Poster No. 2144

Impact of Immunogenicity on Clinical Outcomes in Postmenopausal Women with Osteoporosis: Results from a Randomized Controlled Phase 3 Study to Compare CT-P41 (Proposed Denosumab Biosimilar) and Reference Denosumab

Jean-Yves Reginster[1], Stuart L. Silverman[2], Edward Czerwinski[3], Przemyslaw Borowy[4], Tomasz Budlewski[5], Joanna Kwiatek[6], Svitlana Postol[7], Airi Poder[8], Jerzy Supronik[9], Sung Hyun Kim[10], Jee Hye Suh[10], Go Eun Yang[10], Noo Ri Han[10], Na Hyun Kim[10], Seo Hee Bae[10]

1 College of Science, King Saud University, Riyadh, Saudi Arabia, 2 Cedars Sinai Medical Center, Beverly Hills, United States, 3 Krakow Medical Centre, Kraków, Poland, 4 Krakowskie Centrum Medyczne, Kraków, Poland, 5 Department of Rheumatology, Medical University of Lodz, Lodz, Poland, 6 Centrum Medyczne Poznan - PRATIA, Skórzewo, Poland, 7 Medical Center of Medbud - Clinic LLC, Kyiv, Ukraine, 8 Clinical Research Centre Ltd, Tartu,Estonia, 9 Osteo-Medic s.c., Bialystok, Poland, 10 Celltrion, Inc., Incheon, Republic of Korea (South).

BACKGROUND & OBJECTIVE

- CT-P41 has been developed as a proposed biosimilar to the reference product denosumab (DEN), a fully human monoclonal antibody that binds to the cytokine receptor activator of NF-κb ligand (RANKL).
- The < 1% of patients treated with DEN for up to 5 years had a positive anti-drug antibody (ADA) result, as detected by an electrochemiluminescent (ECL) bridging immunoassay (DEN Prescribing Information 2024).
- In this study, most patients had at least 1 positive ADA result after treatment due to the sensitivity of the assay (in total, 97.9% and 93.3% of patients in Treatment Periods [TPs] I and II, respectively, had positive results)
- However, most of the ADA titer values were low (≤300), and none of the patients had a positive neutralizing antibody result.
- Further impact analysis was performed on the study data to explore any correlation between immunogenicity and clinical outcomes in postmenopausal women with osteoporosis (PMO).

METHOD

- The ADA against denosumab (CT-P41 and DEN) was detected using a Meso Scale Discovery (MSD) – ECL assay which can detect ADA at low levels in all samples regardless of residual serum drug (25 ng/mL of ADA in the presence of 50 μg/mL of CT-P41 and DEN in PMO).
- It indicates that the ADA assay has adequate sensitivity for detecting clinically meaningful ADA levels.
- To investigate the impact of ADA on pharmacokinetic (PK), efficacy, and safety, the ADA status and titer were categorized into 5 groups; ADA negative, ADA positive, ADA titer=100, ADA titer=300, and ADA titer≥900 (900, 2700 8100).

RESULTS

PHARMACOKINETICS

- Predose serum concentrations of denosumab:
  - At Week 2 (the timepoint closest to when the maximum serum concentration of denosumab was observed after the first study drug administration)
    : ADA negative group>ADA positive and titer groups
  - At Week 26, Week 52 (the same timepoint with the primary efficacy endpoint), and Week 78 (end of study visit)
    : ADA negative group<ADA positive and titer groups
  - Both ADA status and ADA titer had no discernible impact on PK (**Figure 1**).

EFFICACY

- % change from baseline in lumbar spine bone mineral density (LS-BMD):
  - At Week 52: ADA negative group<ADA positive and titer groups
  - At Week 78: Similar between the 2 ADA status groups
  - No apparent trend were observed in TPs I and II (**Figure 2**).

