

Long-term safety and tolerability of atabecestat (JNJ-54861911), an oral BACE1 inhibitor, in early Alzheimer's disease spectrum patients: A randomized, double-blind, placebo-controlled study and a two-period extension study

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Abstract

Background Atabecestat, a potent brain-penetrable inhibitor of BACE1 activity that reduces CSF amyloid beta ($A\beta$), was developed for oral treatment for Alzheimer's disease (AD). The long-term safety and effect of atabecestat on cognitive performance in participants with predementia AD in two phase 2 studies were assessed. **Methods** In the placebo-controlled double-blind parent ALZ2002 study, participants aged 50 to 85 years were randomized (1:1:1) to placebo or atabecestat 10 or 50 mg once-daily (later reduced to 5 and 25 mg) for six months. Participants entered ALZ2004, a 12-month-treatment extension with placebo or atabecestat 10 or 25 mg, followed by an open-label phase. Safety, changes in CSF biomarker levels, brain volume, and effects on cognitive performance were assessed. **Results** Of 114 participants randomized in ALZ2002, 99 (87%) completed, 90 entered the ALZ2004 double-blind phase, and 77 progressed to open-label phase. CSF $A\beta$ fragments and sAPP β were reduced dose-proportionately. Decreases in whole brain and hippocampal volumes were greater in participants with mild cognitive impairment (MCI) due to AD, but without apparent relation to treatment. In ALZ2004, change from baseline in RBANS suggested a trend toward worse scores for atabecestat versus placebo. Elevated liver enzyme adverse events reported in 12 participants on atabecestat resulted in dosage modification and increased frequency of safety monitoring. Treatment discontinuation normalized ALT or AST in all except one with pretreatment elevation, which remained mildly elevated. No case met ALT/AST >3X ULN; total bilirubin >2X ULN (Hy's law). **Conclusion** Atabecestat was associated with trend toward declines in cognition, and elevation of liver enzymes.

Background

Cleavage of the amyloid precursor protein (APP) by β -secretase1 (BACE1) is the first and rate limiting step in the production of amyloid beta ($A\beta$), the main constituent of amyloid plaques, a hallmark pathological feature of Alzheimer's disease (AD). Subsequent cleavage by γ -secretase results in the production of $A\beta_{1-42}$, which has a high tendency to aggregate, as well as other $A\beta$ fragments of shorter length, of which $A\beta_{1-40}$ is the most prevalent. These $A\beta$ forms can also aggregate to form oligomers and fibrils [1, 2]. Thus, inhibitors of BACE1 prevent the formation of $A\beta_{1-42}$ as well as $A\beta_{1-40}$, $A\beta_{1-38}$, and $A\beta_{1-37}$ and are potentially disease-modifying therapeutic agents in the treatment of AD.

Supporting this mechanism is the observed correlation between the catalytic efficiency of BACE1 for its substrate APP and the occurrence of AD. The Swedish APP mutant (KM670/671NL), a more efficient substrate for BACE1 (10x), causes a rare familial form of AD that is inherited in the dominant Mendelian fashion. On the other end of the spectrum is an allelic variant of APP (A673T), a less efficient substrate for BACE1 (0.5x), which is protective against sporadic AD [3].

Atabecestat (formerly JNJ-54861911) is a potent brain-penetrable BACE1 inhibitor developed by Janssen Research & Development in collaboration with Shionogi as an oral treatment of AD, with reduction of CSF $A\beta$ as its primary mode of action [4]. In Phase 1 studies in elderly Caucasian and Japanese participants with preclinical AD and mild cognitive impairment (MCI) due to AD, treatment with atabecestat at 10 mg and 50 mg for 4 weeks significantly reduced from baseline CSF levels of $A\beta_{1-40}$ by 67% and 90%, respectively, as compared to placebo and was well tolerated [5]. Similar reductions were observed in all other $A\beta$ fragments. The observed steady state CSF $A\beta_{1-40}$ reductions from baseline were within the 95% confidence interval predicted by pharmacokinetic/pharmacodynamic modeling from a multiple ascending dose Phase 1 study in healthy population (5 to 50 mg once daily for 14 days).

We report two Phase 2 studies (ALZ2002 and ALZ2004) whose primary objectives were to assess the long-term safety and tolerability of atabecestat in patients with early AD (predementia AD; encompasses preclinical AD to mild cognitive impairment [MCI]). The parent study, ALZ2002, was a randomized double-blind, placebo-controlled study designed to investigate the safety profile of atabecestat during 6 months of treatment. This was followed by the longer term ALZ2004 extension study that consisted of 2 sequential treatment phases; a 12-month double-blind placebo-controlled treatment phase of atabecestat, followed by an open-label (OL) active treatment phase.

In the ALZ2004 extension study, the effects of atabecestat relative to placebo over time on cognition, performance of everyday functions, and brain volume as assessed by MRI, were evaluated as secondary endpoints. In both studies, secondary and exploratory endpoints included effect of treatment on the change in CSF levels of downstream biomarkers, including A β fragments (A β ₁₋₃₇, A β ₁₋₃₈, A β ₁₋₄₀, A β ₁₋₄₂), soluble APP (sAPP) fragments (sAPP α , sAPP β , and total sAPP), total tau (t-tau), and phosphorylated tau (p-tau₁₈₁).

Methods

Study Population and Selection Criteria

The ALZ2002 parent study (NCT02260674) and the ALZ2004 extension study (NCT02406027) were multi-center, double-blind, placebo-controlled, randomized, multiple dose safety and tolerability studies in patients in the early (predementia) AD spectrum conducted in sites in Belgium, France, Germany, Netherlands, Sweden, and Spain from February 2016 to June 2018.

The parent ALZ2002 study population consisted of men and women who entered the study either directly as new patients or after completing 4 weeks of double-blind treatment in study ALZ1005, a Phase 1 placebo controlled study in participants meeting the same inclusion criteria [5]. The ALZ2002 patient population included asymptomatic individuals diagnosed as preclinical AD (aged 65 to 85 years) who were cognitively and functionally unimpaired with a clinical dementia rating (CDR) global scale score of 0, and those diagnosed with MCI due to AD (aged 50 to 85 years) who had mild cognitive impairment but were functionally unimpaired with CDR global score of 0.5. Those with CDR global scores higher than 0.5 were excluded. Participants were considered otherwise healthy for their age with a body mass index (BMI) between 18 and 35 kg/m².

Participants were excluded if they had any of the following: a diagnosis of dementia, or another degenerative brain disorder that can cause dementia; evidence of familial autosomal dominant AD, or any brain disease other than potential very early signs of AD; any other abnormality that could explain cognitive deficit such as vitamin B12 or folic acid deficiency, vascular encephalopathy, or strokes including lacunae; any finding on magnetic resonance imaging (MRI) of brain disease, other than mild hippocampal atrophy or typical age-related mild white matter hyperintensity; a Rosen modified Hachinski ischemic scale score of > 4; any contraindications for MRI; chromosome 21 trisomy (Down Syndrome); major depression, as defined by most current Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria; or liver or renal insufficiency, or other clinically significant medical disorders. Treatment of stable medical conditions including use of cognitive enhancers (e.g. cholinesterase inhibitors or memantine) was allowed, if started \geq 30 days prior to first study dose.

All participants had evidence of amyloid pathology at screening based on low CSF A β ₁₋₄₂ level having a concentration below laboratory specific cut-off value of 600 ng/L, analyzed in one central laboratory using INNOTEST[™] β -AMYLOID₁₋₄₂ assay [Fujirebio, Ghent, Belgium] [6, 7] or by a positive amyloid positron emission tomography (PET) scan at screening based on visual inspection of PET imaging scan performed at a core imaging laboratory .

