AB0416

A COMPARATIVE STUDY TO ASSESS THE EFFICACY, SAFETY, AND IMMUNOGENICITY OF YLB113 AND ETANERCEPT REFERENCE PRODUCT FOR THE TREATMENT OF PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS

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Background: YLB113 is an investigational biosimilar of the reference product etanercept (ETN), being developed for the treatment of patients with moderate-to-severe rheumatoid arthritis (RA) and other approved indications of the reference product ETN.

Objectives: The phase 3 study of YLB113 was conducted in Europe, Japan, and India across more than 100 rheumatology clinics to compare efficacy, safety, and immunogenicity of YLB113 with ETN in patients with RA.

Methods: A total of 528 patients with moderate-to-severe RA receiving concomitant treatment with methotrexate were randomized to receive a once-weekly dose of 50 mg of subcutaneously administered YLB113 or ETN. The primary end point was the ACR20 response rate at Week 24, with equivalence confirmed if the 95% confidence interval (CI) was within the range of -15% to 15%. Other efficacy end points, such as DAS28 with safety and immunogenicity end points, were assessed periodically up to Week 52.

Results: The ACR20 response rate at Week 24 was 81.2% for YLB113 and 86.8% for ETN in the full analysis set, with a treatment difference of -5.6% (95% CI: -11.6, 0.5), which was completely within the predefined equivalence margin of -15% to 15%. The result for sensitivity analysis using the per protocol set population revealed that the proportion of subjects who showed ACR20 response at Week 24 was similar between both treatment groups, at -4.6% (95% CI: -10.1, 0.8). The incidence of treatment-emergent adverse events was comparable between YLB113 and ETN (55.5% vs 65.7%), and the incidence of antidrug antibody development up to Week 24 was in favor of YLB113 (0.8% vs 8.3%).

Conclusion: The present comparative study demonstrated the biosimilarity of YLB113 to ETN on the triad of efficacy, safety, and immunogenicity in patients with moderate-to-severe RA, and thus can be extrapolated to other therapeutic indications approved for ETN. The therapeutic equivalence of YLB113 and ETN in terms of the primary efficacy end point at Week 24 and long-term safety comparability until Week 52 was established with lower immunogenicity.

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AB0416B

EFFICACY OF INFLIXIMAB IN RA PATIENTS BASED ON TOTAL COUNT OF INFUSIONS

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Objectives: To analyze the correlation between cumulative dose of infused infliximab and its' therapeutic and antidestructive effect in patients with rheumatoid arthritis (RA).

Methods: 135 patients with confirmed RA were included into a 1-year study. All patients were assigned to a recommended dosing regimen of 3 mg/kg infliximab as an intravenous induction at 0, 2 and 6 weeks followed by a maintenance 3 mg/kg dose every 8 weeks thereafter. Clinical (TJC and SJC), laboratory (CRP and ESR) parameters and quality of life assessments (HAQ) were performed during each visit.

The score trends of DAS28 disease activity scale were used as the primary criterion for evaluation of infliximab therapeutic effect. Sharp Vander Heijde (SvH) modification scoring method was used for dynamic assessment of erosion and for joint space narrowing. All patients were assessed and examined according to the Protocol before each infusion of infliximab. Therapeutic results were evaluated in all ITT population at Week 54 from the initiation of treatment (including those who did not complete the envisaged course of infliximab).

The patients were divided into three groups:

1. those who received ≤ 4 infusions of infliximab (N=63);
2. those who received 5-7 infusions of infliximab (N=31);
3. those who received ≥ 8 infusions of infliximab (N=41).

Patients from Group 1 received at average 2.5 infusion of infliximab, from Group 2 - 5.8 infusion, and from Group 3 - 8.8 infusion.

Results: High disease activity based on DAS 28 (>5.1) score was documented in the majority of participants at baseline: in 69% - in Group 1, in 86.6% - in Group 2, and in 62.1% - in Group 3. Moderate RA activity (3.2 < DAS 28 $\leq$ 5.1) was found in 31% in Group 1, in 13.4% - in Group 2, and in 37.9% - in Group 3.

All patients demonstrated rapid (already by Week 14 on-treatment) and significant (p<0.05) decrease of RA activity. This reduction remained significant by the end of the study at Week 54 as compared to baseline scores. Meanwhile, by the end of the study the mean DAS 28 score in Group 1 was significantly higher compared to Groups 2 and 3. No significant differences were found between Groups 2 and 3 during the FUP.