Figure 1. Boxplot of Serum Concentration of Denosumab (μg/mL) by ADA Status and Titer (PK Set and PK-TP II Subset)

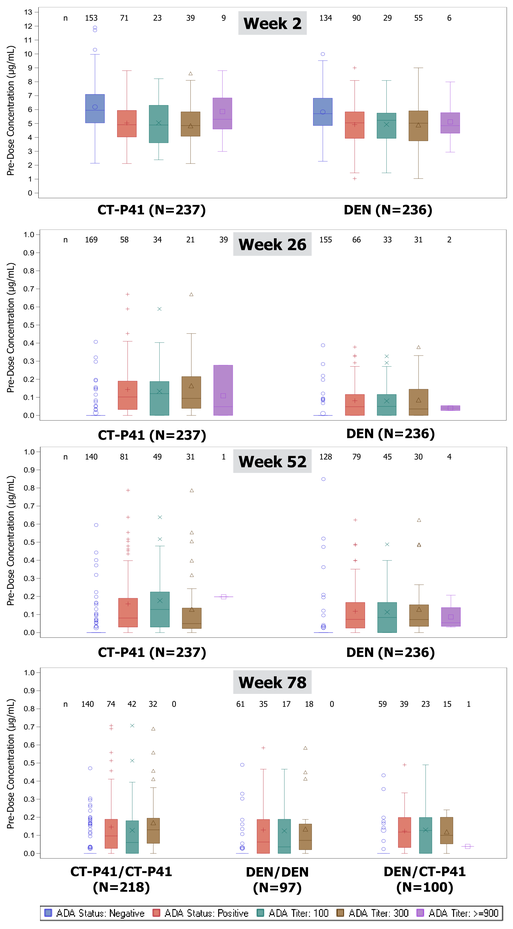
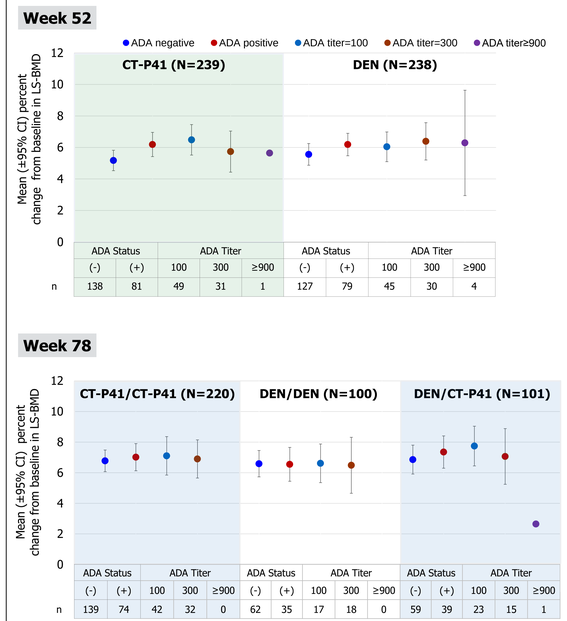


Figure 2. Mean (±95%CI) Percent Change from Baseline in BMD for Lumbar Spine by ADA Status and Titer (FAS and FAS-TP II Subset)



Note: 95% CI of the mean in each treatment group was calculated based on normal distribution.
Abbreviation: ADA, Anti-drug antibody; CI, confidence interval; FAS, full analysis set; LS-BMD, Lumbar spine bone mineral density.

SAFETY

- There was no clear correlation between the incidence of treatment-emergent adverse events (TEAEs) and ADA in all ADA positive and titer groups during TPs I and II.
- The incidences of TEAEs were comparable between the treatment groups across the ADA status and titer groups (**Table 1**).

Table 1. Summary of Treatment-emergent Adverse Events by ADA Status and Titer (Safety Set and Safety-TP II Subset)

