Featured Article

Profiling the dynamics of CSF and plasma Aβ reduction after treatment with JNJ-54861911, a potent oral BACE inhibitor

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Abstract

Objectives: Safety, tolerability, pharmacokinetics, and pharmacodynamics of a novel β-site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibitor, JNJ-54861911, were assessed after single and multiple dosing in healthy participants.

Methods: Two randomized, placebo-controlled, double-blind studies were performed using single and multiple ascending JNJ-54861911 doses (up to 14 days) in young and elderly healthy participants. Regular blood samples and frequent CSF samples, up to 36 hours after last dose, were collected to assess the pharmacokinetic and pharmacodynamic (Aβ, sAPPα,β,total levels) profiles of JNJ-54861911.

Results: JNJ-54861911 was well-tolerated, adverse events were uncommon and unrelated to JNJ-54861911. JNJ-54861911 showed dose-proportional CSF and plasma pharmacokinetic profiles. Plasma- and CSF-Aβ and CSF-sAPPβ were reduced in a dose-dependent manner. Aβ reductions (up to 95%) outlasted exposure to JNJ-54861911. *APOE* ε4 carrier status and baseline Aβ levels did not influence Aβ/sAPPβ reductions.

Conclusion: JNJ-54861911, a potent brain-penetrant BACE1 inhibitor, achieved high and stable Aβ reductions after single and multiple dosing in healthy participants.

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Keywords: JNJ-54861911; Alzheimer's disease; Amyloid β; β-secretase enzyme; BACE1; BACE inhibitors

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive memory loss and cognitive decline. The neuropathologic hallmarks of AD are extracellular plaques of insoluble amyloid β (Aβ), intracellular neurofibillary tangles (NFT) composed of hyperphosphorylated tau protein and atrophy of the cerebral cortex [1]. All these pathologic changes begin years before the onset of symptoms [2].

Multiple lines of evidence support the amyloid cascade hypothesis stating that Aβ accumulation and deposition are the initiating factors for the pathogenesis of AD [3,4]. The hypothesis puts forward factors such as increased production or decreased clearance of Aβ from the central nervous system (CNS), driving the Aβ accumulation in brain. As a consequence, agents preventing formation of Aβ could have disease-modifying properties for AD. Aβ is generated from the amyloid precursor protein (APP). The amyloidogenic processing of APP is initiated by β-site APP cleaving enzyme 1 (BACE1). BACE1 is an aspartyl protease, cloned initially by several groups [5,6], that cleaves the N-terminus of Aβ, followed by γ-secretase cleaving the C-terminal end. In this process, BACE1 cleavage is the first and rate-limiting step. Subsequent γ-secretase cleavage results in formation of Aβ species of different lengths, from which $A\beta_{1-40}$ is the predominant one. The cleavage site for another APP processing enzyme, α-secretase, lies within the Aβ sequence and thus precludes Aβ formation. The relationship of physiological α-secretase to β-secretase processing is not fully understood, and BACE1 inhibition studies suggest that APP can be shifted to other pathways [7]. The amino terminal fragment generated through α-secretase or β-secretase cleavage is called soluble APP (sAPP) α or β, respectively.

Inhibitors of BACE1 prevent the formation of Aβ and would therefore be potential therapeutic agents for AD.

BACE1 has emerged over the past decade as the drug target of choice for reducing central Aβ levels in AD. Several BACE inhibitors are currently in clinical development for different stages of AD [8–13]. JNJ-54861911 is the first BACE inhibitor being developed by Janssen in collaboration with Shionogi. Herein, we describe the safety and tolerability, and peripheral and central pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of JNJ-54861911 after single and multiple dosing. Confirmation of peripheral and central BACE1 inhibition, and as such target engagement of JNJ-54861911, was assessed primarily by $A\beta_{1-40}$ levels in plasma and cerebrospinal fluid (CSF).

2. Methods

2.1. Clinical studies

Two randomized, placebo-controlled, double-blind, single-site clinical studies were performed using single-(SAD) and multiple-ascending dose (MAD) administrations in young healthy men and elderly healthy men and women.

Both study protocols and amendments were reviewed by an Investigational Review Board (Commissie voor Medische Ethiek, Ziekenhuis Netwerk Antwerpen (ZNA), Antwerp, Belgium). All procedures followed were in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before participation. The studies are registered on ClinicalTrials.gov: NCT01827982 and NCT01887535.

2.2. Study population

Young men (18–54 years; body mass index [BMI], 18 to 30 kg/m^2) and elderly men or women (55–75 years; BMI, 18 to 32 kg/m^2) considered healthy based on medical history, physical examination, 12-lead ECGs, and clinical laboratory evaluations (see Supplemental data for key inclusion criteria) were enrolled in the SAD and MAD studies from April 2013 to December 2013 at SGS, Life Science Services, Clinical Pharmacology Unit, Belgium.

2.3. Clinical study designs and treatments

In the SAD study, young participants (N = 8) received a single dose of 1-mg JNJ-54861911 (N = 6) or placebo (N = 2). Elderly participants (N = 48) received escalating single dose levels as oral suspension of 1, 3, 10, 30, 90, or 150 mg of JNJ-54861911 (N = 6/cohort) or placebo (N = 2/cohort).

