

# Real-life Tolerability and Effectiveness of Adalimumab Biosimilar in Ankylosing Spondylitis: the Adalimumab biosimilar Patient Registry Data

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# Background /Objective & Methods

- Adalimumab is a well-established anti-tumor necrosis factor therapy for patients with ankylosing spondylitis (AS). An indigenously developed biosimilar adalimumab (bADA) (ZRC-3197; Exemptia) is approved for prescribing in India.
- This study assessed the effectiveness and tolerability of this bADA in real-life Indian patients with AS from the Adalimumab Biosimilar Patient Registry (ASPIRE)
- ASPIRE is post-marketing surveillance registry evaluating the real-life clinical use of this ADA in AS patients in India. The study is also reflective of the real-time prescription patterns and clinical practice of managing such patients in India.
- For this report, data available until 24 weeks of bADA treatment for patients with AS who were included in the registry were evaluated

# Background /Objective & Methods



- The Adalimumab Biosimilar Patient Registry (ASPIRE) is an ongoing, multicenter, non-interventional, open-label, and observational data collection registry (ISRCTN: 16838474) to evaluate real-life patients with autoimmune rheumatic conditions who are treated with bADA (Exemptia).
- The registry was initiated in November 2015 across multiple centers in India by Cadila Healthcare Ltd. as part of their post marketing regulatory obligations.
- Independent ethics committee approval was sought for the data analysis and publication.
- Eligible patients diagnosed with AS, who had voluntarily consented to receive bADA as their preferred biologic at the participating centers were included in the registry. All patients tested negative for tuberculosis (Mantoux and interferon gamma release assay), hepatitis B and C, and human immunodeficiency virus tests and had normal blood counts, normal liver and renal functions, and an elevated erythrocyte sedimentation rate and C-reactive protein level.

# Background /Objective & Methods



- Patients had received standard nonsteroidal anti-inflammatory drug (NSAID) treatment for at least 3 months before biologic therapy as per routine clinical care.
- Patients received 40 mg of bADA subcutaneously every other week along with concomitant, stable doses of methotrexate (MTX) or other disease-modifying antirheumatic drugs (DMARDs) and/or NSAIDs as per the treating physician's discretion.
- All data available up to 24 to 28 weeks after the start of bADA therapy for all enrolled patients was taken.
- Key efficacy outcomes included Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), visual analogue scale (VAS) score, and global efficacy assessment ratings by the physician and patient using a 4-point Likert scale.
- Safety and tolerability data were based on adverse events recorded by the physician or patient.

# Result

- As of the cutoff date for the data analysis (May 2017), 502 patients with various autoimmune inflammatory disorders, such as RA (149 patients), juvenile idiopathic arthritis (JIA) (26 patients), psoriatic arthritis (PsA) (19 patients), and AS (308 patients), were included in the registry.
- Data for 308 patients with AS were considered for analysis and are reported here.
- Data were collected for all patients only as available from their regular clinical visits that matched their feasibility and the physician's advice.

# Result

- In some cases, bADA therapy was discontinued as per the treating physician's discretion, whereas some patients missed their visit or had a delayed follow-up not coinciding with the data collection schedule for the study, and some patients did not undergo all clinical and diagnostic evaluations as anticipated on their visits because of a center-specific follow-up approach. Hence, not all data and outcome measures were completely reported for each patient who entered the registry at the end of 24 weeks.
- As a result of this, complete data available for 100 odd patients were evaluated for efficacy outcome analysis.
- Overall global efficacy and global safety assessments reporting at 24 weeks was performed for 250 odd patients and reported.

# Result

- The median age for the group was 35.0 (range 17-68) years, and the BMI was 25.35 (range 12.60-30.00); 19% of the patients were women.
- The median duration of disease was 5.2 (range 0.3-26) years.
- About 29% of patients received concomitant DMARDs, mostly MTX and sulphasalazine.
- Comorbid conditions included uveitis, psoriasis, and vitiligo in 5% of patients. The baseline VAS score ranged from 4 to 10, and the mean BASDAI score was  $6.3 \pm 1.39$ .

# Table 1. Baseline demographic and clinical characteristics of patients with AS

Patient Characteristic	AS (n = 308)	Patients Analyzable for Disease Outcome Scores (n = 107)
Sex (male female), %	81:19	82:18
Age, y	36.5 ± 10.58	37.8 ± 9.7
BMI, kg/m <sup>2</sup>	25.0 ± 4.03	25.7 ± 3.7
ESR, mm/hour	98.0 ± 18.09	103.98 ± 10.6
CRP, mg/L	41.4 ± 55.63	38.3 ± 26.4
Proportion of patients with elevated CRP levels	228 (74%)	77 (72%)
Duration of disease, y	5.75 ± 3.7	4.60 ± 1.6
DMARDs (yes)	177 (57.47%)	8 (5.5%)
VAS (pain)	8.3 ± 0.85	8.57 ± 0.6
BASDAI	6.3 ± 1.39	6.2 ± 1.54

Abbreviation: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; VAS, visual analogue scale.

