Safety and Tolerability of Posdinemab in Early Alzheimer's Disease: Results From the Phase 2 Autonomy Trial

Pieter-Jan Berghmans[1], Maggie Fedgchin[2], Paul B. Watkins[3], Jan Snoeys[1], Ronald Tyler[4], Martine Meyer[5], Jennifer Bogert[6], Sandra De Jonghe[1], Angela Jeong[4], Lingjue Li[2], David Henley[7], Howard Greenberg[2], Loreta Marquez[6], Haiyan Xu[2], Arthur Simen[8], Janice Wong[8,*]

[1]Johnson & Johnson, Beerse, Belgium; [2]Johnson & Johnson, Titusville, NJ, USA; [3]Institute for Drug Safety Sciences, Eshelman School of Pharmacy, The University of North Carolina, Durham, NC, USA; [4]Johnson & Johnson, Spring House, PA, USA; [5]Johnson & Johnson, Vashon, WA, USA; [6]Johnson & Johnson, Raritan, NJ, USA; [7]Johnson & Johnson, Hagerstown, IN, USA; [8]Johnson & Johnson, Cambridge, MA, USA

Presenting author

Background

- Posdinemab (JNJ 63733657), an immunoglobulin (Ig)G1 monoclonal antibody, binds mid-domain phosphorylated tau at the p-tau217 epitope.
- Autonomy (NCT04619420) was a Phase 2b, randomised, double-blind (DB), placebo controlled, common-close study that assessed the efficacy and safety of posdinemab in early Alzheimer's disease (AD; mild cognitive impairment [MCI] or mild dementia).
- The trial did not meet its primary endpoint of slowing clinical decline as measured by the integrated AD Rating Scale for Mild Cognitive Impairment (iADRS-MCI).
- Here, we present safety data from the primary DB analysis.

Methods

- 523 participants aged 55–80 years with early AD and intermediate tau positron emission tomography (PET) burden were randomised 1:1:1 to posdinemab 1000 mg, posdinemab 3000 mg, or placebo, administered intravenously every 4 weeks. Safety and tolerability were evaluated as a secondary objective.
- Safety and tolerability were assessed by treatment-emergent adverse events (TEAEs), vital signs, physical examinations, laboratory evaluations, electrocardiograms (ECGs), suicidal ideation and behaviour assessment (C-SSRS), and brain magnetic resonance imaging (MRI).
- An Independent Data Monitoring Committee was established to ensure the continuing safety of the participants enrolled in this study while the study sponsor was blinded.
- Cases of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥3x upper limit of normal (ULN) were evaluated with additional hepatic laboratory tests (e.g. trending ALT, AST, alkaline phosphatase [ALP], bilirubin, gamma-glutamyl transferase [GGT], glutamate dehydrogenase [GLDH] until improvement), along with international normalised ratio (INR), C-reactive protein (CRP), and ferritin, where feasible. However, most of this was implemented after several cases were identified, so these data are not available for most retrospective cases.
- An independent blinded Hepatic Adjudication Committee (HAC) reviewed these cases to determine the likelihood of drug-induced liver injury (DILI).
- Comprehensive mechanistic investigations were undertaken, where feasible, to evaluate potential etiologies of these hepatic findings.
  - **Viral serology:** Hepatitis A IgM antibody; HBsAg and total HBcAb (IgG and IgM antibodies) with reflex to HBV-DNA if positive; Hepatitis C IgG antibody with reflex to HCV-RNA if positive; cytomegalovirus IgM; Epstein-Barr virus capsid antigen IgM; Hepatitis E IgM; and HSV-1 and -2 IgG.
  - **Autoimmune antibodies:** Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins.
  - **Liver biopsy immunopathology:** Liver biopsy was performed if clinically indicated in consultation with local hepatology specialist. In addition to standard histopathology by a hepatopathologist, exploratory analyses (e.g., immunofluorescence stains for cluster of differentiation [CD]4, CD8, CD3, CD20, CD138, Granzyme B, and FoxP3) to further characterize the immune cell infiltrate were performed.
  - **Pharmacokinetics and immunogenicity (PK/ADA):** The potential influence of the systemic posdinemab exposure (steady state AUC_{τ}, C_{max}, and C_{trough}) or treatment-emergent anti-drug antibody (ADA) status on the probability to have an ALT and/or AST ≥3xULN event was investigated using binomial logistic regression.

