(BL) in modified Total Sharp Score (mTSS), joint space narrowing (JSN), and erosion scores (ES) as well as the proportion of pts with no radiographic progression (Δ mTSS ≤ 0) at Weeks 24/26 and 48 were determined in both RCTs. Data were analyzed by linear extrapolation (LE) for missing data imputation and treatment switching, and as observed (AO).

Results: BL demographics have been reported previously^{2,3}. At Weeks 24/26, UPA as monotherapy and in combination with background MTX significantly inhibited radiographic progression measured by mean Δ mTSS and the proportion of pts with no radiographic progression vs MTX and PBO, respectively (LE and AO, **Table**). The significant inhibition of radiographic progression with UPA was maintained through Week 48 vs MTX (LE and AO) in EARLY and vs PBO (LE) in COMPARE. Following the switch of all PBO pts to UPA in COMPARE by Week 26, no further change in mean mTSS was observed through Week 48 (AO, **Table**). The inhibition of radiographic progression vs comparators was not only observed for the overall mTSS scores but also its components – the JSN and ES in both RCTs (LE and AO).

Abstract THU0188 –Table 1.

Table: Radiographic Progression at Weeks 24/26 and 48 in SELECT-EARLY and SELECT-COMPARE trials.

METHOD OF IMPUTATION: Linear Extrapolation	MTX-naïve (SELECT-EARLY)						MTX-IR (SELECT-COMPARE)					
	Week 24			Week 48			Week 26			Week 48		
	MTX (N=264)	UPA 15 mg QD (N=280)	UPA 30 mg QD (N=273)	MTX (N=268)	UPA 15 mg QD (N=287)	UPA 30 mg QD (N=283)	PBO (N=402)	ADA 40 mg QD (N=297)	PBO-UPA 15 mg QD (N=596)	ADA 40 mg QD (N=599)	UPA 15 mg QD (N=298)	UPA 15 mg QD (N=604)
LMM differences in Δ mTSS (within group)	0.66	0.03	0.10	1.00	0.03	0.14	0.94	0.19	0.16	1.73	0.39	0.28
LMM differences in Δ mTSS (UPA or UPA-MTX vs Control)	—	-0.63***	-0.56***	—	-0.97***	-0.87***	—	—	-0.79*** (vs PBO/ADA)	-1.44*** (vs PBO/ADA)	-0.11 (vs ADA)	-0.11 (vs ADA)
Non-progressors, %	78.0	90.4***	90.8***	74.3	89.9***	90.8***	73.9	88.2	87.4***	74.1	87.9	86.4***
METHOD OF IMPUTATION: None (As Observed)												
	Week 24			Week 48			Week 26			Week 48		
	MTX (N=268)	UPA 15 mg QD (N=281)	UPA 30 mg QD (N=275)	MTX (N=247)	UPA 15 mg QD (N=264)	UPA 30 mg QD (N=262)	PBO (N=588)	ADA 40 mg QD (N=291)	UPA 15 mg QD (N=584)	PBO-UPA 15 mg QD (N=574)	ADA 40 mg QD (N=276)	UPA 15 mg QD (N=589)
	0.65	0.03	0.10	0.85	0.07	0.09	0.67	0.14	0.16	0.51	0.14	0.26
LMM differences in Δ mTSS (within group)	0.65	0.03	0.10	0.85	0.07	0.09	0.67	0.14	0.16	0.51	0.14	0.26
LMM differences in Δ mTSS (UPA or UPA-MTX vs Control)	—	-0.62***	-0.55***	—	-0.78***	-0.76***	—	—	-0.52*** (vs PBO/ADA)	-0.26 (vs PBO/ADA)	-0.11 (vs ADA)	-0.11 (vs ADA)
Non-progressors, %	78.4	90.4***	90.9***	74.9	89.0***	91.6***	74.1	88.3	86.6***	75.8	85.9	84.7***

Results are summarized by randomised group. In SELECT-EARLY, non-progressors (CDR improvement ≥ 1 in 50 or more counts) were recruited from UPA monotherapy and UPA monotherapy to UPA-MTX at Week 26. In SELECT-COMPARE, non-progressors were recruited from PBO to UPA, UPA to ADA and ADA to UPA at Weeks 14 to 26 (and all remaining non-progressed PBOs were switched to UPA at Week 26). In ADA analysis, observed data at Week 48 are summarized under the randomized group regardless of rescue. In LE analysis, data after rescue are imputed by linear extrapolation.