In the MAD study, elderly participants (N = 38) received, double blind, JNJ-54861911 (N = 6/cohort), or placebo (N = 2/cohort) as oral suspension at escalating doses of 5, 30, 50, or 90-mg QD or open label as solid dose formulation of 25-mg QD (N = 6) for 14 days. A single young healthy men cohort to explore safety and tolerability at higher dose level received 150-mg JNJ-54861911 (N = 6) or placebo (N = 2) as solid-dose formulation for 7 days. An additional enlarged cohort of elderly participants to assess potential QTc liabilities received JNJ-54861911 (N = 18) or placebo (N = 6) as oral suspension for 7 days (See Supplemental data for a detailed description).

2.4. Safety assessments

Safety was assessed before and after dosing by recording adverse events (AE), physical and neurological examinations, vital signs, 12-lead ECGs, 24-hour Holter monitoring, and clinical laboratory tests. All participants were included in the safety analysis.

2.5. PK and PD assessments

Plasma and urine concentrations of JNJ-54861911 and PD effects in plasma were evaluated at regular time points (limited PD assessments were applied in the QT cohort; see Supplemental data).

For all elderly participants (except for the QT cohort), PK and PD effects of JNJ-54861911 were assessed in CSF on day 1 (SAD; 6 mL/sample) and day 14 (MAD; 4 mL/sample) using serial CSF sampling through an indwelling subarachnoid lumbar catheter from 2 hours before until 36 hours after the last dosing, as described previously [14].

In addition, in the MAD study, a baseline CSF sample was collected by single lumbar puncture (LP) predose on day 1 (12 mL).

From all participants, a pharmacogenomic sample was collected and *APOE* ε4 carrier status was analyzed [15].

2.6. Bioanalytical methods

2.6.1. Analysis of JNJ-54861911

Plasma, urine, and CSF JNJ-54861911 samples were analyzed using a scientific validated [16], specific, and sensitive liquid chromatographic–mass spectrometry/mass spectrometry method (see Supplemental data). The lower limit of quantification (LLOQ) was 1 ng/mL.

2.6.2. Analysis of plasma and CSF Aβ concentrations

A qualified prototype multiplex immunoassay based on Meso Scale Discovery (MSD; Gaithersburg, MD) electrochemiluminescence detection (ECL) technology was used for simultaneous detection of 4 Aβ species ($A\beta_{1-37}$, $A\beta_{1-38}$, $A\beta_{1-40}$, and $A\beta_{1-42}$) [17,18]. Plasma samples were analyzed after pretreatment with Heterophilic Blocking Reagent-9 (HBR-9, Scantibodies, Laboratory, Inc., CA). As in plasma most of the concentrations of $A\beta_{1-37}$, $A\beta_{1-38}$, and $A\beta_{1-42}$ were near or lower than LLOQ, only $A\beta_{1-40}$ concentrations are reported.

2.6.3. Analysis of CSF sAPP concentrations

sAPPα, sAPPβ, and sAPP total were quantified in CSF using MSD ECL detection technology. For the MAD study, day 1 and day 14 predose samples together with samples taken at day 14 at 10, 24, and 36 hours after dose were analyzed. sAPPα and sAPPβ CSF concentrations were measured using MSD 96-well MULTI-SPOT sAPPα/sAPPβ assay according to manufacturer's instructions [19].

For sAPP total, an MSD ECL assay developed by Janssen Research & Development was used (see Supplemental data).

Both Aβ and sAPP were determined using a standard curve with 4-parameter logistic model with $1/Y^2$ weighting function. All samples from each participant were analyzed in duplicate on the same assay plate. Only mean values with replicate well coefficient of variation (CV) of ≤20% were accepted.

2.6.4. Analysis of baseline CSF $A\beta_{1-42}$, P-tau$_{181P}$, and T-tau levels

Baseline $A\beta_{1-42}$, phosphorylated tau at position threonine 181 (P-tau$_{181P}$) and total tau (T-tau) concentrations were measured using INNO-BIA AlzBio3 kit reagents and Luminex analytical platform [20,21].

2.7. Statistical analysis

2.7.1. Sample size

For mean % change in CSF $A\beta_{1-40}$, a dose group of six participants and a pooled placebo group of 10 participants was expected to provide a 1-sided 90% confidence interval for between treatment difference with a precision of ±9, based on a SD of 12 observed earlier [14].

3. Results

3.1. Demographic characteristics

All participants completed the studies, except one in the MAD study, who withdrew consent on day 28. Eight elderly participants in the SAD and four elderly participants in the MAD study had $A\beta_{1-42}$ concentrations below the threshold (249 pg/mL), suggestive of cerebral amyloid plaque deposition [21], but none had elevated T-tau or P-tau$_{181P}$ values (data not shown). Overall, 28.6% (n = 16/56) and 27.1% (n = 19/70) of all participants enrolled in the SAD and MAD study respectively were identified as *APOE* ε4 carriers. Across both studies, a total of 94 participants, mainly Caucasian, received one or more doses of JNJ-54861911 (Table S1).

In the SAD study, 8 young men (1 mg; mean age, 44.8 years) and 48 elderly men and women (1–150 mg; mean age, 64.2 years) participated in the study.