Similar patterns in RA activity differentiation were identified within individual groups: the highest proportion of pts with high laboratory activity at Week 54 was found in Group 1, receiving ≤ 4 infliximab infusions. The Group 3 showed the highest proportion of patients with low laboratory RA activity at Week 54 (including patients in remission according to DAS 28 criteria) (53.9% compared to 27.3% and 50% in Groups 1 and 2, respectively). Percentages of remissions in Groups 3 and 2 were comparable (28.6% and 23.1%, respectively), while in Group 1 the remission rates were lower (18.2%).

We analyzed the dynamics of total Sharpe score during 54 weeks FUP in all three groups, and found that patients receiving ≤ 4 infliximab infusions demonstrated more significant radiological progression as compared to patients from two other groups.

Conclusion: Low cumulative dose of infliximab can induce a long-lasting clinical effect, but does not significantly inhibit further destruction of joints. There were no significant differences between Groups 2 and 3 in the degree of radiological progression.

Disclosure of Interests: None declared

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AB0416C

THE RESULTS OF THE USE OF TOFACITINIB (TOFA) IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA) IN MOSCOW. ANALYSIS DATA FROM MOSCOW UNIFIED ARTHRITIS REGISTRY(MUAR)

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Background: Moscow Unified Arthritis Registry (MUAR) started at 01 DEC 2012. By 01 DEC 2017, 829 RA patients were included in the register.

Objectives: The aim of the study was to evaluate the effectiveness and treatment survival of TOFA and identify predictors of the effectiveness of TOFA.

Methods: The inclusion criteria were diagnosis of RA, established at any time according to ACR (1987) or ACR/EULAR (2010) criteria; persons receiving or planning to receive targeted therapy for RA; signed informed consent to participate in the study. All episodes of treatment with TOFA in which there was at least 1 visit not earlier than 6 months since the start of the drug were included for efficacy analysis.

Results: Data of 48 patients treated with TOFA were extracted from the registry. Women were 41 (85.4%), mean age was 55.1 ± 12.4 years; age at the disease beginning was 44.3 ± 14.0; 6 (12.5%) of patients were smokers; mean time on TOFA was 552 ± 259 days. One of the independent predictors of achieved DAS28 was sex - 0.49 lower in men (p<0.001). There was no correlation of achieved disease activity with number of previous failures with biologics. Patients seropositive for rheumatoid factor achieved significantly lower activity (p = 0.015). There was also a trend towards lower achieved activity in patients with rheumatoid nodules (p = 0.059).

On the first line of targeted treatment, survival of TOFA was significantly better than Infliximab, Adalimumab and Certolizumab pegol. On the second line - better than Infliximab. On the following lines TOFA was better than Adalimumab, but worse than Etanercept. Due to the fact that most of treatment episodes with TOFA are not completed, the average duration of treatment may be underestimated. There was no significant decrement of retention on therapy after multiple treatment failures (tab.).

Conclusion: The effectiveness and treatment survival of TOFA does not depend on the number of previous failures with biologics; the best results of TOFA can be expected in men and seropositive patients; the presence of rheumatoid nodules can be considered as a special indication for TOFA.

Table. Retention of targeted therapies in patients with rheumatoid arthritis

Drug	The 1-st line of therapy		The 2-nd line of therapy		The 3-d and subsequent lines of therapy	
	Number of cases / completed	Average duration estimate (95% confidence interval)	Number of cases / completed	Average duration estimate (95% confidence interval)	Number of cases / completed	Average duration estimate (95% confidence interval)
Tofacitinib	27/3	64.7 (55.8; 73.5)	27/7	28.5 (22.9; 34.2)	25/4	28.0 (23.5; 32.4)
Abatacept	81/24	109.1 (87.9; 130.3)	73/34	63.4 (43.7; 83.1)	36/18	73.7 (43.5; 103.8)
Adalimumab	166/82	57.1 (47.3; 66.9)*	36/23	44.6 (28.6; 60.6)	16/11	23.6 (12.1; 35.0)*
Certolizumab pegol	39/27	49.8 (31.7; 68.0)*	13/8	22.7 (10.5; 34.9)	5/3	25.8 (5.77; 45.9)
Etanercept	117/43	99.2 (77.5)	53/19	98.8 (73.2; 124.4)	24/13	43.7 (27.1; 60.2)*
Infliximab	129/115	28.1 (22.6; 33.5)*	14/12	11.3 (6.26; 16.2)*	3/2	14.8 (4.25; 25.4)
Rituximab	74/26	78.4 (64.2; 92.7)	41/18	66.1 (46.4; 85.7)	31/11	54.2 (37.8; 70.5)
Tocilizumab	74/27	101.3 (77.6; 125.0)	24/9	59.4 (43.3; 75.5)	20/6	41.2 (31.5; 50.9)
All	707/347	74.7 (66.5; 82.9)	281/130	67.2 (54.3; 81.1)	160/68	69.8 (46.5; 93.2)

