agreements with Karolinska Institutet with JA as principal investigator, mainly in the context of safety monitoring of biologics via the ARTIS national safety monitoring system.

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OP0115 EFFICACY AND SAFETY OF ABBV-3373, A NOVEL ANTI-TNF GLUCOCORTICOID RECEPTOR MODULATOR ANTIBODY DRUG CONJUGATE, IN PATIENTS WITH MODERATE TO SEVERE RHEUMATOID ARTHRITIS DESPITE METHOTREXATE THERAPY: A PHASE 2A PROOF OF CONCEPT STUDY

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Background: ABBV-3373 is a novel antibody drug conjugate composed of adalimumab (ADA) linked to a proprietary and highly potent glucocorticoid receptor modulator (the anti-inflammatory payload) currently evaluated for the treatment of rheumatoid arthritis (RA).

Objectives: To assess the efficacy and safety of ABBV-3373 vs ADA in RA patients (pts).

Methods: This was a 24-week (wk) randomized, double-blind, double-dummy, active-controlled Phase 2a study of intravenously (IV)-administered ABBV-3373 100 mg (for 12 wks followed by placebo [PBO] for 12 wks) vs subcutaneous injections of ADA 80 mg every other wk (for 24 wks) in pts on background methotrexate. The primary endpoint was the change from baseline (BL) in DAS28(CRP) at Wk 12. Pre-planned statistical methods incorporating pre-specified historical ADA data both alone (pre-specified success criterion, 2-sided $P \leq 0.1$) and supplemented with in-trial ADA data (pre-specified success criterion, probability >95%) were used to achieve adequate statistical power with a reduced trial size. Assay sensitivity was evaluated through construction of a synthetic PBO arm by propensity score matching, using individual pt-level PBO data from 3 recent sponsor-run trials of similar populations and trial settings. Secondary endpoints at Wk 12 included 1) mean change from BL in CDAI, SDAI, DAS28(ESR), HAQ-DI; 2) proportion of pts achieving DAS28(CRP)≤3.2, ACR20/50/70 responses, HAQ-DI≤-0.22. Continuous and categorical efficacy variables were analyzed using mixed effect model repeated measurements and Cochran-Mantel-Haenszel test, respectively; non-responder imputation was applied to missing categorical data. Treatment-emergent adverse events were summarized through Wk 12.

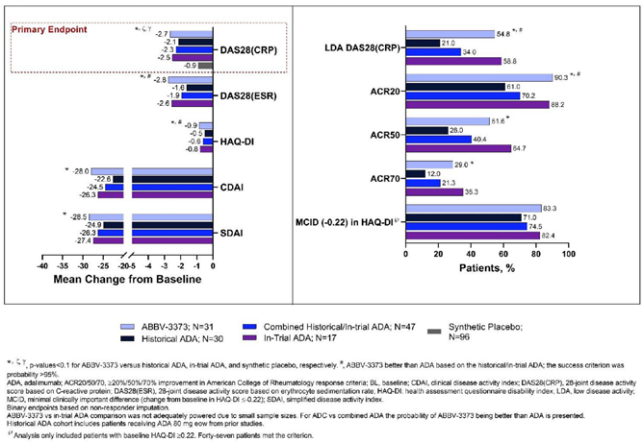
Results: A total of 48 pts were randomized and treated (ABBV-3373: 31; ADA: 17); 46 pts (96%) completed 12 wks of study treatment. BL demographics and disease characteristics were indicative of established RA and similar among the 2 treatment arms and the synthetic PBO arm. ABBV-3373 demonstrated significant improvement in mean DAS28(CRP) at Wk 12 vs the pre-specified historical ADA (-2.65 vs -2.13; P=0.022) and numerically greater improvement vs the combined in-trial and historical ADA arm (-2.65 vs -2.29; probability 90%; Figure). Comparable improvements in disease activity and targets were observed for ABBV-3373 and in-trial ADA. Assay sensitivity was supported by the fact that both ABBV-3373 and ADA arms were superior to synthetic PBO (P<0.001). For secondary endpoints, greater efficacy was observed with ABBV-3373 vs historical ADA; ABBV-3373 was predicted with 79-99% probability to be better than ADA based on the combined in-trial and historical ADA data. 2 serious infections were reported with ABBV-3373 (pneumonia, upper respiratory tract infection) and none with ADA through Wk 12 (Table). 1 event of anaphylactic shock reaction was reported with ABBV-3373. After increasing the duration of IV administration from 3 min to 15-30 min, no similar events were observed.