In the MAD study, 62 elderly men and women (5–90 mg; mean age, 64.8 years) and 8 young men (150 mg; mean age, 39.6 years) were enrolled. Within studies, the average measures for age, height, BMI, $A\beta_{1-42}$, P-tau$_{181P}$, and T-tau at baseline were comparable among treatments for the elderly participants enrolled in cohorts measuring CSF in the SAD (P = not significant [NS] for all, F test) and MAD (P = NS for all) study. Gender and *APOE* ε4 status were comparable among treatments (P = NS, Fisher exact test) in the SAD study, whereas there was a slight imbalance of these parameters in the MAD study (both P = .08, Fisher's exact test; Table S1).

3.2. Safety and tolerability

Single and multiple oral doses of JNJ-54861911 ranging between 1 and 150 mg were well-tolerated. AEs were uncommon, occurred with similar frequency in the placebo and JNJ-54861911 treatment groups, and are probably attributable to the LP procedure (Table S2).

In participants receiving JNJ-54861911, the most common AEs (≥10 participants) were headache (SAD, 16/42 [38.1%] vs placebo, 7/14 [50%]; MAD, 13/52 [25.0%] vs placebo, 1/18 [5.6%]) and back pain (SAD, 10/42

[23.8%] vs placebo, 0/14 [0%]; MAD, 11/52 [21.2%] vs placebo, 2/18 [11.1%]). All other AEs were observed in ≤8 participants receiving either a single or multiple dose of JNJ-54861911 or placebo. There were no apparent trends in AEs with regard to dose.

There were no serious AEs (SAEs) or significant changes noted in vital signs, physical, and neurological measurements, or ECG (12-lead ECG; Holter monitoring), nor were there any investigator-identified laboratory AEs or clinically relevant laboratory abnormalities.

3.3. Pharmacokinetic properties of JNJ-54861911

An overview of the plasma and CSF PK parameters and profiles is provided as Supplementary Material (Supplementary Table S3–S6 and Supplementary, Figs. S1 and S2). After single and multiple doses, plasma JNJ-54861911 C_{max} and AUC increased dose-proportionally from 1 to 150 mg and appeared similar between healthy young and elderly participants. JNJ-54861911 plasma PK profiles were characterized by rapid absorption (median T_{max} of 0.75–2 hours following single dose, and 2–4 hours after multiple dosing) and essentially biphasic decline at all dose levels (Supplementary Figs. S1). After multiple dosing, mean $T_{1/2}$ on day 14 ranged from 14.4 to 18.5 hours compared to 9.0 to 16.1 hours after single dose. Steady state JNJ-54861911 concentrations following multiple dosing were reached by day 5 for all cohorts, which is consistent with the observed $T_{1/2}$. Mean accumulation ratios for steady-state C_{max} and AUC_{τ} on day 14 ranged from 1.27 to 1.73 ng/mL and 1.34 to 2.17 ng h/mL, respectively. Mean renal clearance values of JNJ-54861911 between day 1 (single dose; data not shown) and day 14 (Supplementary Table S5) were similar (0.111 vs 0.115 L/h) and comparable across studies.

JNJ-54861911 levels in CSF were assayed only in elderly participants (Supplementary Tables S4 and S6). Single-dose CSF concentrations of JNJ-54861911 were generally below the LOQ for the 1-mg and 3-mg dose level. After single and multiple doses, both C_{max} and AUC in CSF increased dose proportionally across doses studied (10–150 mg). Maximal mean concentrations in CSF (2.94–22.7 ng/mL) on day 1 were reached between 2.0 and 3.0 hours. After multiple dosing, median T_{max} in CSF on day 14 was approximately 4 hours and mean $T_{1/2}$ ranged from 11.7 to 14.4 hours across doses studied. Plasma and CSF T_{max} after single and multiple dose were similar. Dose-normalized plasma and CSF PK were comparable between formulations used (Supplementary Tables S4 and S5). Finally, CSF PK profiles appeared to be parallel to corresponding plasma PK profiles at each dose group (Supplementary Figs. S1 and S2). CSF concentrations were approximately 3% of total plasma concentrations, and 50%–60% of free plasma concentrations, estimated based on a plasma-free fraction of 6%.

3.4. Pharmacodynamics of JNJ-54861911

3.4.1. Plasma and CSF Aβ

To investigate target engagement, CSF and plasma Aβ levels were monitored over time.

In the SAD study, dose-dependent reduction of plasma and CSF $Aβ_{1-40}$ concentrations versus baseline was observed (Fig. 1 and Supplementary Fig. S3). The reduction in plasma (Fig. 1A and Supplementary Fig. S3A) was characterized by a fast onset with strongest reduction during the first 4 hours after dose, approaching (close to) maximal effects in all doses. In young healthy men (1-mg dose), a similar plasma Aβ profile was seen as in elderly healthy participants (data not shown). Higher doses (10, 30, 90, and 150 mg) achieved 70% to 80% Aβ reduction at 4 hours after dose, and the reduction compared to baseline was long lasting. Analysis of later time points showed a slow return to baseline concentrations for all dose groups, with reductions remaining up till 96 hours after dose for all groups from 3–150 mg.

