)*

FIGURE 3 A, Adjusted mean changes from baseline on the secondary endpoint ADAS-Cog and (B) adjusted means on the secondary endpoint CIBIC+ over the 24-week treatment period in the mITT population (*n* = 265). Treatment comparisons were based on a mixed model for repeated measures. Error bars are 95% CI. ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; CI, confidence interval; CIBIC+, Clinician Interview-Based Impression of Change plus caregiver interview; mITT, modified intent to treat; SE, standard error

4 | DISCUSSION

HEADWAY-DLB did not meet its efficacy objectives. Both doses of intepirdine failed to demonstrate a statistically significant difference versus placebo on DLB motor function, as measured by UPDRS-III, over the 24-week treatment period. The intepirdine groups also failed to show improvement over placebo at 24 weeks on cognition, as measured by ADAS-Cog, and global function, as measured by CIBIC+. All other efficacy endpoints demonstrated a similar lack of meaningful treatment effects. There were no statistical signals of a dose-response. Given the results from previous randomized controlled trials in DLB as well as previous trials of intepirdine in AD dementia, the treatment

period duration of 24 weeks was likely sufficient to observe a treatment effect, had one existed.[7–10,18,20,35,36]

Consistent with previous studies, intepirdine demonstrated a favorable safety profile that was generally comparable to placebo. The incidence of most TEAEs was similar between placebo and intepirdine groups, and study completion rates were high across groups (83.6% overall). However, in contrast to previous studies, both intepirdine groups demonstrated a higher incidence of GI-related TEAEs relative to placebo. This finding could suggest that intepirdine increased peripheral neurotransmitter action, leading to an exacerbation of GI disturbances similar to AChEIs. Because GI dysfunction has been shown to be more severe in DLB patients compared to PD patients, DLB patients may be particularly susceptible to this adverse drug effect.[37] Nevertheless, this trend could also be a result of the small sample size within each treatment arm as prior studies of intepirdine, including the phase 3 MINDSET study assessing placebo versus a 35 mg/day dose across 1315 AD dementia patients, showed no evidence of increased GI events.[19] Overall, HEADWAY-DLB was the first large study to show that intepirdine administered at a dose of 70 mg/day over several months is generally well tolerated.

HEADWAY-DLB enrolled subjects in countries across North America and Europe. Although enrollment from individual sites was insufficient in sample size to allow for assessment of site-specific treatment outcomes, subgroup assessment of sites pooled by region were performed to elucidate differences across geographies. While there were minor differences among the regions with respect to some endpoints, no overarching trends were observed that reflected meaningful differences in treatment effects. This outcome suggests that study procedures were performed consistently across geographic regions, thereby helping to maintain low variability estimates.

HEADWAY-DLB was the first multi-continent and second industry-sponsored clinical trial in DLB patients, representing a landmark effort for the field.[5] At the time, the trial enrolled the most patients ever in a single DLB-specific clinical study. Completed within 2 years, HEADWAY-DLB demonstrates that large-scale international DLB trials are feasible within a reasonable timeframe. The study was designed and made possible through academic–industry collaboration, with important input and buy-in from regulatory agencies around the world as well as the European DLB Consortium (E-DLB).[38] Such global networks will be critical for successful development of novel therapeutics in the future.[1] Although it was negative, HEADWAY-DLB paves the way for future late-phase studies in this debilitating condition with no Food and Drug Administration or European Medicines Agency approvals and a growing patient population.

There were several limitations to the study. First, the study relied on diagnosis of probable DLB using the 2005 Consensus criteria that has since been updated in 2017, now including a more lenient definition of parkinsonism.[1,22] Given the overlapping symptomology between DLB and other forms of dementia, DLB diagnosis remains challenging. Second, outcome measure selection is difficult in DLB because of the clinical heterogeneity across patients and the lack of standardized guidelines around randomized controlled trials. Indeed, HEADWAY-DLB was originally designed to use CIBIC+ and CDR as co-primary out-

TABLE 2 Adverse events reported over the 24-week treatment period in the safety population (n = 268)