Study Design

The ALZ2002 parent study included a 90-day screening period, followed by 6 months of double-blind treatment randomized 1:1:1 to placebo or atabecestat 10 mg or 50 mg once-daily (given as 2 identical tablets of placebo, 5 mg, or 25 mg). Individuals that had completed the ALZ1005 study continued the same blinded treatment to which they had originally been randomized. After completion of Month 6 of the ALZ2002 study, participants had the option to enroll in the ALZ2004 extension study; otherwise, they returned for a follow-up visit 7 to 28 days after last dose. Those who had progressed to dementia (CDR global score \geq 1) in ALZ2002 were not eligible for enrollment in the ALZ2004; in case of progression to a dementia state during the course of ALZ2004, a renewed consent to remain in the study was obtained from the participant or a representative, provided they chose to continue and the investigator judged potential benefits of treatment outweighed foreseeable risks for that participant.

ALZ2004 consisted of 2 sequential treatment periods. In the initial 12-month double-blind phase, participants who were originally assigned to 50 mg atabecestat once-daily in ALZ2002 were reduced to 25 mg, while those receiving 10 mg atabecestat or placebo continued their previously assigned treatment. This was followed by an open-label phase, where participants on 25 mg continued to receive that dosage, those on atabecestat 10 mg were decreased to 5 mg, and those on placebo were randomized with equal probability to 5 mg or 25 mg. The rationale for the 5 mg dosage was to identify a dose that may not require monitoring of hepatic enzymes, while still providing adequate target CSF $A\beta_{1-40}$ reduction of 52% (95% CI:27–72%) [4]. The sequence of dosing in all phases of ALZ2002 and ALZ2004 is summarized graphically in Fig. 1.

Approximately 3 months after completion of enrollment in study ALZ2002, the design of the study was substantially amended due to observations of elevated liver enzymes in some patients. Participants who had not yet completed ALZ2002 had a reduction in dosage of blinded study drug from 2 to 1 tablet per day (thus, from 50 mg, 10 mg, or placebo to 25 mg, 5 mg, or placebo, respectively). More frequent monitoring of serum chemistry and rules for stopping treatment were implemented for: alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 8x upper limit of normal (ULN); ALT or AST > 5x ULN for more than 2 weeks; ALT or AST > 3x ULN and total bilirubin > 2xULN or international normalized ratio > 1.5; or ALT or AST > 3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%) [8]. Because of the continued high frequency of elevated liver enzymes observed in this study as well as in a separate parallel running Phase 2b/3 trial of atabecestat in preclinical AD (the EARLY study, ALZ2003, NCT02569398), the sponsor judged that the risks did not merit continued treatment and dosing in all atabecestat trials was terminated in May 2018.

Assessments

Cognition

Cognitive assessments performed prior to initiation of treatment in ALZ2002 included the CDR-Sum of Boxes (CDR-SB), from which a global score was calculated to establish eligibility, the Mini Mental State Examination (MMSE), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (performed twice, with the second session serving as the baseline measurement), and the California Verbal Learning Test – Second Edition [CVLT-II] performed prior to dosing on Day 1 (see Supplementary material for descriptions). The CDR-SB, MMSE, and RBANS were repeated at the 6-month visit in ALZ2002. Those participants entering ALZ2004 then had the CDR-SB and MMSE repeated at week 52 in the double-blind treatment period, and thereafter every 48 weeks in the open-label period. The RBANS was repeated at weeks 24 and 52 in the double-blind period, and thereafter every 24 weeks in the open-label period. The CVLT was repeated only at week 12 in the double-blind period. A patient-reported outcome, the Cognitive Function Index (CFI), was first administered on Day 1 of ALZ2004, and was repeated at weeks 24 and 52 in the double-blind period and thereafter every 24 weeks in the open-label period.

Biomarkers

The pharmacodynamic effects of atabecestat on BACE1 activity were evaluated through effects relative to baseline on CSF concentrations of $A\beta$ fragments ($A\beta_{1-37}$, $A\beta_{1-38}$, $A\beta_{1-40}$, and $A\beta_{1-42}$), with $A\beta_{1-40}$ being the most abundant and primary determinant of atabecestat activity. A qualified Janssen multiplex immunoassay based on Meso Scale Discovery (MSD) (Gailithersburg, MD, USA) electrochemiluminescence (ECL) detection technology was utilized for simultaneous detection of all 4 $A\beta$ fragments in CSF and plasma [9, 10]. In addition, exploratory measurements of CSF levels of sAPP fragments (sAPP α , sAPP β) and other CSF biomarkers (i.e., CSF p-tau and t-tau) were performed by a central laboratory as previously described by Timmers et. al [4]. Potential atabecestat treatment effects on brain volume were assessed with MRI at baseline and Month 6 in ALZ2002 and at double-blind period weeks 24 and 52 and thereafter every 48 weeks in ALZ2004, using the boundary shift integral method [11].

Pharmacokinetics

The plasma PK data were described by a two-compartment model, with distribution of drug between central (i.e. plasma) compartment and a peripheral compartment, and with linear elimination from the central compartment. Absorption was described as a linear process characterized by sequential zero- and first-order absorption from the depot compartment into the central compartment. This linear model adequately described the data and confirmed the dose-proportional PK of atabecestat in the dose range between 5 and 50 mg [4, 5]. Individual estimates of AUC_{0-24h} by dose are summarized in Supplementary Table S1. Participants who underwent dose reduction were included in the summary statistics with both their starting and final doses. Overall the exposure parameters were in line with previous studies at corresponding doses [4, 5].

Safety Assessments

All participants who received study treatment were included in the safety analysis population. Safety and tolerability were assessed by recording adverse events (AEs) and clinically significant abnormalities on clinical laboratory tests (hematology, biochemistry, including liver function tests), 12-lead electrocardiogram, vital signs, and abnormalities on physical or neurological exams, and potential dermatologic and ophthalmologic abnormalities (e.g. melanin deposition changes and retinal abnormalities). In order to monitor for potential changes in melanin deposition and retinal abnormalities [12], all included participants had a baseline ophthalmological examination, optical coherence tomography, and examination of the skin by a dermatologist. These examinations were repeated in case of abnormality at baseline or new visual signs or symptoms.

MRI was used to monitor for amyloid-related imaging abnormalities (ARIA) with edema or effusion (ARIA-E) or with hemosiderin (ARIA-H), as previously reported with several anti-amyloid monoclonal antibodies [13]. AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or later. Possible effects on anxiety or mood were assessed by the Geriatric Depression Scale, the State-Trait Anxiety Inventory and the Columbia Suicide Severity Rating Scale (C-SSRS), performed at screening and on scheduled visits thereafter.

Statistical Analysis

No formal hypothesis testing was planned and sample sizes for the studies were not based on formal statistical testing. However, using assumptions that an AE occurred at the rates of 1%, 5% or 10% in a single treatment group, then the chances of observing such an AE among 30 participants receiving that treatment was estimated to be 26%, 79% or 96%, respectively. Thus, planned enrollment of 100 participants (approximately 33 per group) was considered sufficient for clinical judgment of safety and tolerability of atabecestat.

Percent change from baseline in CSF concentration of each of the A β fragments (A β_{1-37} , A β_{1-38} , A β_{1-40} and A β_{1-42}), of sAPP α , and sAPP β , and of p-tau and t-tau was summarized by box and whisker plots separately by treatment group and by baseline CDR status (i.e. preclinical AD, MCI due to AD) for Month 6 in ALZ2002 and Week 52 in the double-blind period of ALZ2004.

Change in cognition at Week 52 of the double-blind period in ALZ2004 relative to baseline in ALZ2002 was analyzed with an ANCOVA model which included treatment group, actual baseline CDR status, and baseline score as a covariate. For non-biomarker assessments, baseline for the ALZ2004 double-blind period safety analysis set was the value taken prior to first study drug dose in the ALZ2002. For the open-label period in ALZ2004, baseline was the last value taken before first dose in that period.