Results

- Out of 523 randomised participants, 521 participants were included in the DB safety analysis set.
- Overall rates of TEAEs (including deaths and serious TEAEs) were similar across posdinemab and placebo groups.[1]
- By system organ class, rates of TEAEs with at least 10% incidence were similar across posdinemab and placebo groups (**Table 1**).
- Infusion-related reactions were uncommon; none were serious AEs and all were mild or moderate in severity.[1]
- MRI safety findings (central read) for cerebral amyloid angiopathy-related imaging markers (microhaemorrhages, superficial siderosis, and vasogenic oedema) and white matter changes were similar across groups.[1]

Table 1. Participants With Treatment-emergent Adverse Events with Incidence ≥10% in any Treatment Group by System Organ Class and Preferred Term

System Organ Class Preferred Term, n (%)	JNJ-63733657 1000 mg N=171	JNJ-63733657 3000 mg N=175	Placebo N=175
Participants with ≥1 TEAE	158 (92.4%)	163 (93.1%)	165 (94.3%)
Infections and infestations	92 (53.8%)	90 (51.4%)	106 (60.6%)
COVID-19	44 (25.7%)	38 (21.7%)	35 (20.0%)
Urinary tract infection	14 (8.2%)	20 (11.4%)	15 (8.6%)
Nasopharyngitis	11 (6.4%)	17 (9.7%)	22 (12.6%)
Nervous system disorders	64 (37.4%)	82 (46.9%)	71 (40.6%)
Headache	21 (12.3%)	22 (12.6%)	18 (10.3%)
Injury, poisoning and procedural complications	66 (38.6%)	61 (34.9%)	64 (36.6%)
Fall	24 (14.0%)	26 (14.9%)	33 (18.9%)
Musculoskeletal and connective tissue disorders	52 (30.4%)	60 (34.3%)	70 (40.0%)
Back pain	13 (7.6%)	19 (10.9%)	19 (10.9%)
Arthralgia	13 (7.6%)	12 (6.9%)	20 (11.4%)
Investigations	43 (25.1%)	52 (29.7%)	42 (24.0%)
AST increased	18 (10.5%)	21 (12.0%)	19 (10.9%)

Note: Participants are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA version 28.0.
AST=Aspartate aminotransferase; COVID-19=Coronavirus disease 2019; MedDRA=Medical dictionary for regulatory activities; TEAE=Treatment-emergent adverse event.

Hepatic safety

- Review of unblinded data at the primary DB analysis revealed that most cases of ALT or AST ≥3xULN were on posdinemab treatment (**Table 2**).

Table 2. Number of Participants With Elevations in Liver Enzyme Laboratory Values

Laboratory Test	JNJ-63733657 1000 mg N=171	JNJ-63733657 3000 mg N=175	Placebo N=175
ALT (Enzyme U/L), N	**170**	**175**	**174**
>ULN to <3xULN	29 (17.1%)	22 (12.6%)	23 (13.2%)
≥3xULN to ≤5xULN	1 (0.6%)	2 (1.1%)	1 (0.6%)
>5xULN	3 (1.8%)	5 (2.9%)	0
AST (Enzyme U/L), N	**170**	**175**	**174**
>ULN to <3xULN	24 (14.1%)	40 (22.9%)	30 (17.2%)
≥3xULN to ≤5xULN	6 (3.5%)	2 (1.1%)	1 (0.6%)
>5xULN	1 (0.6%)	4 (2.3%)	0
Liver enzyme criteria, N	**171**	**175**	**175**
ALT or AST >5xULN for more than 2 weeks	3 (1.8%)	5 (2.9%)	0
ALT or AST ≥3xULN and TBL >2xULN[a]	0	1 (0.6%)	0
ALT or AST ≥3xULN	8 (4.7%)	8 (4.6%)	1 (0.6%)
ALT >1.5xULN	14 (8.2%)	16 (9.1%)	8 (4.6%)
ALT or AST >ULN	45 (26.3%)	54 (30.9%)	41 (23.4%)

Note: For individual lab tests, N: number of participants with at least 1 postbaseline value for the specified lab test. For liver enzyme criteria, N: number of participants in the safety analysis set. Note: Including both central laboratory data and local laboratory data.
[a]Treatment-emergent TBL elevation occurring at the same time as the ALT or AST elevation.
Per protocol, a confirmed Hy's Law case is defined by the occurrence of ALT and/or AST ≥3×ULN together with TBL ≥2×ULN, and additionally, it requires that after a comprehensive work-up no alternative explanation has been identified.
ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; INR=Prothrombin international normalised ratio; TBL=Total Bilirubin; ULN=Upper limit of normal.

- Of 17 participants with ALT or AST ≥3×ULN during the DB period, 16 were on posdinemab treatment (1000 mg and 3000 mg posdinemab, n=8 each). Cases are briefly described in **Table 3**.
- One participant had suspected unexpected serious adverse reaction (SUSAR) of DILI that met the definition for a confirmed Hy's Law case. (3000 mg posdinemab, n=1).
- Two participants had SUSARs of suspected DILI (1000 mg and 3000 mg posdinemab, n=1 each).
- More stringent requirements for pre-dose liver function monitoring and prespecified hepatic thresholds for treatment interruption and discontinuation were implemented upon identification of SUSARs.
- There were no other serious or severe liver events in the DB period once increased monitoring was employed.