<sup>a</sup>Data are presented as mean ± SD or number of patients (percentage) unless otherwise indicated.



# Result

- AS disease outcome measures i.e. Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] and visual analogue scale [VAS] score showed a gradual and significant decrease ( $p < 0.0001$  for all) in patients after 24 weeks of bADA therapy.
- BASDAI score was lower than 4 in about 94% of patients after 24 weeks of therapy, and 95% of patients achieved BASDAI50 response.
- The global assessment for efficacy by physicians and patients was “excellent to good” in 98% of patients ( $n = 250$ ).
- The therapy was tolerated well, and there were no new unexpected adverse reactions with the biosimilars use during this study.

# Table 2. Summary of AS disease-outcome scores at 6 months of biosimilar adalimumab therapy in patients with AS



**Summary of AS disease-outcome scores at 6 months of biosimilar adalimumab therapy in patients with AS**

Parameters	n <sup>#</sup>	Baseline, Mean±SD, Median (Range)	6mo, Mean±, Median (Range)	Change From Baseline, Mean ±SD <sup>b</sup>	
				Change	% Change
BASDAI	107	6.2±1.54, 6.85 (1.15-8.25)	2.1±0.64, 2.05 (0.20-4.60)	-4.8±0.85	-9.37±9.30
VAS (Pain)	101	8.3±0.98, 8.0 (4-9)	2.4±0.65, 2 (2-5)	-6.2±0.81	-72.3±7.60

Abbreviation: AS, ankylosing spondylitis; BASDAI, Bath ankylosing spondylitis disease activity index; VAS, Visual analogue scale  
n= number of evaluable patients with data recorded  
p= <0.001, calculated using the Wilcoxon signed rank test

# Result

- In general, common adverse events such as headache, nausea, fatigue, arthralgia, and rashes were reported by 10% to 15% of the patients, whereas the infection rate was 5% to 10%. Events of tuberculosis were reported in 2% of the population, and there were no injection-site reactions received in the registry database.
- Therapy was discontinued in 9% of patients because of adverse events and in 2% of patients because of lack of efficacy.
- The therapy was tolerated well, and there were no new unexpected adverse reactions with the biosimilars use during this study.
- The global tolerability assessment ratings were good to excellent for 98% to 100% of patients (n = 251).

Table 3. Summary of overall effectiveness and tolerability of biosimilar adalimumab in patients with AS at 6 months

Rating	Overall Assessment of Tolerability		Overall Assessment of Efficacy	
	Physician's Global Assessment (n = 251)	Patient's Global Assessment (n = 251)	Physician's Global Assessment (n = 250)	Patient's Global Assessment (n = 250)
Excellent	170 (67.73)	177 (70.52)	171 (68.40)	201 (80.40)
Good	81 (32.27)	72 (28.69)	75 (30.00)	43 (17.20)
Fair	0	2 (0.80)	4 (1.60)	5 (2.00)
Poor	0	0	0	1 (0.40)

Abbreviation: AS, ankylosing spondylitis.

<sup>a</sup>Data are presented as number of patients in the specified category (percentage).

<sup>b</sup>n = total number of evaluable patients with data recorded.

# Conclusion

- The overall global assessment for efficacy and tolerability was ‘good’ to ‘excellent’ for a majority of the patients ( $\geq 98\%$ ), as rated by physicians as well as patients.