Results

Demographics, Baseline Characteristics and Disposition

A total of 114 participants were enrolled in the ALZ2002 parent study, including 27 who entered from ALZ1005 (placebo, n = 11; atabecestat 10 mg, n = 8; and atabecestat 50 mg, n = 8). Ninety participants were classified with MCI due to AD and 24 with preclinical AD. Participant demographics, apolipoprotein E ϵ 4 (APOE ϵ 4) carrier status, and global CDR score are summarized in Table 1 by treatment group at start of the study. These baseline characteristics were generally well balanced across treatment groups. Nearly all participants were Caucasians. APOE genotype was available for 69% of individuals: majorities were carriers of the ϵ 4 allele. Baseline/day 1 predose scores for clinical scales and cognitive assessments by treatment groups at start and by CDR diagnostic group are shown in Table 2. In general, scores were comparable across treatment groups; however, patients classified with MCI due to AD showed more pronounced impairment on the MMSE, CDR-SB, RBANS, and CVLT-II, compared to those with preclinical AD.

Table 1
Baseline demographics characteristics of patients enrolled in the ALZ2002
(Safety set)

Baseline Characteristics	Treatment Group at Start ALZ2002			
	Placebo	10 mg	50 mg	Total
N	39	37	38	114
Sex, Men, n (%)	16 (41.0)	18 (48.6)	20 (52.6)	54 (47.4)
Age, years, Mean (SD)	70.3 (5.38)	70.9 (6.58)	68.1 (8.55)	69.8 (6.99)
Range	(59; 80)	(52; 81)	(50; 82)	(50; 82)
Race, White, n (%)	37 (94.9)	36 (97.3%)	38 (100.0)	111 (97.4)
Other, n (%)	2 (5.1)	1 (2.7)	0 (0.0)	3 (2.6)
APOE ϵ 4 Carrier Status known, n	27	30	22	79
Yes, n (%)	17 (63.0)	18 (60.0)	10 (45.5)	45 (57.0)
No, n (%)	10 (37.0)	12 (40.0)	11 (50.0)	33 (41.8)
Preclinical AD, CDR=0, n (%)	7 (17.9)	8 (21.6)	9 (23.7)	24 (21.1)
MCI due to AD, CDR=0.5, n (%)	32 (82.1)	29 (78.4)	29 (76.3)	90 (78.9)

Table 2

Baseline clinical and cognitive characteristics of patients in parent study ALZ2002 by treatment group at start and by their Clinical Dementia Rating classification (Safety analysis set)

Baseline Characteristics	Treatment Group at Start		
	Placebo (N = 39)	Atabecestat	
Clinical and Cognitive Scales		10 mg (N = 37)	50 mg (N = 38)
CDR-SB†, N	39	37	38
All Mean (SD)	1.5 (1.25)	1.6 (1.24)	1.6 (1.09)
Preclinical AD, N	7	8	9
Mean (SD)	0.1 (0.19)	0.4 (0.73)	0.8 (0.97)
MCI due to AD, N	32	29	29
Mean (SD)	1.8 (1.16)	1.9 (1.16)	1.8 (1.04)
CVLT-II, All Recall Types ‡, N	36	36	37
All Mean (SD)	31.1 (39.54)	35.9 (25.47)	28.8 (27.03)
Preclinical AD, N	7	8	9
Mean (SD)	7.3 (11.95)	34.5 (23.34)	18.7 (26.41)
MCI due to AD, N	29	28	28
Mean (SD)	36.9 (41.79)	36.3 (26.44)	32.0 (26.88)
MMSE Subscale Scores‡, N	39	37	38
All Mean (SD)	26.3 (2.90)	24.9 (4.14)	26.2 (2.47)
Preclinical AD, N	7	8	9
Mean (SD)	29.0 (1.15)	27.8 (2.55)	27.8 (2.64)
MCI due to AD, N	32	29	29
Mean (SD)	25.8 (2.84)	24.1 (4.18)	25.7 (2.24)

Notes:

† The Clinical Dementia Rating-Sum of Boxes with scores ranging from 0 to 18 with higher scores indicating more pronounced impairment;

‡ The California Verbal Learning Test-Second Edition, sub-scores included: immediate recall, long-delay recall, short delay recall, and long-delay recognition. The higher the score the more pronounced the impairment;

‡ The Mini Mental State Examination is a questionnaire that rates participants on orientation (total score, 10), registration (total score, 3), attention, calculation (total score, 5), recall (total score, 3), and language (total score, 9). The maximum score is 30. The lower the score the more pronounced the impairment;

¶ The Repeatable Battery for the Assessment of Neuropsychological Status, subsets included: attention index, language index, visuospatial/constructional index, immediate memory index, and delayed memory index. The lower the score the more pronounced the impairment.

Baseline Characteristics	Treatment Group at Start		
RBANS – Total Scale Score¶, N	39	37	38
All, Mean (SD)	80.2 (17.10)	72.4 (21.99)	80.1 (17.44)
Preclinical AD, N	7	8	9
Mean (SD)	99.7 (14.68)	91.4 (23.89)	92.9 (17.49)
MCI due to AD, N	32	29	29
Mean (SD)	75.9 (14.55)	67.2 (18.66)	76.2 (15.68)
Notes:			
† The Clinical Dementia Rating-Sum of Boxes with scores ranging from 0 to 18 with higher scores indicating more pronounced impairment;			
‡ The California Verbal Learning Test-Second Edition, sub-scores included: immediate recall, long-delay recall, short delay recall, and long-delay recognition. The higher the score the more pronounced the impairment;			
§ The Mini Mental State Examination is a questionnaire that rates participants on orientation (total score, 10), registration (total score, 3), attention, calculation (total score, 5), recall (total score, 3), and language (total score, 9). The maximum score is 30. The lower the score the more pronounced the impairment;			
¶ The Repeatable Battery for the Assessment of Neuropsychological Status, subsets included: attention index, language index, visuospatial/constructional index, immediate memory index, and delayed memory index. The lower the score the more pronounced the impairment.			

By the time dosage of blinded study drug was reduced due to elevated hepatic enzymes, all participants had been enrolled in ALZ2002 and had completed at least 3 months of treatment. The resulting treatment exposures over 6 months (mean daily dose) were relatively similar between those that underwent dosage reduction and those that completed Month 6 on the originally assigned dosage (9 mg vs 10 mg for 5 mg [dose-reduced] and 10 mg [completed on original dose], and 40 mg vs 50 mg for 25 mg [dose-reduced] and 50 mg [completed on original dose], respectively). Participant disposition and study completion for ALZ2002 study are shown in Fig. 2. Of the 114 participants enrolled 99 (87%) completed 6 months of double-blind treatment in ALZ2002. The most common reason for discontinuation of the study drug was an AE in 9 (7.9%) participants.

In ALZ2004, 90 participants enrolled into the double-blind period of the study; 77 (85.6%) of these completed the double-blind period and progressed to the open-label period (Fig. 2). Of the 29 participants who received placebo in the double-blind period and progressed to open-label, 15 were re-randomized to atabecestat 5 mg and 14 to atabecestat 25 mg. Twenty-six participants that had received 10 mg in the double-blind period were reduced to 5 mg in open-label, while 22 who had received 25 mg remained on that dosage. At the time the decision was made by the sponsor to discontinue all dosing (17 May 2018), 62 of 77 (80.5%) participants were still receiving atabecestat in the open-label period, while the remainder had already discontinued.