Compared to plasma, reduction of CSF $Aβ_{1-40}$ concentrations showed a later onset and slower kinetics (Fig. 1B and Supplementary Fig. S3B). As anticipated based on earlier findings reported by Van Broeck et al. 2015 [14], the high-frequency CSF collection scheme resulted in an initial mean increase of $Aβ_{1-40}$ levels over baseline. Over the first 6 hours, no apparent treatment effect was observed. After 6 hours, a dose-dependent reduction of $Aβ_{1-40}$ levels started. Although doses of 1 and 3 mg trended slightly below placebo, no relevant $Aβ_{1-40}$ reduction could be observed. Increasing doses yielded a dose-dependent reduction of $Aβ_{1-40}$ concentrations. The maximum observed reduction after single dosing was 75% (36 hours after 150 mg). The Aβ-lowering effect was persistent over 36 hours for the highest doses (90 and 150 mg), whereas participants treated with lower doses showed a trend for return to baseline 36 hours after dose.

In the MAD study, reduction of plasma and CSF $Aβ_{1-40}$ levels from baseline was stable until at least 24 hours after last dose in participants receiving a once daily dose of JNJ-54861911 for 14 days (Fig. 2). Plasma reductions were dose dependent with participants dosed with 5 mg JNJ-54861911 having reductions of 60%–75%, at 30 mg 75%–85%, at 50 mg around 90%, and at 90-mg 90%–95% (Fig. 2A). The reductions in the 25-mg tablet group were close to those in the 30-mg oral suspension group. Similar to the SAD study, no notable changes from baseline were observed in participants receiving placebo. Analysis of time points beyond 36 hours showed a slow return to baseline concentrations, with reductions remaining up till 72 hours after dose for all treatment groups.