The above mTSS values are from a second reading session of radiographs from Weeks 24/26 and 48 in both RCTs, previously presented data were from the first reading session and consisted of data for Weeks 24 and 26 for EARLY and COMPARE RCTs, respectively.

Non-progressors are defined as patients in whom Δ mTSS ≤ 0 . Comparison to control (EARLY: MTX or COMPARE: PBO/ADA) was calculated by ANCOVA, *p<0.05, ***p<0.001.

LMM, least squares means; QD, every other week; UPA, leuprolide; ADA, adalimumab; PBO, placebo; QD, once-daily.

Conclusion: UPA both as monotherapy, and in combination with background MTX, was effective in inhibiting the progression of structural joint damage through Week 48 in MTX-naïve, and MTX-IR patients, respectively.

REFERENCES:

- [1] Smolen JS et al. Ann Rheum Dis 2017;0: 1–18.
- [2] van Vollenhoven R, et al. Arthritis Rheumatol. 2018; 70 (suppl 10) [ACR 2018 abstract].
- [3] Fleischmann R, et al. Arthritis Rheumatol. 2018; 70 (suppl 10) [ACR 2018 abstract].

Acknowledgement: AbbVie, Inc was the study sponsor, contributed to study design, data collection, analysis, interpretation, writing, reviewing, and approval of the final version of the abstract. Medical writing support: Siddharth Mukherjee, PhD, from AbbVie, Inc.

Disclosure of Interests: Charles Peterfy Shareholder of: Spire Sciences, Inc, Consultant for: AbbVie, Acerta, Amgen, AstraZeneca, Bristol-Myers Squibb, Centrexion, Daiichi Sankyo, Five Prime Therapeutics, Genentech, Hoffmann-La Roche, Janssen, Lilly USA, MedImmune, Merck, Novartis, Plexxikon, Pfizer, Sanofi, Salix-Santarus, Samsung, Employee of: Spire Sciences, Inc, Speakers bureau: Amgen, Mark C. Genovese Grant/research support from: Sanofi/Genzyme, Genentech/Roche, RPharm, Consultant for: Sanofi/Genzyme, Genentech/Roche, RPharm, In-Ho Song Shareholder of: AbbVie Inc, Employee of: AbbVie Inc, Alan Friedman Shareholder of: AbbVie, Employee of: AbbVie, Stephen Hall Grant/research support from: AbbVie Inc, BMS, Lilly, Janssen, Pfizer, UCB, and Novartis, Consultant for: AbbVie Inc, BMS, Lilly, Janssen, Pfizer, UCB, and Novartis

, Eduardo Mysler Grant/research support from: AbbVie, Bristol-Myers Squibb, Eli Lilly, Pfizer, Novartis, Janssen, Grant/research support from: AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, MedImmune, Pfizer Inc, and Roche, Consultant for: AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, MedImmune, Pfizer Inc, and Roche, Speakers bureau: AbbVie, Bristol-Myers Squibb, Eli Lilly, Pfizer, Novartis, Janssen, Speakers bureau: AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, MedImmune, Pfizer Inc, and Roche, Patrick Durez Speakers bureau: Bristol-Myers Squibb, Eli Lilly, Sanofi, Celltrion, Xenofon Baraliakos Grant/research support from: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Centocor, Chugai, Janssen, MSD, Novartis, Pfizer Inc, Roche and UCB, Grant/

research support from: AbbVie, Pfizer, Merck Sharp & Dohme, UCB Pharma, Novartis, Consultant for: AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Chugai, Janssen Biologics, Novartis, Pfizer, UCB Pharma, Galapagos, Speakers bureau: AbbVie, Chugai, Janssen, Novartis, Pfizer, UCB Pharma, Jose Jeffrey Enejosa Shareholder of: AbbVie Inc, Employee of: AbbVie Inc, Tim Shaw Shareholder of: AbbVie Inc, Employee of: AbbVie Inc, Yihan Li Shareholder of: AbbVie, Employee of: AbbVie, Su Chen Shareholder of: AbbVie Inc, Employee of: AbbVie Inc, Vibeke Strand Consultant for: AbbVie, Amgen, Bayer, BMS, Boehringer Ingelheim, Celgene, Celltrion, CORONA, Crescendo, EMD Serono, Genentech/Roche, GSK, Horizon, Inmedix, Janssen, Kezar, Lilly, Merck, Novartis, Pfizer, Regeneron, Samsung, Sandoz, Sanofi, Servier, UCB.