Fluid And Imaging (vmri) Biomarker Analysis

In the ALZ2002 study, at Month 6 (day 168) there was a dose-dependent mean (standard deviation [SD]) percent reduction from baseline in the CSF $A\beta_{1-40}$ levels: -42.4% [15.3] for 5 mg (dose-reduced), -58.7% [10.5] for 10 mg (original dose), -81.6% [10.8] for 25 mg (dose-reduced), and -83.3% [9.5] for 50 mg (original dose) groups as shown in Fig. 3A. Similar and proportionate effects of dosage on reductions from baseline were observed for CSF $A\beta_{1-37}$, $A\beta_{1-38}$, and $A\beta_{1-42}$ fragments (data not shown). Plasma $A\beta_{1-40}$ levels were reduced during the treatment period with atabecestat compared with their baseline similar to CSF $A\beta_{1-40}$ (Supplementary Fig. 1A). No change was observed in the placebo group. There were no

significant changes on CSF A β fragment levels on placebo. There were no apparent differences in the change from baseline for CSF A β_{1-40} , and A β_{1-42} between APOE ϵ 4 carriers or non-carriers.

At Month 6, there was a dose-dependent decrease in the CSF sAPP β , and in contrast, a dose-dependent increase in sAPP α fragment levels as compared to their baseline levels, which is consistent with atabecestat mode-of-action in inhibition of β -secretase proteolytic cleavage of APP (Fig. 4A). No change in sAPP α and sAPP β was observed in patients treated with placebo. There was no change in CSF levels of t-tau and p-tau₁₈₁ over the 6-month treatment period across atabecestat and placebo groups.

Box and whisker plots of change from baseline value in ALZ2002 to week 52 in ALZ2004 double-blind period are shown in Fig. 3B for CSF A β_{1-40} , in Supplementary Fig. 1B for plasma A β_{1-40} , and in Fig. 4B for sAPP α and sAPP β . The magnitude of change from baseline increased with the dose administered and was similar to that of Month 6 in ALZ2002. No relevant changes were observed for tau proteins.

Summary statistics of changes in whole brain, total hippocampal, and ventricular volume during the 52-week double-blind period in ALZ2004, quantified by BSI, are presented in Table 3. Overall, as shown, numerical decreases in whole brain and hippocampal volumes and increases in ventricular volumes from baseline were greater in participants with MCI due to AD relative to preclinical AD, though there were no clear differences related to treatment.

Table 3

Changes in brain volumes from baseline in ALZ2002 to the end of the double-blind period in ALZ2004, by treatment group (safety analysis set)

Dosage	Region	Preclinical AD				MCI due to AD			
		Double Blind Week 24		Double Blind Week 52		Double Blind Week 24		Double Blind Week 52	
		n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)
Placebo	Total Hippocampus	6	-61.183 (152.8617)	4	-192.691 (286.0535)	23	-148.955 (110.0055)	16	-208.173 (139.2326)
	Bilateral Ventricles	6	1213.479 (1297.2666)	4	2384.305 (1765.8039)	23	1877.688 (1868.2961)	16	2554.255 (1619.2302)
	Whole Brain	6	-4513.446 (6744.6900)	4	-3966.134 (6897.1749)	21	-5202.949 (5310.6112)	15	-6398.921 (6057.7712)
10 mg	Total Hippocampus	8	-130.472 (133.3899)	4	-314.289 (190.6022)	18	-130.601 (100.9252)	16	-308.766 (198.3581)
	Bilateral Ventricles	8	1317.472 (1089.6703)	4	3254.365 (1326.9982)	18	1294.812 (1190.6962)	16	3349.908 (2563.2821)
	Whole Brain	8	-7197.703 (7409.7046)	4	-17698.910 (5463.6862)	17	-5736.212 (6275.3521)	16	-10815.252 (9814.0704)
25 mg	Total Hippocampus	5	-12.221 (92.4995)	5	-129.273 (81.0670)	16	-122.374 (86.0882)	13	-235.946 (145.2177)
	Bilateral Ventricles	5	538.445 (965.7828)	5	1999.089 (1514.6993)	16	1399.116 (1085.9684)	13	2853.589 (1945.9111)
	Whole Brain	5	-1144.502 (7511.2280)	5	-4524.925 (6112.8815)	14	-6634.464 (5868.5297)	13	-9624.766 (8707.2218)

All values are changes in regional volume measured by the BSI (boundary shift integral) method, relative to baseline in ALZ2002; units are mm³.

Clinical Scales And Cognitive Effects

Mean MMSE and RBANS total scores from baseline in ALZ2002 to the end of the double-blind period in ALZ2004 are presented in Fig. 5 (A) and (B) respectively by treatment and diagnostic group. ANCOVA adjusting for baseline score and diagnosis revealed that the differences in LS means relative to placebo were not significant for the MMSE (10 mg: 0.43 [95% CI:-1.58; 2.44], $p = 0.6699$; 25 mg: 0.55 [95% CI: -1.41; 2.52], $p = 0.5751$) but suggested a trend towards greater worsening with atabecestat for Total RBANS (10 mg: -4.05 [95% CI: -9.59; 1.50], $p = 0.1499$; 25 mg: -5.60 [95% CI: -11.44; 0.24], $p = 0.0600$) (Supplementary Table S2).

Mean (SD) values and standard error (SE) for change from baseline for CDR-SB, and CFI-participant and partner by treatment group are summarized in Supplementary Table S3. There were no consistent differences related to treatment effect. Scores on the CDR-SB worsened over time during the treatment period. No consistent change was seen for the CVLT though the interval between tests was shorter (9 months). Of note, CFI-partner scores did not change for preclinical AD but increased (worsened) for MCI due to AD, while CFI-participant scores showed slight improvement regardless of baseline diagnosis, consistent with the observation that patients with MCI lose insight into their cognitive worsening, compared to observation made by independent raters [14].

Clinical Safety

Adverse events other than abnormal liver enzymes

Safety analyses included data from all randomized participants who received at least 1 dose of study drug. A summary of incidence of treatment-emergent (TE) adverse events (AEs) by treatment groups for ALZ2002 and ALZ2004 is shown in Table 4. Overall, 81/114 (71.1%) of participants experienced at least 1 TEAE in ALZ2002. The numbers of participants with at least 1 AE, serious AE, or AE leading to discontinuation were more commonly seen on the higher atabecestat dosages in ALZ2002 and the double-blind period in ALZ2004 (50 mg or 25 mg, respectively). Only 1 participant receiving placebo discontinued because of an AE during ALZ2004 double-blind treatment, but only participants transitioning from placebo to atabecestat discontinued because of AEs in the open-label period. There was 1 death in the study: a 77-year old woman in the ALZ2002 atabecestat 10 mg group died on day 170 of a cholangiocarcinoma which the investigator expected to have been pre-existent, not related to study drug, and not likely to have developed within the short treatment duration.

Table 4

Summary of overall treatment emergent adverse events by treatment group for parent study ALZ2002 and extension study ALZ2004 (safety analysis set)

	Treatment Group at Start ALZ2002				Treatment Group in ALZ2004									
	Double-Blind Parent				Double-Blind Period†				Open-Label Period‡					
	Placebo	10 mg	50 mg	Total	Placebo	10 mg	25 mg	Total	Atabecestat					
									PBO→5 mg	PBO→25 mg	10mg →5 mg	25 mg	Total	
Safety Analysis Set														
N	39	37	38	114	35	29	26	90	15	14	26	22	77	
Total patients with TEAEs, n (%)	27 (69.2)	23 (62.6)	31 (81.6)	81 (71.1)	22 (62.9)	15 (51.7)	21 (80.8)	58 (64.4)	10 (66.7)	11 (78.6)	19 (73.1)	16 (72.7)	56 (72.7)	
Serious TEAEs, n (%)	4 (10.3)	2 (5.4)	8 (21.1)	14 (12.3)	3 (8.6)	4 (13.8)	4 (15.4)	11 (12.2)	2 (13.3)	4 (28.6)	0 (0)	1 (4.5)	7 (9.1)	
TEAEs leading to Death, n (%)	0 (0)	1 (2.7)	0 (0)	1 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Any AE Leading to Discontinuation or withdrawal (%)	1 (2.6)	2 (5.4)	5 (13.2)	8 (7.0)	0 (0)	2 (6.9)	1 (3.8)	3 (3.3)	2 (13.3)	2 (14.3)	0 (0)	0 (0)	4 (5.2)	
Notes: † Adverse events (AEs) with onset on or after the first dose of study drug in ALZ2004 through the last dose in Period 1 are included. For a participant who withdrew during Period 1, adverse events through the day of last dose plus 7 days are included;														
‡ AEs with onset on or after the first dose of study drug in Period 2 of ALZ2004 through the day of last dose in Period 2 plus 7 days are included;														
TEAE = treatment-emergent adverse events, coded using MedDRA version 21.0.														