Similarly in CSF, a dose-dependent decrease in $Aβ_{1-40}$ levels was observed compared to baseline (Fig. 2B). The $Aβ_{1-40}$ reduction in plasma was numerically stronger compared to CSF at the lowest dose of 5 mg. In contrast to the SAD study, no marked increase above baseline was
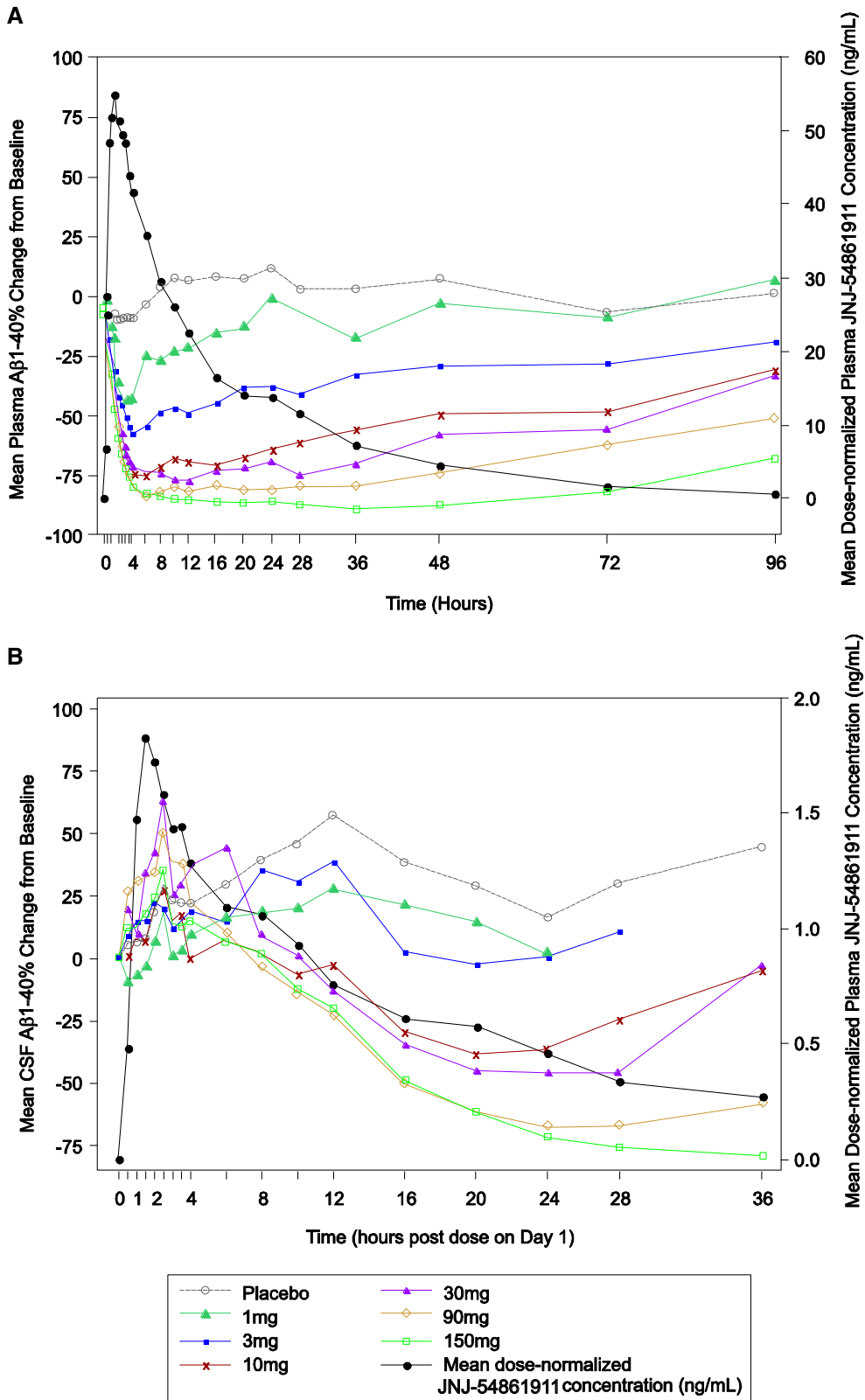
Fig. 1. Dose-dependent plasma (A) and CSF (B) Aβ$_{1–40}$ reduction with mean dose normalized plasma and CSF JNJ-54861911 concentrations in the SAD study. Aβ data are represented as mean percent change from baseline over time. 1-mg cohort was only analyzed till 24 hours after treatment. CSF analysis of 3-mg cohort was performed till 28 hours after dose (data 36 hours were rejected). Plasma and CSF JNJ-54861911 concentrations presented as mean dose normalized profiles, obtained by dose-normalizing all individual PK profiles and averaging them at each time point.
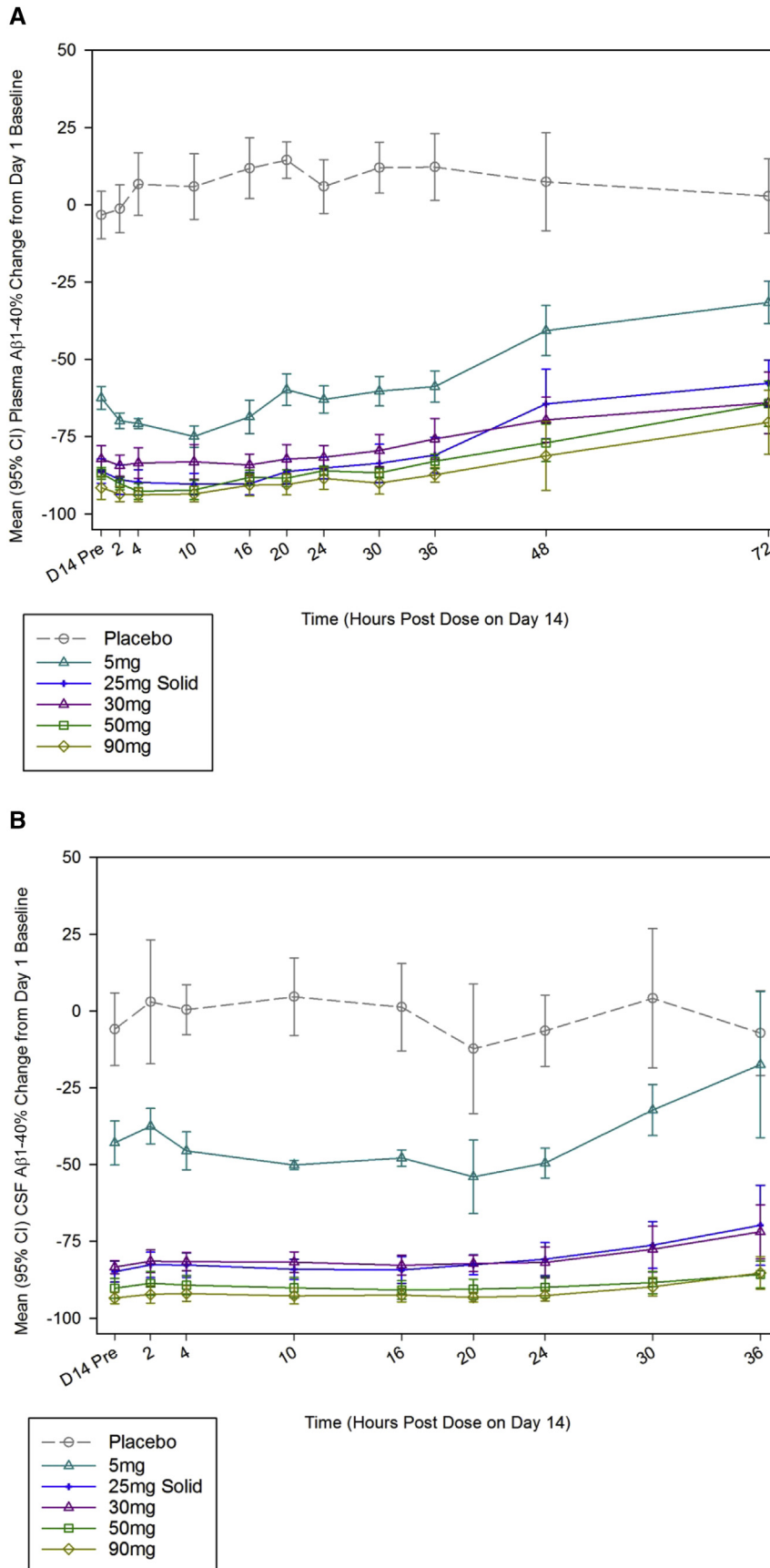
Fig. 2. Stable and dose-dependent plasma (A) and CSF (B) $A\beta_{1-40}$ reduction in the MAD study as measured 14–15 days after repeated dosing with JNJ-54861911. Data of day 14 are represented as mean percent change from baseline (day 1) over time (including 95% CI bars [CI, confidence interval]). Plasma samples were taken during a longer period (up to 72 hours) as compared to CSF (up to 36 hours).

present in the placebo group. For JNJ-54861911, dose dependent $A\beta_{1-40}$ reductions were seen: 50% at 5 mg/day, 80% to 85% at 30 mg; about 90% at 50 mg; and 90% to 95% at 90 mg. The reductions after treatment with the 25-mg tablet were similar to those with 30-mg oral suspension. Similar to the observed reductions in plasma, all reductions in CSF were stable up till 24 hours after the last dose on day 14, not only on a group mean level, but also at an individual level (data not shown). Thirty-six hours after the last dose, there was a trend toward normalization for the lowest dose of 5 mg, whereas reductions remained relatively stable for the higher dose groups.