	Placebo (n = 91)	Intepirdine 35 mg (n = 89)	Intepirdine 70 mg (n = 88)
TEAE, n (%)	74 (81.3)	77 (86.5)	68 (77.3)
Fall	19 (20.9)	17 (19.1)	18 (20.5)
Urinary tract infection	8 (8.8)	7 (7.9)	9 (10.2)
Constipation	5 (5.5)	9 (10.1)	6 (6.8)
Orthostatic hypotension	12 (13.2)	3 (3.4)	5 (5.7)
Nasopharyngitis	7 (7.7)	8 (9.0)	1 (1.1)
Diarrhea	3 (3.3)	7 (7.9)	5 (5.7)
Hallucination, visual	4 (4.4)	6 (6.7)	4 (4.5)
Confused state	3 (3.3)	5 (5.6)	5 (5.7)
Dizziness	4 (4.4)	3 (3.4)	5 (5.7)
Back pain	0 (0)	7 (7.9)	5 (5.7)
Nausea	2 (2.2)	4 (4.5)	5 (5.7)
Upper respiratory tract infection	6 (6.6)	3 (3.4)	2 (2.3)
Anxiety	3 (3.3)	5 (5.6)	2 (2.3)
Hypertension	5 (5.5)	1 (1.1)	2 (2.3)
TEAE by MedDRA SOC, n (%)	74 (81.3)	77 (86.5)	68 (77.3)
Infections and infestations	32 (35.2)	26 (29.2)	21 (23.9)
Psychiatric disorders	26 (28.6)	27 (30.3)	22 (25.0)
Gastrointestinal disorders	12 (13.2)	33 (37.1)	24 (27.3)
Injury, poisoning, and procedural complications	25 (27.5)	19 (21.3)	22 (25.0)
Nervous system disorders	21 (23.1)	16 (18.0)	16 (18.2)
Musculoskeletal and connective tissue disorders	10 (11.0)	14 (15.7)	13 (14.8)
Vascular disorders	18 (19.8)	6 (6.7)	13 (14.8)
Investigations	11 (12.1)	9 (10.1)	10 (11.4)
Skin and subcutaneous tissue disorders	13 (14.3)	10 (11.2)	6 (6.8)
General and administration site disorders	13 (14.3)	7 (7.9)	8 (9.1)
Renal and urinary disorders	12 (13.2)	10 (11.2)	4 (4.5)
Respiratory, thoracic, and mediastinal disorders	6 (6.6)	10 (11.2)	5 (5.7)
Cardiac disorders	5 (5.5)	7 (7.9)	5 (5.7)
Metabolism and nutrition disorders	7 (7.7)	5 (5.6)	5 (5.7)
TEAE leading to study withdrawal, n (%)	6 (6.6)	7 (7.9)	11 (12.5)
GI SOC-associated TEAE leading to study withdrawal, n (%)	0 (0)	2 (2.2)	4 (4.5)
Treatment emergent SAE, n (%)	8 (8.8)	14 (15.7)	9 (10.2)
Death, n (%)	1 (1.1)	1 (1.1)	2 (2.3)

Notes: All TEAEs that occurred in at least 5% of patients in any treatment group are shown. All TEAEs by SOC that occurred in at least 5% of patients in any treatment group are shown. No death was considered related to study treatment by the site investigator.

Abbreviations: GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event.

come measures, but the UPDRS-III was ultimately chosen to be the sole primary assessment in a protocol amendment on November 15, 2017 prior to unblinding. This decision was motivated by multiple factors, including intepirdine's potential for benefit on parkinsonian features, regulatory communications, and the failure of the phase 3 MINDSET study in AD dementia.[19] Although we chose UPDRS-III as the primary outcome measure, parkinsonism is a less defining feature of DLB, and cognitive measures may have been more suitable in the context of intepirdine's cholinergic mechanism of action: 10.6% of patients in the study had little motor impairment (UPDRS-III ≤10), potentially

TABLE 3 Change from baseline to week 24 on the tertiary endpoints in the mITT population ($n = 265$)