The most common AEs (occurring in at least 2 participants and $\geq 5\%$ in any one treatment group) are presented for each study period in Table 5. In ALZ2002, diarrhea was the most frequently reported TEAE associated with active treatment, occurring in 10 individuals (8.1% of those for 10 mg and 18.4% of those for 50 mg). Other frequent AEs, occurring more commonly for atabecestat than placebo, included gastroesophageal reflux and influenza, 2 (5.3%) participants each for 50 mg. AEs that occurred more commonly on placebo included nasopharyngitis (12.8%), urinary tract infection (10.3%), and headache (10.3%), as well as vomiting, hypertension, and syncope, occurring in 7.7% each. In the double-blind period of ALZ2004, AEs occurring more commonly on atabecestat included bronchitis (11.5%) and nasopharyngitis (7.7%) for the 25 mg dosage, and falls, depressive symptoms, and malaise (6.9% each) for the 10 mg dosage. Cataracts (17.1%) occurred more commonly on placebo.

Table 5

Incidence of most frequent (> 5%) adverse events occurring in ALZ2002 and the ALZ2004 double-blind and open-label periods

Body System/Preferred term	Treatment Group				
ALZ2002 (Double-Blind)	Placebo		Ata 10 mg	Ata 50 mg	Total
N	39		37	38	114
Diarrhoea	2 (5.1%)		3 (8.1%)	7 (18.4%)	12 (10.5%)
Nasopharyngitis	5 (12.8%)		3 (8.1%)	3 (7.9%)	11 (9.6%)
Headache	4 (10.3%)		2 (5.4%)	2 (5.3%)	8 (7.0%)
Back pain	2 (5.1%)		2 (5.4%)	2 (5.3%)	6 (5.3%)
Hypertension	3 (7.7%)		2 (5.4%)	1 (2.6%)	6 (5.3%)
Transaminases increased	0		2 (5.4%)	3 (7.9%)	5 (4.4%)
Urinary tract infection	4 (10.3%)		1 (2.7%)	0	5 (4.4%)
Influenza	1 (2.6%)		0	2 (5.3%)	3 (2.6%)
Syncope	3 (7.7%)		0	0	3 (2.6%)
Vomiting	3 (7.7%)		0	0	2 (2.6%)
Cataract	2 (5.1%)		0	0	2 (1.8%)
Gastroesophageal reflux disease	0		0	2 (5.3%)	2 (1.8%)
Alanine aminotransferase increased	0		2 (5.4%)	3 (7.9%)	5 (4.4%)
Vitamin B12 decreased	2 (5.1%)		0	0	2 (1.8%)
ALZ2004, Double-Blind Period	Placebo		Ata 10 mg	Ata 25 mg	Total
N	35		29	26	90
Cataract	6 (17.1%)		0	2 (7.7%)	8 (8.9%)
Nasopharyngitis	2 (5.7%)		2 (6.9%)	2 (7.7%)	6 (6.7%)
Bronchitis	1 (2.9%)		1 (3.4%)	3 (11.5%)	5 (5.6%)
Fall	2 (5.7%)		2 (6.9%)	0	4 (4.4%)
Diarrhoea	1 (2.9%)		1 (3.4%)	1 (3.8%)	3 (3.3%)
Depressive symptom	0		2 (6.9%)	0	2 (2.2%)
Insomnia	0		0	2 (7.7%)	2 (2.2%)
Malaise	0		2 (6.9%)	0	2 (2.2%)
ALZ2004 Open-Label Period	Placebo/ Ata 5 mg	Placebo/ Ata 25 mg	Ata 5 mg	Ata 25 mg	Total
N	15	14	28	22	77
Nasopharyngitis	1 (6.7%)	3 (21.4%)	3 (11.5%)	1 (4.5%)	8 (10.4%)
Headache	0	2 (14.3%)	3 (11.5%)	1 (4.5%)	6 (7.8%)
Back pain	1 (6.7%)	0	0	3 (13.6%)	4 (5.2%)

Body System/Preferred term	Treatment Group				
Pneumonia	0	2 (14.3%)	2 (7.7%)	0	4 (5.2%)
Cataract	0	0	2 (7.7%)	1 (4.5%)	3 (3.9%)
Macular fibrosis	0	0	0	2 (9.1%)	2 (2.6%)
Depression	2 (13.3%)	0	0	1 (4.5%)	3 (3.9%)
Nightmare	2 (13.3%)	1 (7.1%)	0	0	3 (3.9%)
Insomnia	0	0	0	2 (9.1%)	2 (2.6%)
Confusional state	0	1 (7.1%)	0	0	1 (1.3%)
Delirium	1 (6.7%)	0	0	0	1 (1.3%)
Psychotic disorder	0	1 (7.1%)	0	0	1 (1.3%)

Retinal AEs occurred in 2 participants receiving open-label 25 mg (macular fibrosis) and in 3 receiving placebo (retinal degeneration, retinal detachment, and retinal exudates, respectively). There were no changes on examination by the ophthalmologist that were considered possibly related to study drug. Pigmentary changes were seen in 1 individual in the 10 mg group in ALZ2002 (skin hypopigmentation) and in 2 in the placebo group in ALZ2004 (change in hair coloration).

Eight individuals endorsed statements related to suicidal ideation on the Columbia Suicide Severity rating Scale (though none had plan or intent) which occurred in 1 individual on placebo, 1 on placebo and later 5 mg, 3 on 5 or 10 mg, and 2 on 25 mg. Sleep disorders have been reported for other BACE1 inhibitors in other trials [15]. Sleep-related complaints in this study included insomnia (1 patient on placebo, 1 on 10 mg, and 2 on 25 mg), nightmares (1 on placebo, 1 on 25 mg, and transitioning from placebo to 5 mg [2] or 25 mg [1]), parasomnias (1 on 10 mg), and rapid eye movement sleep abnormalities (1 on 25 mg).

AEs related to elevated liver enzymes

Hepatic-related AEs were reported only in the atabecestat treatment groups and not in the placebo group in ALZ2002 and in the double-blind period in ALZ2004. The reported AE terms included increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased transaminases, increased hepatic enzymes, and increased gamma-glutamyl transferase (GGT). Five individuals, including 4 for 50 mg and 1 for 10 mg, had these reported as serious AEs during double-blind treatment in ALZ2002 and in the double-blind period in ALZ2004, and 2 had these reported as serious AEs transitioning from placebo to 5 mg or to 25 mg in open-label period. These individuals all discontinued treatment because of these AEs.

Treatment-emergent increases in ALT or AST (> 1 to < 2X ULN, 2 to < 3X ULN, and > 3X ULN) are presented in Table 6 for starting dosage in ALZ2002 and for the double-blind and open-label periods in ALZ2004. Mild increases (< 3X ULN) were seen more commonly on atabecestat than on placebo. Only 1 participant had an increase in ALT > 3X ULN while receiving placebo, due to acute cholecystitis. A total of 12 participants had an increase in ALT > 3X ULN while receiving atabecestat, including 5 in ALZ2002, 3 in the double-blind period of ALZ2004, and 4 in participants transitioning from placebo to 5 mg (1 case) or to 25 mg (3 cases).