For all cohorts, CSF concentrations of all measured $A\beta$ species ($A\beta_{1-37}$, $A\beta_{1-38}$, $A\beta_{1-40}$, and $A\beta_{1-42)}$ demonstrated similar changes in $A\beta$ levels versus baseline (Fig. 3).

3.4.2. Pharmacodynamics of CSF sAPP

To obtain direct evidence of specific BACE1 inhibition in the CNS, sAPPα, sAPPβ, and sAPP total were measured in a selection of CSF samples of the MAD study (Fig. 4).

sAPPβ concentrations decreased in a dose-dependent and stable manner after 14 days dosing comparable to $A\beta_{1-40}$. sAPPα increased to a similar extent in 30-, 50-, and 90-mg cohorts, not exceeding a 2-to-2.5-fold increase versus baseline levels (Fig. 4). sAPP total levels remained rather constant over the full observation period.

Additionally, *APOE* ε4 carrier status and baseline $A\beta$ levels (data not shown) did not impact the mean of the maximum percent $A\beta$ or sAPPβ reduction from baseline (Fig. 5).

3.4.3. PK/PD relationship in plasma and CSF

Comparison between PK and PD parameters in plasma and CSF revealed clear differences. In plasma, the onset of $A\beta$ lowering is parallel to the PK profile, with maximum $A\beta$ reduction close to T_{max} (Fig. 1A). In CSF, $A\beta$ lowering was delayed compared to CSF PK, with $A\beta$ reduction starting only 6 hours after dose (Fig. 1B).

4. Discussion

Preclinical studies in transgenic animal models have demonstrated a link between BACE1 inhibition and lowering of $A\beta$ levels in the brain, as well as prevention or even reversal of amyloid deposition [22–24]. These findings, together with results from genetic studies [25], underscored the potential of BACE1 inhibitor treatment in AD, and currently several compounds are in various stages of clinical development [13].

We describe the results of first-in-human studies in which the safety and tolerability, PK and PD of a novel BACE1
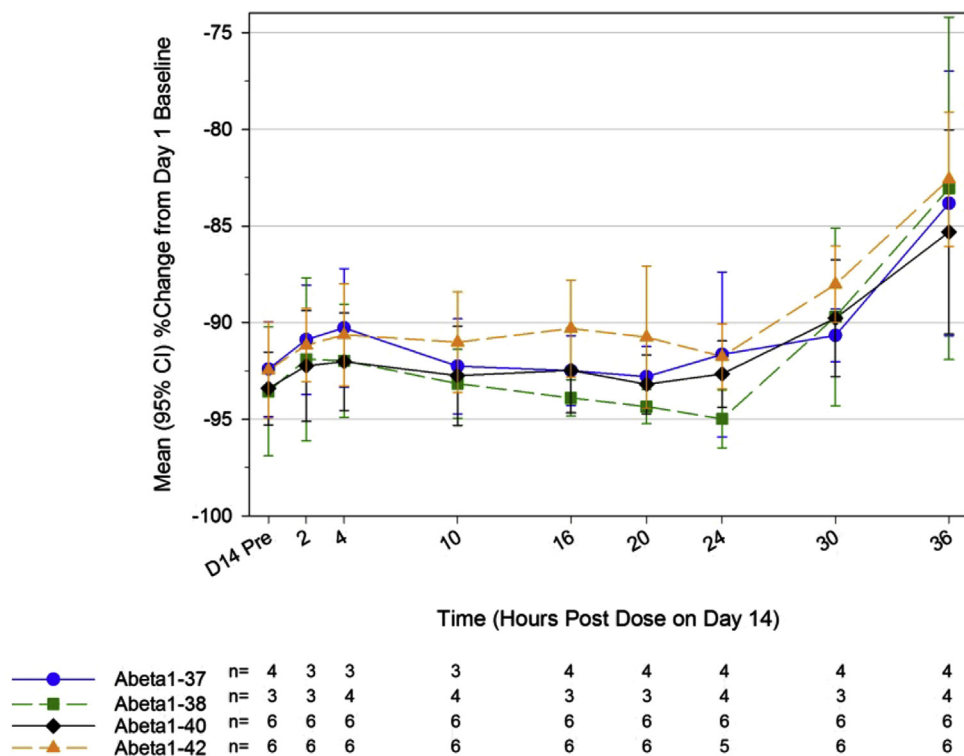