Adverse Event	TP I (Week 0 ~ 52)		TP II (Week 52 ~78)		
	CT-P41 (N=239)	DEN (N=238)	CT-P41/CT-P41 (N=220)	DEN/DEN (N=100)	DEN/CT-P41 (N=101)
Number of patients with ≥ 1 TEAE, n/N (%)					
ADA Negative	102/140 (72.9)	92/128 (71.9)	73/140 (52.1)	26/62 (41.9)	29/59 (49.2)
ADA Positive	64/81 (79.0)	53/79 (67.1)	37/74 (50.0)	13/35 (37.1)	26/39 (66.7)
ADA Titer = 100	38/49 (77.6)	30/45 (66.7)	18/42 (42.9)	5/17 (29.4)	15/23 (65.2)
ADA Titer = 300	25/31 (80.6)	21/30 (70.0)	19/32 (59.4)	8/18 (44.4)	10/15 (66.7)
ADA Titer ≥ 900	1/1 (100)	2/4 (50.0)	0/0	0/0	1/1 (100)
Number of patients with ≥ 1 Grade 3 or higher TEAE, n/N (%)					
ADA Negative	5/140 (3.6)	10/128 (7.8)	4/140 (2.9)	4/62 (6.5)	0/59 (0.0)
ADA Positive	2/81 (2.5)	3/79 (3.8)	2/74 (2.7)	0/35 (0.0)	1/39 (2.6)
ADA Titer = 100	1/49 (2.0)	1/45 (2.2)	1/42 (2.4)	0/17 (0.0)	1/23 (4.3)
ADA Titer = 300	1/31 (3.2)	1/30 (3.3)	1/32 (3.1)	0/18 (0.0)	0/15 (0.0)
ADA Titer ≥ 900	0/1 (0)	1/4 (25.0)	0/0	0/0	0/1 (0)
Number of patients with ≥ 1 TESAE, n/N (%)					
ADA Negative	4/140 (2.9)	4/128 (3.1)	5/140 (3.6)	3/62 (4.8)	0/59 (0)
ADA Positive	1/81 (1.2)	4/79 (5.1)	2/74 (2.7)	0/35 (0)	0/39 (0)
ADA Titer = 100	1/49 (2.0)	0/45 (0)	1/42 (2.4)	0/17 (0)	0/23 (0)
ADA Titer = 300	0/31 (0.0)	3/30 (10.0)	1/32 (3.1)	0/18 (0)	0/15 (0)
ADA Titer ≥ 900	0/1 (0.0)	1/4 (25.0)	0/0	0/0	0/1 (0)
Number of patients with ≥ 1 TEAE classified as drug-related hypersensitivity/allergic reactions, n/N (%)					
ADA Negative	0/140 (0.0)	1/128 (0.8)	1/140 (0.7)	0/62 (0)	0/59 (0)
ADA Positive	0/81 (0.0)	1/79 (1.3)	0/74 (0)	0/35 (0)	0/39 (0)
ADA Titer = 100	0/49 (0)	0/45 (0.0)	0/42 (0)	0/17 (0)	0/23 (0)
ADA Titer = 300	0/31 (0)	1/30 (3.3)	0/32 (0)	0/18 (0)	0/15 (0)
ADA Titer ≥ 900	0/1 (0)	0/4 (0)	0/0	0/0	0/1 (0)

Note: ADA negative and positive groups were considered at Week 52 for TP I and Week 78 for TP II; ADA titer subsets of 100, 300, and ≥ 900 were considered at Week 52 for TP I and Week 78 for TP II. Percentages are calculated by using the number of patients in each ADA groups as denominator.
Abbreviations: ADA, anti-drug antibody; N, number of patients in each treatment group; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; TP, Treatment Period.

CONCLUSION

- The results showed that ADA formation had no discernible impact on PK, efficacy, and safety of both CT-P41 and DEN.
- Despite the high ADA incidence compared to the DEN historical studies, it can be concluded that ADA to CT-P41 and DEN has no clinical impact considering the high sensitivity and specificity of the assay used and further evaluation of immunogenicity impact.

Disclosures: Jean-Yves Reginster has received consulting fees from Celltrion, Inc. Stuart L. Silverman has received grant/research support from Amgen, Radius, and Tissuegene, and received consulting fees from Celltrion, Inc. Edward Czerwinski has received consulting fees, investigator fee, and honoraria from Amgen and received grant/research support from Celltrion, Inc. Przemyslaw Borowy has received grant/research support from Celltrion, Inc. Tomasz Budlewski has received grant/research support from Celltrion, Inc. Joanna Kwiatek has received grant/research support from Celltrion, Inc. Svitlana Postol has received grant/research support from Celltrion, Inc. Airi Põder has received grant/research support from Celltrion, Inc. Jerzy Supronik has received grant/research support from Celltrion, Inc. Sung Hyun Kim, Jee Hye Suh, Go Eun Yang, Noo Ri Han, Na Hyun Kim, and Seo Hee Bae are employees of Celltrion, Inc.