Table 6
Incidence of treatment-emergent abnormal value of ALT or AST

Study	ALZ2002			ALZ2004						
	Double-Blind			Double-Blind			Open-Label			
Treatment Group	Placebo	Ata 10 mg	Ata 50 mg	Placebo	Ata 10 mg	Ata 25 mg	Placebo/ 5 mg	Placebo/ 25 mg	5 mg	25 mg
AST or ALT, n	39	34	37	35	29	26	15	14	26	22
>ULN-<=2xULN, n (%)	0	5 (14.7)	8 (21.6)	2 (5.7)	1 (3.4)	7 (26.9)	4 (26.7)	2 (14.3)	3 (11.5)	7 (31.8)
>2xULN-<=3xULN, n (%)	0	2 (5.9)	1 (2.7)	0	2 (6.9)	1 (3.8)	0	2 (14.3)	0	0
>3xULN, n (%)	1 (2.6)	2 (5.9)	2 (5.4)	0	2 (6.9)	1 (3.8)	1 (6.7)	3 (21.4)	0	0
ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal;										
For Double-blind period 1 baseline is defined as the pre-dose baseline value from the preceding parent ALZ2002 study;										
For Open-label period 2, baseline is defined as the last value taken on or before the day of first dose of study drug in the open-label period.										
Figure 1. Trial design and treatment sequence of atabecestat and placebo										

All cases of ALT or AST > 3X ULN occurred within the first year of exposure, including 7 between Days 33–168, 4 between Days 259–343, and 1 at Day 201, 32 days after last dose. In 3 cases, transaminases normalized with continued treatment, in 8 it resolved with discontinuation, and in 1 with abnormal ALT at baseline (2.7 X ULN) remained mildly elevated after discontinuation. All individuals were asymptomatic, except a 78-year old man receiving 50 mg who presented on Day 33 with a “flu-like” illness and a cholestatic pattern of abnormalities (ALT 5.4X ULN, alkaline phosphatase 3.6 ULN, and GGT 14.1 X ULN). This resolved by Day 56 following discontinuation of atabecestat, but recurred on Day 89, in the setting of fever and other constitutional symptoms, a markedly elevated erythrocyte sedimentation rate, and temporal arteritis on biopsy. This resolved on a course of corticosteroids. A cholestatic pattern of liver enzymes is known to occur in approximately one-third of cases of temporal arteritis [16]. In all other cases, the pattern was hepatocellular, with ALT > AST. The highest elevations of ALT occurred in 1 participant receiving 50 mg (15.7 X ULN) and in 1 receiving 25 mg (13.9X ULN). No abnormalities meeting “Hy’s Law” criteria (ALT or AST > 3X ULN and total bilirubin > 2X ULN) were observed.

Discussion

The effect of atabecestat on lowering CSF A β levels was dose-proportional and was maintained over a longer term in the extension study, confirming its pharmacodynamic effects of reducing the production of A β by central inhibition of BACE1 cleavage of APP. The A β reduction was consistent with previous findings from the ALZ1005 study which showed mean percent reduction from baseline in CSF A β_{1-40} of 67.3% and 89.9% for 10 mg and 50 mg respectively, after 4 weeks of treatment [5]. This finding was not associated with statistically-significant change in cognition or clinical scales, though a trend for a worsening of RBANS total score in the 10 mg and 25 mg groups relative to placebo was observed. There were no consistent changes in volumetric MRI related to treatment.

In this study, treatment-emergent increases in serum ALT, surpassing 3 X ULN, were seen in 12 of 104 (11.5%) individuals exposed to atabecestat (including 8 of 75 in double-blind treatment and 4 of 29 participants transitioning from placebo to atabecestat). Though the frequency was similar for the higher and lower doses of atabecestat, there was limited experience in

those receiving 5 mg as the only dosage (only 14 participants). These AEs were nearly all asymptomatic and resolved either spontaneously or after discontinuation of treatment.

In a separate Phase 2b/3 double-blind placebo-controlled study of atabecestat in preclinical AD (EARLY trial, ALZ2003), conducted concurrently with ALZ2004, mean decreases from baseline in PACC and RBANS scores (worsening) for participants on atabecestat treatment, were statistically significant for the 25 mg group versus placebo at 6 and 12 months and 3 months respectively [17]. The clinical significance of cognitive decline in atabecestat treatment groups relative to placebo is unclear, but similar results favoring placebo were reported with other BACE1 inhibitors such as verubecestat in Phase 3 trials for prodromal AD and mild-to moderate AD [15, 18]. Knopman [19] noted that these observations may suggest that lowering BACE1 activity could result in adverse effects on normal synaptic functions possibly due to excessive BACE1 inhibition and only a low degree of inhibition may be needed to decrease A β production. The cognitive changes described for several BACE inhibitors may be due to effects on other BACE substrates given diverse physiological function of BACE1 besides APP processing. While relevance of BACE inhibitor's nonselective blockage of BACE2, a close homolog of BACE1, remains unknown, it may theoretically lead to some AEs [20, 21]. Hence, the amount of A β reduction may not correlate with the effect on cognitive worsening and as such may warrant further investigation.

The EARLY trial had an active data safety monitoring board ensuring participant safety in the clinical trials. Because of the hepatic enzyme elevations observed in ALZ2002 as well as in EARLY, rigorous hepatic safety case management and hepatic safety algorithms had been implemented. With accumulation in the number and severity of hepatic enzyme elevations the sponsor decided on 18 May 2018 to stop treatment in all atabecestat clinical trials.

Late phase clinical trials of other BACE1 inhibitors were recently terminated early or stopped for futility due to lack of efficacy or for safety reasons, including studies of verubecestat (Merck, NJ, USA) in patients with mild-to-moderate AD (EPOCH study, NCT01739348) [15] and with amnesic MCI (APECS study, NCT 01953601) [18], and studies of lanabecestat (AstraZeneca, UK, and Eli Lilly IN, USA) in patients with MCI due to AD or mild AD dementia (AMARANTH NCT 02245737, DAYBREAK NCT02783573), [22]. Two Phase 3 trials of elenbecestat (Biogen, MA USA and Eisai) in early AD spectrum (MISSION AD1 NCT02956486, MISSION AD2 NCT03036280) were expected to report findings by 2021 but were recently terminated for safety concerns. Although evidence of liver toxicity in patients does not appear to be a BACE inhibitor class effect, there were previous reports that Phase 2 trials of LY-2886721 (Eli Lilly, IN, USA) were stopped due to abnormal liver biochemistry values flagged in 4 out of 45 patients during routine safety monitoring. Liver abnormalities were considered to be an off-target effect of that compound [23].

Interpretation of some of the analyses was limited by early termination of the ALZ2004 extension study and the small sample size, particularly the limited number of participants with normal cognition.

Conclusions

In the 6-month ALZ2002 parent study, an atabecestat 50 mg dose was generally less well tolerated than lower doses with a higher frequency of participants discontinuing treatment early. Hepatic transaminase elevations were observed in the atabecestat treatment groups but not in the placebo group, resulting in dose reduction and discontinuation of the 50 mg dose. In addition, safety measures for monitoring hepatic function tests were implemented.

In the longer-term extension study, some participants on active treatment in ALZ2004 double-blind and open-label periods exhibited transaminase elevations, including markedly abnormal ALT elevations accompanied by elevations in AST and in some cases by elevations in GGT. The elevations occurred between 3 and 12 months of treatment and all resolved after discontinuation of study treatment except for one with a baseline elevation in transaminases. A trend for decreases from baseline in RBANS scores with 10 mg and 25 mg atabecestat treatment was observed in the extension study, indicating worsening of cognitive performance consistent with reports of other BACE inhibitors.

Given the frequency of hepatic enzyme elevations and concern for managing participant safety outside the structure of a clinical trial, dosing of atabecestat in ALZ2004 and EARLY was halted. The EARLY data, as well as data from multiple other BACE inhibitors, confirmed the trends for worsened cognition seen for the RBANS in the ALZ2002 and ALZ2004 studies. While BACE inhibition remains an intriguing mechanism to slow AD progression, a better understanding of BACE substrates is important prior to additional human studies.