DOI: 10.1136/annrheumdis-2019-eular.2871

THU0189 A PROSPECTIVE STUDY OF TAPERING CONVENTIONAL DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (C-DMARDS) IN PATIENTS WITH RHEUMATOID ARTHRITIS (RA) IN STABLE REMISSION

SHAH ROMI, Canchi Balakrishnan. P. D. Hinduja Hospital and Medical Research Centre, Mumbai, India

Background: Remission in RA is being achieved more often nowadays with effective early aggressive therapy with DMARDS. Studies ((1 2 3 4)) have shown that it is possible to taper and stop biologic DMARDS in patients with RA in stable remission. However there are no such studies or recommended protocols for c-DMARDS treated patients.

Objectives: To study the incidence and timing of flares in RA patients in sustained remission of at least 6 months duration on slow withdrawal of c-DMARDS and to identify predictors of flares.

Methods: Consenting adult (age >18 years) RA patients satisfying the ACR 2010 criteria attending our outpatient department with a disease duration of minimum 1 year and a stable remission (CDAI <2.8 on consecutive 2 visits at 3 months interval in last 6 months) on c-DMARDS were included. Patients receiving steroids or biologics were excluded.

Protocol for tapering:

On monotherapy: 50% dose reduction 3 weekly and stop eventually
On combination therapy: sequential dose reduction as monotherapy followed by stoppage of cDMARDS (in order from first to last: hydroxychloroquine, sulphasalazine, leflunomide, methotrexate)
Flare was defined as CDAI of >2.8. Number of RA flares and timing of flares were noted. Predictors of flare were analysed using univariate and multivariate regression

Results: 66 patients satisfied inclusion criteria of which 5 did not consent, 5 committed protocol violation and 2 lost to follow up.

Total 54 patients were included in the final analysis. 42 patients (77.78%) flared during the study period. Of these 42 patients, 29 (69.05%) flared whilst on the tapering protocol whereas, 13 (30.95%) flared after complete withdrawal of c-DMARDS. 20 patients (47.62%) flared within first 3 months of the tapering regimen and total 31 patients (73.8%) flared within first 6 months of tapering regimen. Baseline CDAI scores were significantly higher in patients who developed flare compared to those who remained in remission (0.82 ± 0.82 v/s 0.29 ± 0.54 , $p=0.04$).

RF positivity and age more than 60 years were predictors of flare in univariate regression analysis. With multivariate logistic regression, RF positivity was the only variable significantly associated with risk of flare ($p=0.0098$, $SE=1.62$ OR 66.31).

Conclusion: We found that on tapering of c DMARDS at 3 weekly interval in RA patients with stable remission the incidence of flare was 78%. Most flared during tapering therapy itself and not after the drugs were stopped. Rheumatoid factor positivity seemed to predict flares. Although within the definition of remission, CDAI scores at baseline were significantly higher in patients who developed flare compared to those who remained in remission. CDAI has limitation in defining remission and inclusion of imaging in defining remission may lead to better remission on tapering cDMARDS.

REFERENCES:

- [1] Schett G, Emery P, Tanaka Y, Burmester G, Pisetsky DS, et al. Tapering biologic and conventional DMARD therapy in rheumatoid arthritis: current evidence and future directions. Ann Rheum Dis. 2016 Aug;75(8):1428–37.
- [2] Haschka J, Englbrecht M, Hueber AJ, Manger B, Kleyer A, et al. Relapse rates in patients with rheumatoid arthritis in stable remission tapering or stopping antirheumatic therapy: interim results from the prospective randomised controlled RETRO study. Ann Rheum Dis. 2016 Jan 1;75(1):45–51.
- [3] Fautrel B, Pham T, Alfaiate T, Gandjbakhch F, Foltz V, et al. Step-down strategy of spacing TNF-blocker injections for established rheumatoid

arthritis in remission: results of the multicentre non-inferiority randomised open-label controlled trial (STRASS). *Ann Rheum Dis.* 2016 Jan;75(1):59–67.