Fig. 3. Stable reduction in $A\beta$ species ($A\beta_{1-42}$, $A\beta_{1-40}$, $A\beta_{1-38}$, $A\beta_{1-37}$) in CSF compared to baseline as measured 14–15 days after repeated dosing with 90-mg JNJ-54861911. Data of day 14 are represented as mean percent change from baseline (day 1) over time (including 95% CI bars). Data of the 90-mg dose level presented are representative for all other cohorts. Number of participants for whom samples could be analyzed and for which levels were above LOQ is indicated below figure.
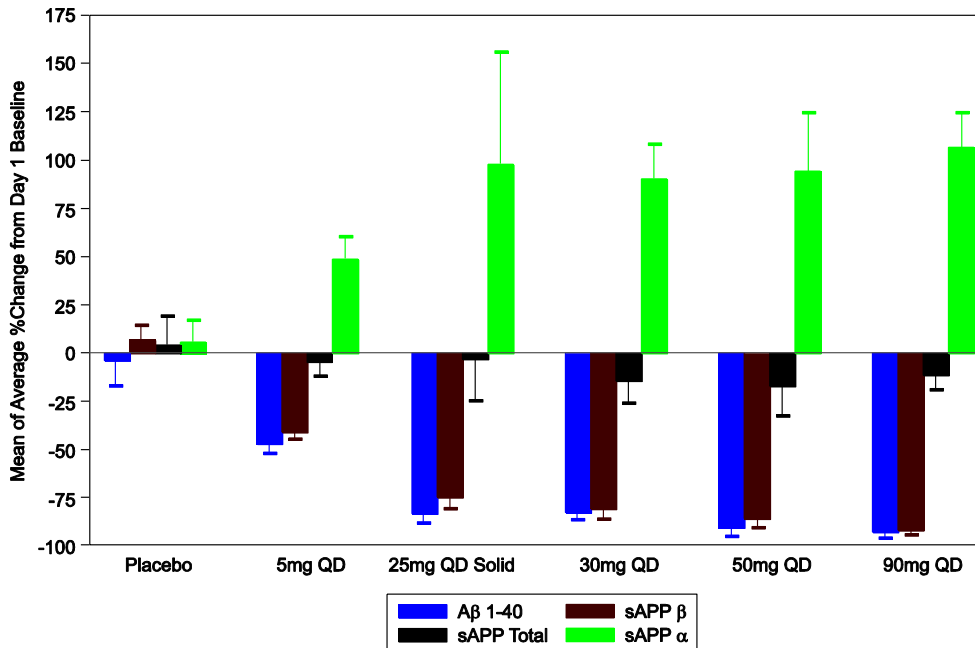
Fig. 4. CSF sAPPα increase and sAPPβ decrease in the MAD study as measured 14–15 days after repeated dosing with JNJ-54861911. Data are represented as mean of the average percent change from baseline (day 1) over 24 hours, 14–15 days after repeated dosing (± standard deviation). Total sAPP levels remained rather constant over the observation period. CSF $A\beta_{1-40}$ reduction is included to allow comparison with measured changes in sAPP species.

inhibitor, JNJ-54861911, were evaluated in healthy participants after single and multiple doses.

In general, JNJ-54861911 was well tolerated in both studies. Overall AEs observed and reported were uncommon, occurred with similar frequency in placebo and JNJ-54861911 treatment groups and were probably attributable to the LP procedures. AE profiles related to the LP procedures were comparable to previously reported LP-related AEs [14]. There were no apparent trends in AEs reported with regard to dose. No significant differences in AE profiles were observed between tablet and oral suspension formulation.
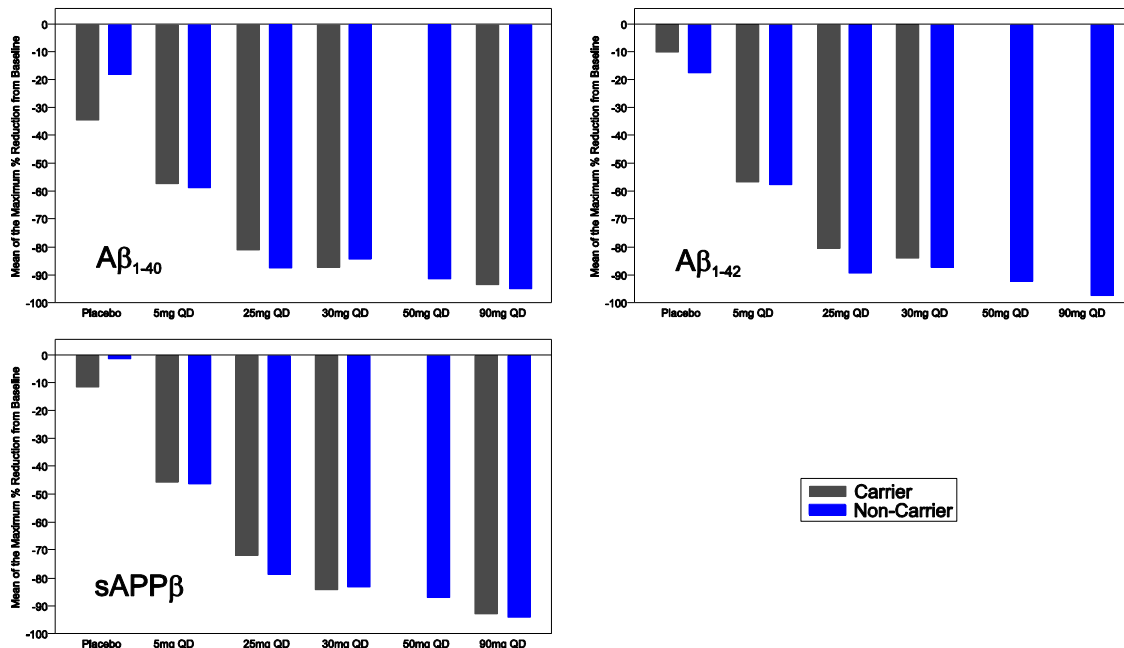

Fig. 5. *APOE* ε4 carrier status has no impact on Aβ or sAPPβ reduction. Data are represented as mean of maximum percent change from day 1 baseline on day 14 (24 hours).