Declarations

List of abbreviations

APP: amyloid precursor protein; BACE1: b-secretase1 enzyme; A β : Amyloid-beta; AD: Alzheimer's disease; CSF: cerebrospinal fluid; MCI: mild cognitive impairment; OL: open-label; sAPP: soluble amyloid precursor protein; t-tau: total tau; p-tau₁₈₁: phosphorylated tau; CDR: Clinical Dementia Rating Scale; BMI: body mass index; MRI: magnetic resonance imaging; DSM: Diagnostic and Statistical Manual of Mental Disorders; PET: positron emission tomography; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GCT: gamma-glutamyl transferase; ULN: upper limit of normal; CDR-SB: CDR-sum of boxes; MMSE: Mini Mental State Examination; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; CVLT-II: California Verbal Learning Test-Second Edition; CFI: Cognitive Function Index; ECL: electrochemiluminescence; MSD: Meso Scale Discovery; PK: pharmacokinetic; AUC_{0-24h}: area under the plasma-concentration-time curve at steady state; CL/F: estimate of oral clearance; AEs: adverse events; SOC: System Organ Class; TEAEs: treatment emergent adverse events; SAE: serious adverse event; ARIA-E: amyloid-related imaging abnormalities with edema or effusion; ARIA-H: ARIA with hemosiderin; C-SSRS: Columbia Suicide Severity Rating Scale; ANCOVA: analysis of covariance; vMRI: volumetric MRI; LS: least squares; SD: standard deviation; SE: standard error

Ethics approval and consent to participate

The study protocol and amendments were approved by the appropriate Independent Ethics Committee/Institutional Review Board. Written informed consent was obtained from all participants before their participation. All study procedures followed were in accordance with current ICH guidelines on Good Clinical Practice (GCP), applicable regulatory and country-specific requirements and the principals of the Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and materials

The datasets analyzed during the present study are not publicly available, but they are available at <http://yoda.yale.edu/johnson-johnson>. Requests for access to the study data can be submitted through this independent site for review.

Conflict of interest/disclosures:

All authors, except Dr Engelborghs report personal fees (current or former employment) from Janssen Research & Development, a Division of Janssen Pharmaceutica NV, Beerse, Belgium, or Janssen Research & Development, LLC, Raritan, NJ, USA, or Janssen Research and Development LLC, Titusville, NJ, USA and all own stock/stock options in the company.

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Authors' contributions:

Drs. Streffer and Novak were the study medical officers and participated in the study design and conduct of the trial, data analysis plan, interpretation and review of the manuscript. Dr. Engelborghs was the principal investigator for the European trial, involved in patient recruitment, study operation, study management, data collection, interpretation and review and finalization of the study report. Drs. Timmers, Henley, Brashear, Tesseur, Tritsmans, and Van Nueten, were responsible for study design, data interpretation and review of the manuscript. Drs. Brashear, Novak and Bogert were responsible for safety data review committee and its charter. Dr. Russu was responsible for PK data interpretation, and modeling and simulation. Dr. Tesseur was responsible for bioanalyses of pharmacodynamic biomarkers data. Jennifer Bogert and Luc Janssens were the project clinical biostatisticians and responsible for data collection and analyses. All authors participated in interpretation of the data and drafting of the manuscript. All authors met ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data, provided direction and comments on the manuscript, made the final decision about where to publish these data, and approved the final draft and submission to this journal.

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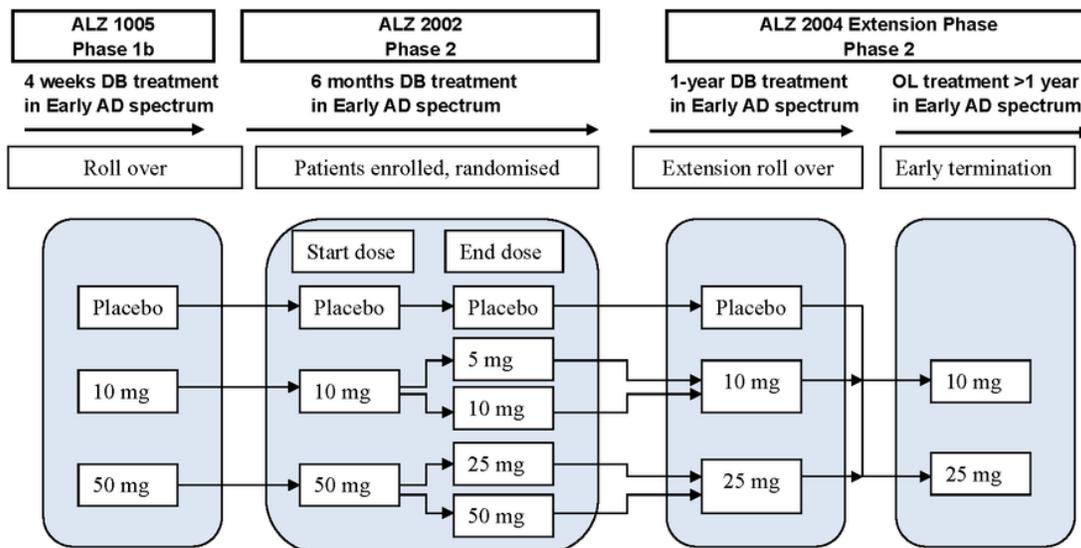
Supplementary Files Legend

The supplementary material has been provided by the authors to give readers additional information about the study and results.

Supplement to: Gerald Novak, Johannes Rolf Streffer, Maarten Timmers, David Henley et al. Long-term safety and tolerability of Atabecestat (JNJ-54861911), an oral BACE1 inhibitor in early Alzheimer's disease spectrum patients: Randomized double-blind placebo-controlled and open-label extension studies.

Figures

Figure 1. Trial design and treatment sequence of atabecestat and placebo

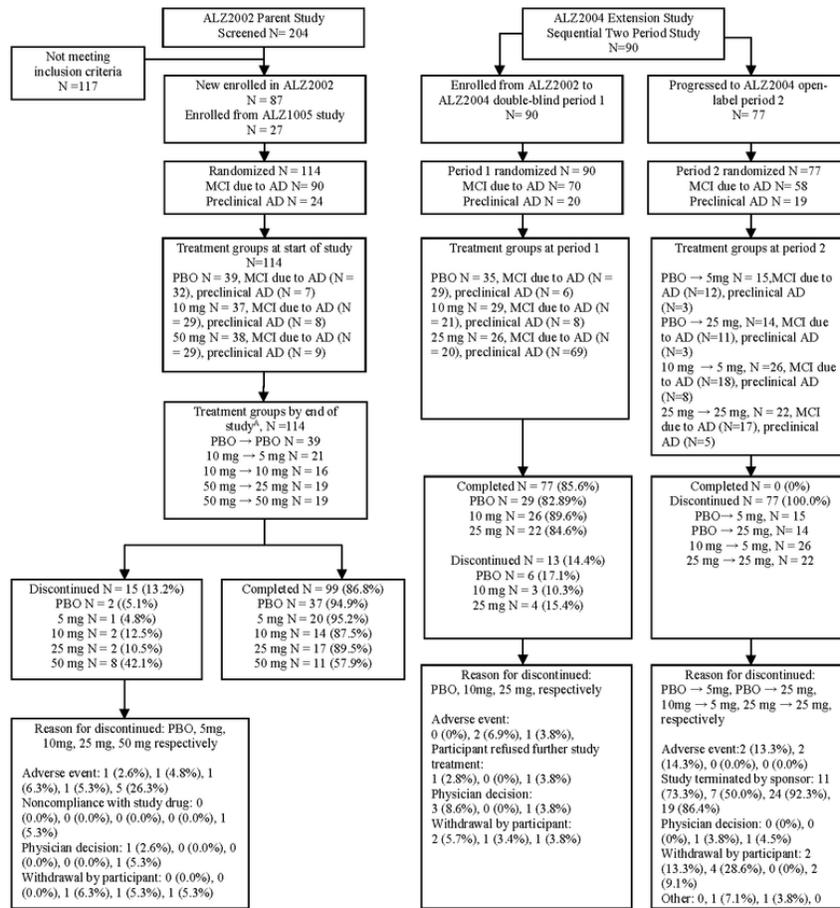


Atabecestat dose reduction occurred during ALZ2002 due to liver injury safety signal, DB= double-blind, OL= open-label