	Placebo ($n = 89$)	Intepirdine 35 mg ($n = 89$)		Intepirdine 70 mg ($n = 87$)	
	Change from baseline to week 24	Change from baseline to week 24	P-value vs. placebo	Change from baseline to week 24	P-value vs. placebo
UPDRS-5*, LS-mean (SE)	−0.84 (0.51)	−0.24 (0.51)	.39	−1.78 (0.52)	.19
ADAS-Cog-13, LS-mean (SE)	1.91 (0.87)	2.61 (0.86)	.56	1.14 (0.89)	.51
ADCS-ADL, LS-mean (SE)	−1.86 (1.03)	−2.38 (1.04)	.71	−2.22 (1.07)	.80
COWAT, LS-mean (SE)	−0.48 (0.75)	−0.67 (0.75)	.86	1.52 (0.77)	.05
NPI					
Parts A+B subscore, LS-mean (SE)	0.60 (0.48)	0.07 (0.48)	.44	−0.71 (0.53)	.07
Parts D+E subscore, LS-mean (SE)	−0.39 (0.41)	-0.22 (0.41)	.77	0.20 (0.43)	.29
CDR, LS-mean (SE)	0.06 (0.36)	−0.31 (0.37)	.45	0.42 (0.37)	.47
NEVHI					
Total severity score, LS-mean (SE)	−0.30 (0.84)	0.32 (0.83)	.60	−0.02 (0.93)	.83
Total distress score, LS-mean (SE)	−0.18 (0.33)	−0.85 (0.33)	.14	−0.18 (0.35)	.99
Total presence score, LS-mean (SE)	−0.39 (0.14)	−0.58 (0.13)	.31	−0.19 (0.14)	.28
CAF					
Cognition severity score, LS-mean (SE)	1.07 (0.54)	0.44 (0.53)	.40	0.76 (0.58)	.69
Confusion severity score, LS-mean (SE)	1.05 (0.64)	0.48 (0.60)	.50	−0.01 (0.62)	.22
DS, LS-mean (SE)	0.49 (0.23)	0.47 (0.22)	.95	0.24 (0.24)	.40

Notes: There were no statistically significant differences in either intepirdine dose over placebo for any of the tertiary endpoints at week 24. There was a positive trend toward significance versus placebo on the COWAT and NPI Parts A and B favoring the 70 mg/day dose group. *Treatment differences were based on the UPDRS primary analysis population ($n = 258$). Treatment comparisons were based on a mixed model for repeated measures.
Abbreviations: ADAS-COG = Alzheimer's Disease Assessment Scale–Cognitive Subscale. ADAS-COG-13, ADAS-Cog 13-Item Scale; ADCS-ADL, Alzheimer's Disease Cooperative Study–Activities of Daily Living; CAF, Clinician Assessment of Fluctuation; CDR, Cognitive Drug Research; COWAT, Controlled Word Association Test; DS, Dependence Scale; LS, least squares; NEVHI, North-East Visual Hallucinations Interview; NPI, Neuropsychiatric Inventory; SE, standard error; UPDRS = Unified Parkinson's Disease Rating Scale. UPDRS-5 = UPDRS – Part 5.

making detection of a treatment effect more challenging. The development of patient subtypes based on clinical or biomarker criteria may help guide outcome measure selection in future trials.[1] Third, a significant percentage of patients in the study were taking AChEIs and/or anti-parkinsonian agents as concomitant medications. Although treatment with these medications was required to be stable prior to study entry, these medications are known to provide motor, cognitive, and/or functional benefits,[5] and intepirdine may have had differential effects in the presence or non-presence of concomitant medications. It has been hypothesized that, relative to monotherapy, adjunctive use of 5-HT6 receptor antagonists with AChEIs may be required to achieve a therapeutic benefit in dementia patients.[18,39] Fourth, the relatively large geographical scope of the study may have made a treatment effect more difficult to detect due to added heterogeneity across patients and standards of care, as has been observed in global trials for AD dementia.[40,41]

Ultimately, 35 and 70 mg/day intepirdine failed to demonstrate a statistically significant difference versus placebo on all endpoints, including those measuring motor impairment, cognitive impairment, and global function. HEADWAY-DLB was the first large clinical study to assess an intepirdine dose of 70 mg/day, which was generally well-tolerated. It is unlikely that intepirdine is an effective therapy for DLB patients, particularly in the context of the negative results from previous phase 2 and 3 studies in AD dementia.[11] Despite the early promise of 5-HT6 receptor antagonists, this class of agents has now been disappointing across multiple dementia studies.[11] Nevertheless, as the world population ages and the cases of DLB increase in the coming years, HEADWAY-DLB demonstrates that large-scale international trials for DLB are possible. Further research into DLB subtypes, related biomarkers, and clinical trial standardization will be needed to inform the development of novel therapeutics for this condition in the future.

DATA SHARING STATEMENT

The sponsor will not share data from the study.

CONFLICTS OF INTEREST

AUTHOR CONTRIBUTIONS

FML and DYK led the effort to assemble the manuscript, incorporating input from authors, supporting data interpretation, and reviewing the literature. MDH contributed to the statistical analysis plan and interpretation of the statistical analysis. YM supported data collection, cleaning, analysis, and interpretation. DA, BB, BT, and MS were advisors to Axovant and investigators during the study. All authors provided critical feedback and helped shape the research, analysis, and writing of the manuscript, in accordance with the criteria established by the International Committee of Medical Journal Editors (ICMJE) and Good Publication Practice Guidelines.

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