- [4] Huizinga TWJ, Conaghan PG, Martin-Mola E, Schett G, Amital H, et al. Clinical and radiographic outcomes at 2 years and the effect of tocilizumab discontinuation following sustained remission in the second and third year of the ACT-RAY study. *Ann Rheum Dis.* 2015 Jan 28;74(1):35–43.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.2592

THU0190

THE SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF BMS-986166, A NOVEL, SELECTIVE, PARTIAL AGONIST OF THE SPHINGOSINE-1-PHOSPHATE (S1P) SUBTYPE 1 RECEPTOR IN HEALTHY PARTICIPANTS

Shalabh Singhal, Ihab Girgis, Jenny Xie, Santanu Dutta, Diane Shevell, John Throup. *Bristol-Myers Squibb, Princeton, United States of America*

Background: S1P mediates a number of immune processes including the egress of lymphocytes from lymphoid organs via stimulation of the S1P subtype 1 receptor (S1P1R). S1P1R inhibition has the potential to suppress abnormal immune responses and modulate autoimmune inflammatory diseases.¹ BMS-986166, a novel, selective partial agonist of S1P1R, which is phosphorylated in vivo to its pharmacologically active form, BMT-121795, may have utility for the treatment of autoimmune and/or inflammatory diseases.

Objectives: To investigate safety, pharmacokinetics (PK), and pharmacodynamics (PD) of BMS-986166 in single- and multiple-ascending dose (SAD/MAD) placebo (PBO)-controlled studies in healthy participants.

Methods: SAD study (NCT02790125): BMS-986166 was administered as a single dose of 0.75, 2.0, or 5.0 mg (n=10/group; 4:1 ratio of BMS-986166:PBO); a series of upwardly titrated single daily doses of 0.25, 0.5, 0.75, 1.0, then 1.5 mg over 14 days (n=16; 3:1 ratio); or as a single 2.0-mg dose in participants who were fed, fasted, or administered famotidine prior to dosing (n=8/group). MAD study (NCT03038711): BMS-986166 was administered as once-daily doses of 0.25 (n=12; 2:1 ratio), and 0.75 or 1.5 mg (n=10/dose; 4:1 ratio), for 28 days. Safety, PK, and PD (absolute lymphocyte count [ALC]) were assessed. Cardiac safety was assessed by continuous cardiac monitoring and at intervals by 12-lead electrocardiogram.

Results: 70 (60 BMS-986166, 10 PBO; mean [standard deviation (SD)] age: 32.8 [8.5] years) and 32 (24 BMS-986166, 8 PBO; mean [SD] age: 35.8 [8.6] years) participants were randomised to dosing in the SAD and MAD studies, respectively. Participants were predominantly male. Mean (SD) body mass index was 26.8 (2.9) and 27.2 (2.5) kg/m², respectively. Multiple oral doses of BMS-986166 up to 1.5 mg daily for 28 days were generally well tolerated, and all treatment-related adverse events were mild (Grade 1). In the MAD (Figure 1) and SAD studies, a clinically insignificant, dose-related decrease in mean hourly heart rate (HR) was observed following administration of BMS-986166 compared with PBO, based on a time-matched analysis of nominal hourly HR data from continuous cardiac monitoring over 72 hours post dose. Compared with participants receiving PBO, a mean decrease from baseline in hourly HR was apparent for participants in the 2 higher dose panels (2.0 mg, 5.0 mg) in the SAD study. In the SAD study, the largest decreases in PBO-corrected, time-matched, nadir hourly HR were -0.29, -6.38, and -8.37 bpm for the 0.75, 2.0, and 5.0 mg dose panels, respectively. Similarly, in the MAD study, these numbers were -0.83, -3.46, and -5.54 bpm at the 0.25, 0.75, and 1.5 mg dose levels, respectively. Increases in systemic plasma exposure (maximum concentration and area under the curve from time 0–24 hours) of BMS-986166 and its active metabolite BMT-121795 were approximately proportional to dose increases over the range of 0.75–5 mg with single doses, and of 0.25–1.5 mg on Days 1, 14, and 28 with multiple doses. Decreases in percent change from baseline in ALC with multiple doses of BMS-986166 vs PBO were dose-related over the 28-day treatment period. Between Day 0 and 35, median (range) nadir in lymphocyte reductions were 53.7% (31.7–55.9%), 75.9% (63.3–85.8%), and 81.9% (37.9–92.2%) at 0.25, 0.75, and 1.5 mg BMS-986166 dose levels, respectively. Recovery of ALC levels began 14, 14–21, and 7 days after the last dose of 0.25, 0.75, and 1.5 mg, respectively, on Day 28.