Figure 1

Trial design and treatment sequence of atabecestat and placebo

Figure 2. Participant dispositions for ALZ2002 parent and ALZ2004 extension studies



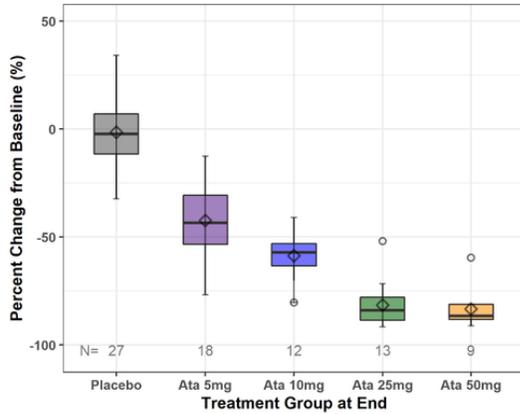
Notes: ^A During the study, due to observation of elevated liver enzymes in some patients an urgent safety measure was implemented and atabecestat doses were immediately reduced in all participants which occurred when all participants had completed a minimum of 3 months of treatment and about half of the participants had completed the treatment as planned. For remaining participants on active treatment, atabecestat 10mg/day was reduced to 5 mg/day, and atabecestat 50mg/day was reduced to 25 mg/day.

Figure 2

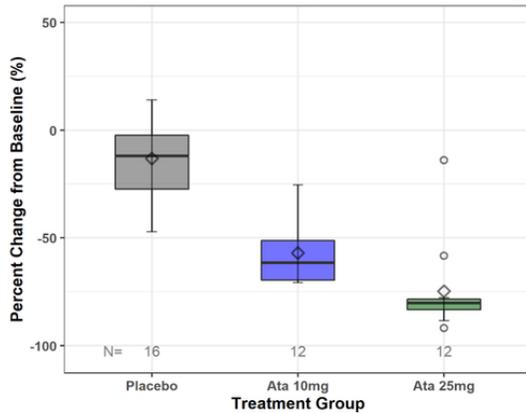
Participant dispositions for ALZ2002 parent and ALZ2004 extension studies

Figure 3. (A) Box-whisker plots of percent change from baseline for CSF A β_{1-40} biomarker level by final dose groups at end of Month 6 of atabecestat treatment in ALZ2002 early AD population. (B) Percent change from baseline time-profile for CSF A β_{1-40} levels to 52 weeks in ALZ2004 double-blind period.

A) Percent change in CSF A β_{1-40} level by ALZ2002 treatment groups at end of Month 6



B) Percent change in CSF A β_{1-40} level by ALZ2004 double-blind period treatment groups



Note: The line inside the box represents the median value, and the symbol represents the mean value. The outer box borders represent the lower and upper quartile (25th and 75th percentiles of the data).

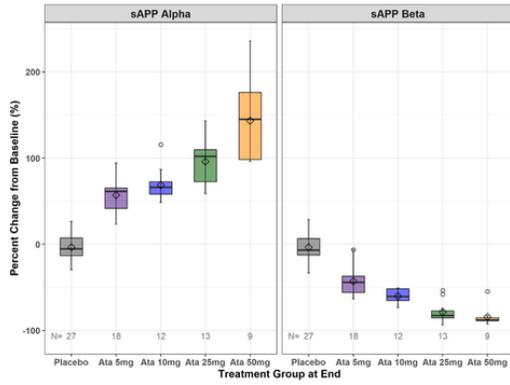
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Figure 3

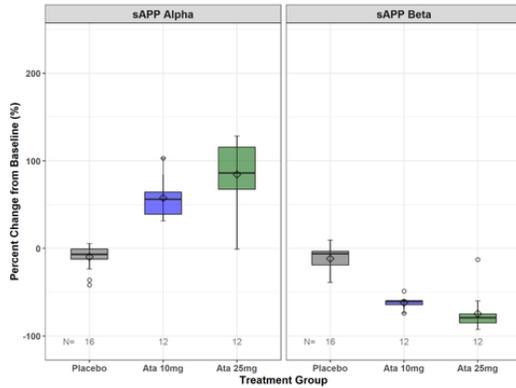
(A) Box-whisker plots of percent change from baseline for CSF A β_{1-40} biomarker level by final dose groups at end of Month 6 of atabecestat treatment in ALZ2002 early AD population. (B) Percent change from baseline time-profile for CSF A β_{1-40} levels to 52 weeks in ALZ2004 double-blind period.

Figure 4. A) Box-whisker plots of percent change from baseline for CSF sAPP α , sAPP β biomarkers by final dose groups at Month 6 of atabecestat treatment in ALZ2002, and B) for percent change from ALZ2002 baseline for CSF sAPP α , and sAPP β to week 52 in ALZ2004 double-blind period

A) ALZ2002 by treatment group at end



B) ALZ2004 double-blind period



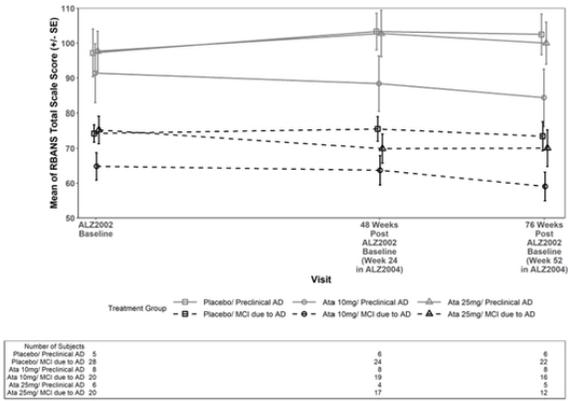
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Figure 4

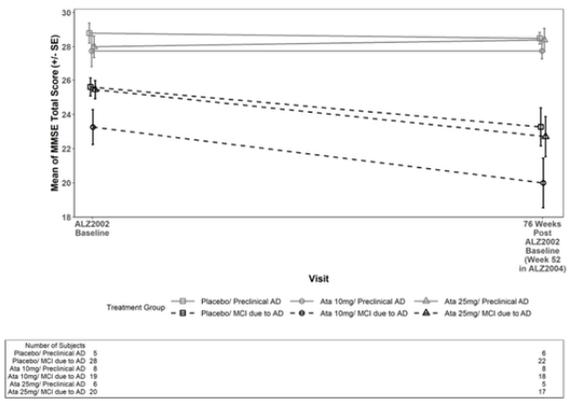
A) Box-whisker plots of percent change from baseline for CSF sAPP α , sAPP β biomarkers by final dose groups at Month 6 of atabecestat treatment in ALZ2002, and B) for percent change from ALZ2002 baseline for CSF sAPP α , and sAPP β to week 52 in ALZ2004 double-blind period

Figure 5. A) RBANS total scale and B) MMSE total score at baseline in ALZ2002 and at the end of the double-blind period in ALZ2004, by baseline CDR status and by treatment group

A) RBANS total scale (mean [SE]) over time



B) MMSE total score (mean [SE]) over time



1

Figure 5

A) RBANS total scale and B) MMSE total score at baseline in ALZ2002 and at the end of the double-blind period in ALZ2004, by baseline CDR status and by treatment group

Supplementary Files

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