JNJ-54861911 mean plasma profiles were similar between young and elderly, across studies and between formulations (suspension vs. tablet). JNJ-54861911 exhibited rapid absorption and multiphasic decline across dose levels. The extent of absorption was similar between populations and studies. Dose linearity was observed across all treatment groups after single and multiple dosing in CSF and plasma (C_{max} and AUC_τ), with doses ranging from 1 to 150 mg.

In the MAD study, steady state plasma levels were reached by day 5. The sustained PD effects outlasted the PK profile, making this drug suitable for once daily dosing.

The decrease in mean plasma $A\beta_{1-40}$ levels was dose dependent. In the SAD study, onset of $A\beta_{1-40}$ reduction was fast and parallel to PK. Even at 96 hours after dosing, reduction in plasma $A\beta_{1-40}$ levels was still present for most dose groups, whereas compound concentrations were low or even below quantification limit at that time point. The reason for these long-lasting effects on plasma $A\beta_{1-40}$ is currently unknown but might be related to intracellular compartmentalization of the compound [11]. The fact that reductions in plasma $A\beta$ can be long lasting has been observed in other studies in healthy participants as well [8,11]. In the MAD study, a stable 90%–95% inhibition of plasma $A\beta_{1-40}$ was noted in the 90-mg dose group after 14 days of dosing. Mean percent change in $A\beta_{1-40}$ levels from baseline was stable up to at least 24 hours in all dose groups.

Analysis of CSF $A\beta_{1-40}$ levels revealed no apparent treatment effect over the first 6 hours after a single dose of JNJ-54861911. After 6 hours, a dose-dependent decrease in CSF $A\beta_{1-40}$ levels was observed which continued in the 150-mg group until the end of the observation period at 36 hours, whereas lower doses trended toward normalization earlier. The initially observed increase in CSF $A\beta_{1-40}$ levels versus predose levels was most probably related to the high frequency and/or volume of CSF sampling [14]. Indeed, in the MAD study, where a lower sampling frequency scheme and volume was applied, $A\beta_{1-40}$ levels in the placebo group did not show significant changes compared to predose samples. Here, a dose-dependent and stable reduction in CSF $A\beta_{1-40}$ levels was observed allowing for a QD dosing regimen. Studies with other BACE inhibitors described various extents of dose-dependent CSF $A\beta$ reductions in healthy participants [8,10,26]. In contrast to the observations in plasma, CSF $A\beta_{1-40}$ reductions showed a delay compared to the PK profile of JNJ-54861911. The rate of onset of CSF $A\beta$ lowering was similar to production rate of new $A\beta$ in CSF of healthy participants [27]. It is plausible that plasma and CSF $A\beta$ reductions are driven by peripheral and central activity, respectively. Additionally, baseline $A\beta$ or *APOE* ε4 genotype had no relevant impact on $A\beta$ reduction.

In accordance with the mechanism of action of BACE1 inhibitors, it was also confirmed that $A\beta$ species of various lengths were reduced in parallel. Moreover, sAPPβ levels were shown to exhibit dose-dependent reduction, providing direct evidence of β-secretase inhibition in the human CNS. In agreement with earlier studies, sAPPβ and $A\beta$ decreased in a similar manner [10]. The concomitant increase in sAPPα indicated increased processing through the α-secretase pathway, as has been demonstrated before in CSF [26,28–31].

5. Conclusions

JNJ-54861911 is a potent, brain-penetrant BACE1 inhibitor, achieving robust and high (up to 95%) CSF $A\beta$ reduction with once daily oral dosing in healthy elderly participants, in absence of significant AEs. $A\beta$ reduction outlasted plasma/CSF pharmacokinetics, leading to sustained PD activity. These results support JNJ-54861911 as a promising candidate to test in patient populations for its potential to mitigate AD disease progression and thus clinically validate the amyloid cascade hypothesis.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.trci.2016.08.001.

RESEARCH IN CONTEXT

1. Systematic review: BACE-1 is an emerging target for potential treatment of Alzheimer's disease (AD). We describe the results of first-in-human phase-1 studies of a novel BACE1 inhibitor, JNJ-54861911, in which the safety and tolerability, pharmacokinetics and pharmacodynamics were evaluated in healthy participants after single and multiple-doses.

2. Interpretation: JNJ-54861911 achieved robust and high (up to 95%) CSF Aβ reduction with once daily oral dosing in healthy elderly participants, and was well tolerated in both studies. Aβ reduction outlasted plasma/CSF pharmacokinetics, leading to sustained pharmacodynamic activity. Our results support the existing hypothesis that BACE-1 inhibition may be of therapeutic benefit in reducing Aβ levels in AD.

3. Future directions: These results support JNJ-54861911 as a promising candidate to test in target patient populations for its potential to mitigate AD disease progression and thus clinically validate the amyloid cascade hypothesis.

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