Figure 1. Mean (SE) time-matched change from Day -1 in HR (bpm) following dosing in the MAD study

bpm=beats per minute; HR=heart rate; MAD=multiple-ascending dose; SE=standard error.

Abstract THU0190 – Figure 1

Conclusion: In healthy participants, multiple daily doses of BMS-986166 in the range of 0.25–1.5 mg were well tolerated, with no clinically relevant lowering of HR. PK were linear and decreases in ALC were dose related.

REFERENCE:

- [1] Urbano M, et al. *Bioorg Med Chem Lett* 2013;23:6377–89

Acknowledgement: Professional medical writing: Lola Parfitt, MRes (Caudex); funding: Bristol-Myers Squibb

Disclosure of Interests: Shalabh Singhal Shareholder of: Bristol-Myers Squibb, Employee of: Bristol-Myers Squibb, Ihab Girgis Shareholder of: Bristol-Myers Squibb, Employee of: Bristol-Myers Squibb, Jenny Xie Employee of: Bristol-Myers Squibb, Santanu Dutta Employee of: Bristol-Myers Squibb, Diane Shevell Shareholder of: Merck, Employee of: Bristol-Myers Squibb, John Throup Shareholder of: Bristol-Myers Squibb, Employee of: Bristol-Myers Squibb

DOI: 10.1136/annrheumdis-2019-eular.1967

THU0191

UPADACITINIB AS MONOTHERAPY IN PATIENTS WITH RHEUMATOID ARTHRITIS: RESULTS AT 48 WEEKS FROM THE SELECT-MONOTHERAPY STUDY

Josef S. Smolen¹, Paul Emery², William Rigby³, Yoshiya Tanaka⁴, Juan Ignacio Vargas⁵, Nemanja Damjanov⁶, Manish Jain⁷, Yunxia Sui⁸, Jeffrey Enejo⁹, Aileen Pangan⁹, Heidi Camp⁹, Stanley B. Cohen⁹. ¹Medical Univ of Vienna, Vienna, Austria; ²Leeds NIHR Biomedical Research Centre, Leeds Inst of Rheumatic and Musculoskeletal Medicine, Leeds, United Kingdom; ³Dartmouth College, Hanover, NH, United States of America; ⁴Univ of Occupational and Environmental Health, Japan, Kitakyushu, Japan; ⁵Quantum Research, Puerto Varas, Chile; ⁶Univ of Belgrade, Belgrade, Serbia; ⁷Great Lakes Clinical Trials, Chicago, IL, United States of America; ⁸AbbVie, Inc., N Chicago, IL, United States of America; ⁹Metropex Clinical Research Center, Dallas, TX, United States of America

Background: In the SELECT-MONOTHERAPY trial, upadacitinib (UPA), an oral JAK1-selective inhibitor, showed efficacy when used as monotherapy over 14 weeks (wks) in rheumatoid arthritis (RA) patients (pts) with an inadequate response to methotrexate (MTX).¹

Objectives: Safety and efficacy of UPA monotherapy were assessed through 48 wks in an ongoing long-term extension period of SELECT-MONOTHERAPY.

Methods: At baseline (BL), pts on stable MTX were randomized to either continue MTX (cMTX, given as a blinded study drug) or switch to once-daily (QD) UPA at 15 (UPA15) or 30 mg (UPA30) monotherapy for 14 wks. From Wk14, the start of a long-term blinded extension, pts randomized to cMTX were switched to UPA15 or 30mg per pre-specified assignment at BL, pts randomized to UPA15 or 30 continued their initial treatment. No dose adjustments for UPA were allowed. Starting at Wk26, for pts who did not achieve CDAI ≤10, background csDMARDS could be initiated. Efficacy data up to the Wk48 visit are reported “As Observed”. Adverse events (AE) per 100 pt yrs (PYs) are summarized up to May 25 2018.

Results: Of 648 pts randomized at BL, 598 (92%) completed 14 wks and continued on to the extension period. By May 25 2018, 16% discontinued study drug; 5% due to AE, 0.5% due to lack of efficacy, 4% withdrew consent, 1% were lost to follow-up, and 6% due to other reasons. Cumulative exposures to UPA15 and UPA30 were 336.0 PYs and 337.1