Table 1. Treatment Emergent Adverse Events up to Week 12

Event, n (%)	ADA (N = 17)	ABBV-3373 (N = 31)
Adverse event (AE)	12 (70.6)	11 (35.5)
AE with reasonable possibility of being drug related[$]	3 (17.6)	2 (6.5)
Severe AE	0	1 (3.2)
Serious AE	0	4 (12.9) [#]
AE leading to Discontinuation of Study Drug	1 (5.9)	1 (3.2)
Serious infections	0	2 (6.5)
Opportunistic infection excluding Tuberculosis	0	0
Allergic Reactions Including Hypersensitivity, Angioedema, and Anaphylaxis	2 (11.8) [&]	1 (3.2) [^]
Systemic glucocorticoid events	0	0
All deaths	0	0

[$]As assessed by investigator.[#]Serious AEs: 1 non-cardiac chest pain, 1 pneumonia, 1 upper respiratory tract disease and 1 anaphylactic shock.[&]1 Type I hypersensitivity, 1 Pruritus[^]1 Anaphylactic shock

Figure. Analysis of Primary, Secondary, and Additional Efficacy Endpoints at Week 12



*, †, ‡, p-values<0.1 for ABBV-3373 versus historical ADA, in-trial ADA, and synthetic placebo, respectively. *, ABBV-3373 better than ADA based on the historical/in-trial ADA; the success criterion was probability >95%.
ADA, adalimumab; ACR20/50/70, ≥20%/50%/70% improvement in American College of Rheumatology response criteria; BL, baseline; CDAI, clinical disease activity index; DAS28(CRP), 28-joint disease activity score based on C-reactive protein; DAS28(ESR), 28-joint disease activity score based on erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire disability index; LDA, low disease activity; MCID, minimal clinically important difference (change from baseline in HAQ-DI ≤-0.22); SDAI, simplified disease activity index.
Binary endpoints based on non-responder imputation.
ABBV-3373 vs in-trial ADA comparison was not adequately powered due to small sample sizes. For ADC vs combined ADA the probability of ABBV-3373 being better than ADA is presented.
Historical ADA cohort includes patients receiving ADA 80 mg eow from prior studies.
[#] Analysis only included patients with baseline HAQ-DI ≥0.22. Forty-seven patients met the criterion.

Conclusion: These data demonstrate the clinical efficacy of ABBV-3373 and its potential to provide improved outcomes for RA pts compared to ADA. The safety profile of ABBV-3373 was generally similar to ADA.

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OP0116 ELDERLY PATIENTS ARE NOT AT INCREASED RISK OF SERIOUS INFECTIONS WHEN RECEIVING BDMARDS OR JAK INHIBITORS COMPARED TO CSDMARD TREATMENT

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Background: Elderly rheumatoid arthritis (RA) patients are generally at increased risk of serious infections (SI). At the same time, treatment with bDMARDs has been associated with a higher SI risk than treatment with csDMARDs (1). However, long-term use of bDMARDs did not increase the risk of SI in a small group of elderly patients over 65 (2). The extent to which elderly patients are exposed to a higher SI risk when treated with JAK inhibitors (JAKi) is an open question.

Objectives: To assess the effects of bDMARDs and specifically JAKi on the risk of SI in elderly patients with RA.

Methods: The German register RABBIT is a prospective, longitudinally followed cohort of RA patients enrolled with a new start of a DMARD after at least one csDMARD failure. This analysis comprises patients over 70 years of age who were enrolled between 01/2007 and 04/2020 and had at least one follow-up.

Results: Of 13,491 patients followed-up in RABBIT, 2274 with an age > 70 years were included in the analysis. 626 SI were observed in 425 of these patients. Baseline characteristics at start of the respective DMARD are shown in Table 1. In most characteristics, patients on JAKi were more comparable to patients under bDMARDs than to those on csDMARDs. JAKi patients received glucocorticoids (GC) less frequently than patients on other treatments. The HR for SI was lower than 1 in patients receiving bDMARDs or JAKi compared to csDMARDs, but without statistical significance (Figure 1). GC use (HR 1.6, 95% CI: 1.2 – 2.2 for ≤ 10 mg/d), higher DAS28-ESR values (HR 1.1, 95% CI: 1.0 – 1.2 per 1 point increase), COPD or pulmonary fibrosis (HR 1. 8, 95% CI: 1.3 – 2.4), chronic kidney disease (HR 1.5, 95% CI: 1.2 – 1.9) and diabetes mellitus (HR 1.3, 95% CI: 1.0 – 1.7) were associated with an increased risk of SI. Better physical capacity was associated with a decreased risk of SI (HR 0.9, 95% CI: 0.88 – 0.98 for a 10 point increase).