# Abridged Prescribing Information

**COMPOSITION:** Exemptia™ (Adalimumab) 40 mg /0.8 mL single use pre filled syringe and 20mg /0.4 mL single use pre filled syringe **DESCRIPTION:** EXEMPTIATM (Adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF- $\alpha$ ). EXEMPTIATM is supplied as a sterile, preservative-free solution of Adalimumab for subcutaneous administration. The solution of EXEMPTIATM is clear and colorless. **MECHANISM OF ACTION:** Adalimumab binds specifically to TNF- $\alpha$  and blocks its interaction with the p55 and p75 cell surface TNF- $\alpha$  receptors. Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement. Elevated levels of TNF- $\alpha$  is found in the synovial fluid of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. **INDICATIONS & DOSAGE:** Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis: The recommended dose of EXEMPTIATM for adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) is 40 mg subcutaneously administered every other week. Methotrexate (MTX), other non-biologic DMARDs, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be continued during treatment with EXEMPTIATM. Juvenile Idiopathic Arthritis: Exemptia™ dosing in JIA is based on weight; for 10 kg (22 lbs) to <15 kg (33 lbs): 10 mg s.c. every other week. For 15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg s.c. every other week and for  $\geq$  30 kg (66 lbs): 40 mg s.c. every other week. Plaque Psoriasis or Non-Infectious Uveitis: Initial dose of 80 mg, followed by 40 mg every other week starting from week one after initial dose. Hidradenitis Suppurativa: 160 mg (Day 1) (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every week. Adult Crohn's Disease and Ulcerative Colitis: Initial dose (Day 1): 160 mg s.c. (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days). Second dose two weeks later (Day 15): 80 mg. Two weeks later (Day 29): Begin a maintenance dose of 40 mg s.c. every other week. For patients with Ulcerative Colitis only: Only continue EXEMPTIATM in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy. Pediatric Crohn's Disease: For weight 17 kg (37 lbs) to < 40 kg (88 lbs): Initial dose (Day 1): 80 mg s.c. (two 40 mg injections in one day). Second dose two weeks later (Day 15): 40 mg s.c.. Two weeks later (Day 29): Begin a maintenance dose of 20 mg s.c. every other week. For  $\geq$  40 kg (88 lbs): Initial dose (Day 1): 160 mg s.c. (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days). Second dose two weeks later (Day 15): 80 mg s.c. (two 40 mg injections in one day). Two weeks later (Day 29): Begin a maintenance dose of 40 mg s.c. every other week. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients, Moderate to severe heart failure, Active tuberculosis or other severe infections such as sepsis and opportunistic infections. **SPECIAL WARNINGS AND PRECAUTIONS:** Serious and fungal infections: Do not start EXEMPTIATM during an active infection. If an infection develops, monitor carefully, and stop EXEMPTIATM if infection becomes serious • Anaphylaxis or serious allergic reactions may occur • Hepatitis B virus reactivation: Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop EXEMPTIATM and begin antiviral therapy • Demyelinating disease: Exacerbation or new onset, may occur • Heart failure: Worsening or new onset, may occur • Lupus-like syndrome: Stop EXEMPTIATM if syndrome develops **USE IN PREGNANCY AND LACTATION:** Pregnancy Category B: Adequate and well controlled studies with EXEMPTIATM have not been conducted in pregnant women. Adalimumab is an IgG1 monoclonal antibody and IgG1 is actively transferred across the placenta during the third trimester of pregnancy. Lactation: No data is available on the absorption of adalimumab from breast milk in newborn or preterm infants. Caution should be exercised when EXEMPTIATM is administered to a nursing woman. **DRUG INTERACTION** Biological Products- Concomitant administration of EXEMPTIATM with other biologic DMARDs (e.g., Anakinra and Abatacept) or other TNF blockers is not recommended • Live Vaccines- Avoid the use of live vaccines with EXEMPTIATM. • Cytochrome P450 Substrates- The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNF $\alpha$ , IL-6) during chronic inflammation. Upon initiation or discontinuation of EXEMPTIATM in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., Warfarin) or drug concentration (e.g., Cyclosporine or Theophylline) is recommended and the individual dose of the drug product may be adjusted as needed. **UNDESIRE EFFECTS:** The most serious adverse reactions include the following • Serious Infections- Tuberculosis and Opportunistic Infections • Malignancies. The Clinical experience has reported Upper Respiratory Tract Infection (URTI), Increased creatine phosphokinase, Headache, Rash, Sinusitis, Nausea, Urinary Tract Infection (UTI), Abdominal pain, Flulike syndrome, Hyperlipidemia, Back pain, Hypercholesterolemia, Hematuria, Hypertension, Increased alkaline phosphatase as common side effects. **STORAGE CONDITION:** Store between + 2°C and + 8 °C, in the carton to protect from light. Do not freeze Exemptia™. Do not use Exemptia™ if frozen, even if it has been thawed. Keep out of reach of children. **PRESENTATION:** a) Injection: 40 mg/0.8 mL in a single-use prefilled syringe b) Injection: 20 mg/0.4 mL in a single-use prefilled syringe.

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Please refer to the full Prescribing Information before starting EXEMPTIA™.

**Please consult full Prescribing Information before prescribing.**

**Zydus Cadila does not recommend the use of any product in any different manner than as described in the prescribing information.**

**Further information is available on request from:**

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Thank you