* - statistically significant difference with Tofacitinib (log-rank test)

Figure 1

Disclosure of Interests: None declared

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Rheumatoid arthritis – non biologic treatment

AB0417

EFFICACY AND SAFETY OF TOFACITINIB IN PATIENTS WITH RHEUMATOID ARTHRITIS ACCORDING TO DURATION OF PRIOR CSDMARD TREATMENT AND NUMBER OF PRIOR CSDMARDS: A POST HOC ANALYSIS OF PHASE 3 AND PHASE 3B/4 TRIALS

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Background: Tofacitinib is an oral JAK inhibitor for the treatment of rheumatoid arthritis (RA). Previous analyses have reported greater improvements in efficacy outcomes with tofacitinib 5 mg twice daily (BID) ± conventional synthetic DMARDs (csDMARDs) in patients (pts) with early vs established RA.^{1,2}

Objectives: To evaluate the efficacy and safety of tofacitinib in pts with RA, stratified by prior csDMARD treatment duration and number of prior csDMARDs.

Methods: This was a post hoc analysis of pooled data from 4 Phase (P) 3 trials (ORAL Scan [NCT00847613]; ORAL Solo [NCT00814307]; ORAL Sync [NCT00856544]; ORAL Standard [NCT00853385]) and 1 P3b/4 trial

(ORAL Strategy [NCT02187055]) of tofacitinib in pts with RA and an inadequate response to ≥1 DMARD. Pts treated with tofacitinib 5 mg BID as monotherapy or with csDMARDs were included. Outcomes were evaluated according to csDMARD treatment duration (≤1, 1–2, >2 years *y+) and number of csDMARDs (1, 2, 3, ≥4) prior to baseline (BL). Efficacy outcomes assessed at Months (M) 3, 6 and 12 were: change from BL (Δ) in CDAI and HAQ-DI, and rates of CDAI-defined low disease activity (LDA; ≤10) and remission (≤2.8). Safety outcomes, including treatment-emergent adverse events (AEs), serious AEs (SAEs) and AEs of special interest, were evaluated throughout the studies.

Results: In total, 1584 pts were included in the analysis; of these, 27.2% (n=431) had received csDMARDs for ≤1 y, 20.5% (n=325) for 1–2 y, and 52.1% (n=825) for >2 y prior to BL (duration unknown for 3 pts). Roughly half (53.2%, n=842) had received 1 prior csDMARD; 26.4% (n=418), 13.8% (n=219) and 6.6% (n=105) had received 2, 3 and ≥4 prior csDMARDs, respectively. Most pts had previously received MTX (50.8%, n=805) or MTX + other csDMARDs (46.3%, n=733); 2.9% (n=46) received other csDMARDs only. Mean BL CDAI and HAQ-DI scores were similar, irrespective of prior csDMARD treatment duration or number of prior csDMARDs (Table). Generally, up to M12, no trends were observed for ΔCDAI, ΔHAQ-DI or CDAI LDA rates regardless of prior csDMARD treatment duration or number of prior csDMARDs (Table). When CDAI remission rates data were stratified by csDMARD treatment duration, no differences between pt groups were observed at M3 and M6; however, a numerically higher proportion of pts with prior csDMARD treatment duration ≤1 y achieved remission at M12 vs 1–2 y and >2 y pts. Use of fewer prior csDMARDs appeared to be associated with higher remission rates up to M12. Although safety outcomes were similar when data were stratified by prior csDMARD treatment duration, there was generally a trend for increased rates of AEs, SAEs and AEs of special interest (serious infections, herpes zoster and opportunistic infections [excluding TB]) with increasing number of prior csDMARDs (Table).

Conclusion: In this post hoc analysis of pooled data from P3 and P3b/4 trials, no differences in the efficacy or safety of tofacitinib 5 mg BID were observed when pts were stratified by prior csDMARD treatment duration. Although pt numbers were small, use of fewer prior csDMARDs may be associated with improved remission rates and safety outcomes for pts treated with tofacitinib.

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Table. Baseline demographics and disease characteristics, and efficacy and safety outcomes for patients treated with tofacitinib 5 mg BID ± background csDMARDs, by prior csDMARD treatment duration and number of prior csDMARDs