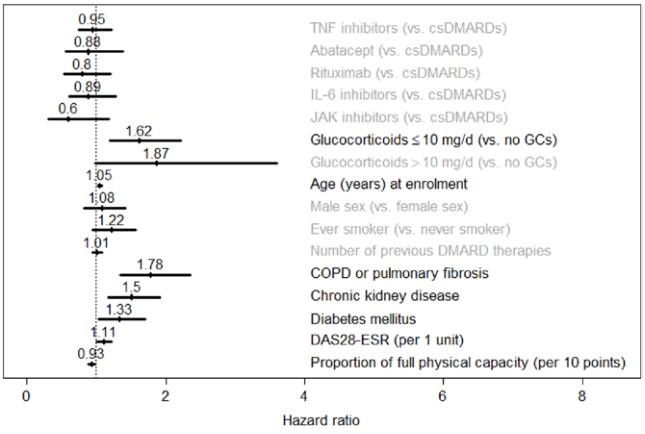

Figure 1. Hazard ratios for serious infections with 95% confidence intervals

Conclusion: Treatment with JAKi as well as treatment with bDMARDs was not associated with an increased risk of SI in elderly patients above 70 years of age. Key comorbidities such as diabetes mellitus, chronic pulmonary and kidney diseases were associated with increased risk, as was concomitant GC use and higher disease activity.

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Table 1. Patient characteristics by treatment at baseline

Parameter	csDMARDs	TNFi	RTX	ABA	IL-6i	JAKi
	N=758	N=840	N=209	N=147	N=212	N=108
Age (years)	75.9 (3.9)	75.5 (3.6)	74.8 (3.6)	76.1 (3.9)	75.9 (3.7)	76.7 (3.7)
Male sex	184 (24.3)	220 (26.2)	50 (23.9)	36 (24.5)	46 (21.7)	28 (25.9)
Ever smoker	249 (32.8)	287 (34.2)	77 (36.8)	50 (34)	73 (34.4)	39 (36.1)
Disease duration (years)	7.9 (8.8)	12.3 (11.4)	17 (11.1)	12.8 (10)	13.8 (11.7)	11.9 (10.9)
Seropositivity	487 (64.3)	671 (79.9)	201 (96.2)	126 (85.4)	182 (85.8)	79 (73.5)
Number of previous DMARDs	1.4 (0.7)	2.5 (1.3)	4.2 (1.8)	3.6 (1.9)	3.3 (1.8)	2.6 (1.5)
DAS28-ESR	4.6 (1.2)	5.1 (1.2)	5.4 (1.3)	5.3 (1.3)	5.3 (1.3)	5 (1.2)
Proportion of full physical function	64.8 (23.1)	57.1 (23.6)	50.4 (23.7)	52.9 (23.5)	55.3 (24.1)	55.2 (23.7)
Number of comorbidities	3.1 (2.5)	3.8 (2.6)	4.2 (2.6)	4.6 (2.9)	3.6 (2.4)	3.8 (2.2)
No comorbidity	52 (6.9)	29 (3.5)	4 (1.9)	4 (2.7)	9 (4.2)	5 (4.6)
Three and more comorbidities	385 (50.8)	528 (62.9)	147 (70.3)	107 (72.8)	131 (61.8)	76 (70.4)
COPD or pulmonary fibrosis	69 (9.1)	89 (10.6)	29 (13.9)	26 (17.7)	12 (5.7)	11 (10.2)
Chronic kidney disease	94 (12.4)	151 (18)	28 (13.4)	21 (14.3)	39 (18.4)	22 (20.4)
Diabetes mellitus	151 (19.9)	172 (20.5)	31 (14.8)	23 (15.6)	42 (19.8)	25 (23.1)
GCs (last 6 months)	347 (45.8)	526 (62.6)	143 (68.8)	82 (56.2)	127 (59.9)	44 (40.7)
GCs (<5mg)	447 (58.9)	384 (45.7)	101 (48.2)	88 (60)	118 (55.8)	72 (66.7)
GCs (5-9mg)	252 (33.3)	375 (44.6)	81 (38.7)	43 (29)	72 (34.2)	27 (25.1)
GCs (>=10mg)	59 (7.8)	82 (9.8)	274 (13.1)	16 (11)	21 (10)	9 (8.2)

Results are presented as mean ± SD for continuous variables and number (percentage) for discrete variables.