Other safety

- Besides with the exception of hepatic enzyme elevations, no safety signals were observed for clinically relevant abnormalities in other clinical laboratory evaluations, vital signs, physical examinations, C-SSRS or ECG.

Analysis of Cases of ALT or AST ≥3×ULN

Table 3. Summary of Cases With ALT or AST ≥3×ULN

Characteristic	Value
Participants with ALT or AST ≥3xULN on posdinemab in DB period	N=16
Sex	Female: N=10; Male: N=6
Age	Range 56–80 years old
Time from first dose to onset of ALT or AST ≥3xULN	≤26 weeks: N=11; ~9–21 months: N=5
Posdinemab dose	1000 mg: N=8; 3000 mg: N=8
Symptomatic at time of ALT or AST ≥3xULN	Yes: N=2[a]; No: N=14
Peak ALT or AST levels	ALT or AST ≥10×ULN: N=5 (including the SUSAR of DILI and 2 SUSARS of suspected DILI); Maximum ALT ≈44×ULN (SUSAR of DILI)
Hepatic SUSARs	SUSARs: N=3; Non-SUSARs: N=13
Dechallenge[b]	Positive: N=11; Unknown: N=1; Not applicable: N=4
Rechallenge[c]	Positive: N=2 (N=1 borderline; N=1 positive, then negative after normalisation); Negative: N=3; Not applicable: N=11
Outcome at last follow-up in DB period	Resolved/improved (ALT and AST <3×ULN): N=16
Treatment for hepatic event	N=1 treated with corticosteroids (SUSAR of DILI)
Probability of DILI[d]	At least possible DILI: N=9; Unlikely DILI: N=7

[a]**Qualitative symptoms of 2 patients are:** N=1 (SUSAR of DILI): Nausea, vomiting, and dark urine; N=1 (non-SUSAR case): Systemic symptoms of fatigue, myalgia, arthralgia, rash, and back pain.
[b]**Dechallenge:** Temporary or permanent discontinuation of the IP to assess whether the ALT/AST elevation improves or resolves. **Positive (dechallenge):** Improvement or resolution of the ALT/AST elevation following interruption of the IP. **Negative (dechallenge):** No improvement or continued worsening of the ALT/AST elevation despite interruption of the IP. **Unknown (dechallenge):** Outcome cannot be assessed because the participant discontinued follow-up after IP interruption and no subsequent laboratory data were available. **Not applicable (dechallenge):** Dechallenge not evaluable because IP dosing was not interrupted during the ALT/AST elevation.
[c]**Rechallenge:** Reintroduction of the IP after dechallenge to evaluate whether the ALT/AST elevation recurs or worsens upon re-exposure.
[d]**At least possible DILI:** Cases assessed by the HAC as probable or possible DILI.
ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; DB=Double-blind; DILI=Drug-Induced liver injury; HAC=Hepatic adjudication committee; IP=Investigational product; SUSAR=Suspected unexpected serious adverse reaction; ULN=Upper limit of normal.

Results of mechanistic investigations were notable for the following:

- **PK analysis:** Absence of a clear dose- or exposure-response relationship.
- **Immunogenicity:** Only 1 case with ALT or AST ≥3×ULN was positive for treatment-emergent ADA (n=22 treatment-emergent ADA across treatment groups), suggesting no association between ADA and hepatic enzyme elevation.
- **Viral serology and autoimmune antibodies:** No evidence for common alternative etiologies. However, many cases of ALT or AST ≥3×ULN were identified retrospectively, limiting sample availability for testing.
- **Liver biopsy (conducted for SUSAR of DILI):** Liver biopsy evaluation and immunophenotyping demonstrated predominantly $CD8^+$ T-cell inflammatory infiltrate (of which some were granzyme B^+) and no clear presence of $CD138^+$ plasma cells (largely excluding autoimmune hepatitis). The findings were supportive of an adaptive, T-cell mediated response and provided supportive evidence for cytotoxic immune-mediated DILI in this participant.

Conclusions

- Posdinemab was generally safe and well tolerated but was associated with increased risk of hepatic enzyme elevations (ALT or AST ≥3×ULN).
- Consistent with available information for other anti-tau monoclonal antibodies, posdinemab was not associated with increased risk of cerebral amyloid angiopathy-related sequelae.
- Mechanistic investigations of hepatic enzyme elevations suggest that etiology was most consistent with an idiosyncratic, adaptive immune-mediated process.
- Systematic hepatic monitoring, independent adjudication, and mechanistic triangulation remain essential when hepatic signals arise during biologic development.

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Alzheimer's Disease

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References:

1. Cohen S, et al. Results from the Phase 2b Autonomy Trial of Anti-p-tau Monoclonal Antibody Posdinemab for Early Alzheimer's Disease. Presented at: Alzheimer's and Parkinson's Disease Conference (ADPD); March 17–21, 2026; Copenhagen, Denmark.