	Prior csDMARD treatment duration			Number of prior csDMARDs			
	≤1 year (N=431)	1-2 years (N=325)	>2 years (N=825)	1 (N=842)	2 (N=418)	3 (N=219)	≥4 (N=105)
Baseline demographics and disease characteristics							
CDAI score, mean (SD)	38.8 (12.8)	37.8 (13.3)	37.7 (12.3)	38.6 (12.4)	37.3 (12.3)	38.6 (12.4)	36.9 (12.7)
HAQ-DI score, mean (SD)	1.5 (0.7)	1.4 (0.6)	1.3 (0.6)	1.5 (0.6)	1.3 (0.7)	1.3 (0.6)	1.3 (0.7)
Efficacy							
ΔCDAI, mean (SD)							
Month 3	-21.4 (13.7)	-21.0 (14.2)	-20.7 (13.2)	-22.3 (13.8)	-19.3 (13.4)	-20.1 (12.6)	-16.9 (12.7)
Month 6	-24.3 (14.1)	-23.7 (14.5)	-23.7 (13.6)	-23.1 (14.2)	-22.4 (13.2)	-23.4 (13.3)	-20.2 (14.3)
Month 12	-27.1 (13.1)	-24.9 (14.6)	-26.3 (13.5)	-27.3 (13.9)	-24.6 (13.2)	-25.9 (13.5)	-23.1 (12.9)
ΔHAQ-DI, mean (SD)							
Month 3	-0.6 (0.7)	-0.5 (0.6)	-0.5 (0.6)	-0.5 (0.6)	-0.5 (0.6)	-0.5 (0.6)	-0.5 (0.5)
Month 6	-0.6 (0.7)	-0.5 (0.6)	-0.5 (0.6)	-0.6 (0.6)	-0.6 (0.6)	-0.6 (0.6)	-0.5 (0.6)
Month 12	-0.7 (0.7)	-0.6 (0.7)	-0.6 (0.6)	-0.7 (0.6)	-0.6 (0.6)	-0.6 (0.6)	-0.6 (0.6)
CDAI-defined LDA (≤10), n (%)							
Month 3	138 (34.0)	95 (31.4)	265 (33.7)	279 (34.8)	139 (33.0)	67 (32.4)	24 (24.5)
Month 6	178 (45.6)	121 (41.4)	346 (45.7)	369 (47.7)	157 (42.0)	81 (40.3)	40 (43.5)
Month 12	168 (58.7)	129 (52.7)	330 (55.8)	352 (56.8)	151 (54.3)	86 (57.0)	38 (52.1)
CDAI-defined remission (≤2.8), n (%)							
Month 3	24 (5.9)	20 (6.6)	45 (5.7)	34 (6.7)	24 (6.1)	10 (4.8)	2 (2.0)
Month 6	46 (11.8)	32 (11.0)	79 (10.4)	92 (11.9)	42 (11.2)	18 (9.0)	6 (6.5)
Month 12	58 (20.3)	37 (15.1)	102 (17.3)	112 (18.1)	51 (18.4)	25 (16.6)	9 (12.3)
Safety							
AEs, n (%)	800 (69.6)	219 (67.4)	532 (64.3)	532 (63.2)	280 (67.0)	163 (74.4)	79 (75.2)
SAEs, n (%)	45 (10.4)	33 (10.2)	85 (10.3)	76 (9.0)	42 (10.0)	27 (12.3)	18 (17.1)
AEs of special interest, IR* (95% CI)							
Serious infections							
	1.14	1.14	1.15	1.09	1.17	0.77	2.26
	(0.39; 1.99)	(0.35; 2.10)	(0.73; 1.70)	(0.62; 1.63)	(0.64; 1.59)	(0.25; 1.80)	(0.97; 4.43)
	[n=12]	[n=10]	[n=24]	[n=19]	[n=14]	[n=3]	[n=8]
	0.77	1.17	1.17	0.94	1.02	0.61	2.83
	(0.33; 1.52)	(0.36; 2.16)	(0.75; 1.74)	(0.35; 1.59)	(0.33; 1.78)	(0.17; 1.60)	(1.29; 5.57)
	[n=8]	[n=10]	[n=24]	[n=17]	[n=12]	[n=4]	[n=9]
	0.19	0.34	0.05	0.11	0.08	0.31	0.28
	(0.02; 0.68)	(0.07; 0.99)	(0.00; 0.28)	(0.01; 0.39)	(0.00; 0.46)	(0.04; 1.11)	(0.01; 1.57)
	[n=2]	[n=3]	[n=1]	[n=1]	[n=1]	[n=2]	[n=1]

*IR as patients with events per 100 patient-years

Opportunistic infections included: toxoplasmosis, cryptococcosis, histoplasmosis, coccidioidomycosis, pneumocystis pneumonia, and other opportunistic infections (n=1)

AE, adverse event; SAE, serious adverse event; CDAI, Clinical Disease Activity Index; CI, confidence interval; csDMARD, conventional synthetic disease-modifying antirheumatic drug; HAQ-DI, Health Assessment Questionnaire-Disability Index; IR, incidence rate; LDA, low disease activity; SAE, serious adverse event; SD, standard deviation; TB, tuberculosis

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