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OP0117

REAL-WORLD EFFECTIVENESS OF TNFI VERSUS NON-TNFI BIOLOGICS ON DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS: DATA FROM THE ACR'S RISE REGISTRY

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Background: Our understanding of how medications such as biologic disease modifying anti-rheumatic drugs and targeted small molecules (b/tsDMARDs) influence disease activity in RA is based largely on randomized controlled trials (RCTs). However, most U.S. trials in RA are limited by small sample sizes and have often excluded patients who are older, male, and from racial/ethnic minorities. Whether effectiveness of b/tsDMARDs varies in these populations has largely been unexplored.
Objectives: We aimed to examine differences in longitudinal RA disease activity by demographic and clinical characteristics using a novel electronic health record data source of rheumatology providers across the U.S. We simulated various treatment assignments of b/tsDMARDs that have been examined in RCTs: namely, TNF-inhibitors (TNFi) and non-TNFi.
Methods: We included 16,448 individuals from the ACR's RISE registry with ≥ 2 RA diagnoses (ICD-9: 714.0) ≥ 30 days apart, who had at least 2 recorded clinical disease activity index (CDAI) scores and no historical b/tsDMARD use documented in RISE. b/tsDMARD use and CDAI scores were assessed at each quarter; covariates included sex, race (white, Black, Asian, other), ethnicity (Hispanic/non-Hispanic), age, smoking, obesity, area deprivation index, other DMARD use, RF status, anti-CCP status, and practice type. Longitudinal targeted maximum likelihood estimation estimated the average treatment effect (ATE) of cumulative TNFi vs. non-TNFi use over a 12-month period on CDAI score among the entire population and across various subgroups based on demographic and clinical characteristics, accounting for censoring and time-varying confounding.
Results: Approximately 75% of patients were female with a mean age of 65.1 (+/- 13.7) years. Sixty percent of patients were white, 8% black, 2% Asian, and 30% other/mixed or unknown race; 6% were Hispanic. The mean CDAI score at baseline was 11.3 (+/- 10.7). For the overall population, there was no significant difference in disease activity between TNFi and non-TNFi at 12 months (ATE= 0.85, 95% CI -0.26, 1.96; Table 1). Stratified analyses found higher disease activity for TNFi compared to non-TNFi among patients of Black and Asian race, non-Hispanic ethnicity, and female sex. Among Black race patients, TNFi use was associated with a 6.08 point higher CDAI score compared to non-TNFi use (95% CI 1.99, 10.17). In contrast, in Hispanic/Latino ethnicity patients, TNFi use was associated with a lower CDAI score compared to non-TNFi use (ATE= -2.64, 95% CI -3.99, -1.30).

Table 1. Average treatment effect (ATE) of cumulative TNFi vs. non-TNFi use at 12-months on CDAI score in patients with RA

	TNFi	Non-TNFi	ATE (95% CI)
Overall (n=16,448)	8.84	7.99	0.85 (-0.26, 1.96)
Race			
White (n=9,814)	8.24	6.81	1.42 (0.03, 2.81)*
Black (n=1,358)	13.91	7.83	6.08 (1.99, 10.17)*
Asian (n=301)	6.54	2.74	3.80 (2.93, 4.67)*
Ethnicity			
Non-Hispanic (n=14,216)	8.92	7.63	1.29 (0.08, 2.51)*
Hispanic (n=938)	5.69	8.33	-2.64 (-3.99, -1.30)*
Sex			
Female (n=12,527)	8.98	7.47	1.51 (0.31, 2.72)*
Male (n=3,921)	8.57	9.49	-0.92 (-3.42, 1.58)

*$P<0.05$

Conclusion: Results from this RCT simulation study suggest that non-TNFi may have an important role as first-line agents in the treatment of Black and Asian patients, but not Hispanic patients. These novel findings fill gaps where RCTs have not been conducted, highlight the need for inclusion of diverse populations in future trials, and have the potential to lead to a more personalized approach to rheumatologic care.

References:

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