particularly nausea. There were no significant effects on clinical laboratory tests, vital signs, ECG or physical examination.

Multiple doses of MBS2320 (75 mg) were also generally well tolerated by subjects with RA when co-administered with MTX. There were no clinically significant findings or trends in the laboratory tests, vital signs or ECG data, and no clinically significant findings on physical examination. No SAEs were reported. The majority of TEAEs were mild in severity with diarrhoea and nausea reported most frequently.

In healthy subjects, MBS2320 was steadily absorbed following doses of 50 to 375 mg MBS2320. Systemic exposure (AUC) increased in a dose-proportional manner across all doses and was unaffected by food. In RA patients there was no indication of a PK interaction between MTX and MBS2320 in either direction.

In patients with RA, serum CTX-1, P1NP and osteocalcin increased following 14 days of treatment, while TRAP5b was decreased or unchanged. Median CRP was decreased relative to baseline in after 7 days' treatment with MBS2320, and remained low on Day 14.

Conclusion: MBS2320 was well tolerated for up to 14 days when administered to healthy volunteers and to patients with RA receiving MTX. Systemic exposure was dose-proportional with no evidence of a pharmacokinetic interaction with MTX. Evaluation of biomarkers of bone turnover and inflammation in RA patients showed changes consistent with those expected of an agent with the potential to directly protect the bone and simultaneously ameliorate inflammation.

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THU0187 EFFICIENCY OF TREATMENT SEQUENCES CONTAINING TOFACITINIB FOR RHEUMATOID ARTHRITIS IN SPAIN

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Background: The availability of oral janus kinase inhibitors, as tofacitinib, has extended the treatment pathways for management of patients with rheumatoid arthritis (RA)

Objectives: To assess the cost-effectiveness of tofacitinib as second-line treatment compared to treatment sequences containing standard biological therapies in patients with moderate to severe RA after failure to disease-modifying antirheumatic drugs (DMARDs) from the Spanish National Health System perspective.

Methods: A patient-level microsimulation model was used to compare the lifetime cost and quality-adjusted life-years (QALY) for treatment sequences initiating with tofacitinib (5mg BID) followed by biological therapies versus sequences of biological treatments excluding tofacitinib. The sequences were selected by a panel of experts based on clinical practice in Spain. Concomitant treatment with methotrexate (MTX) was considered along all the therapies in the treatment sequences.

Model parameters included age, weight, initial Health Assessment Questionnaire (HAQ) score and clinical response to short and long treatment. Efficacy was measured by means of HAQ score changes using mixed-treatment-comparisons (for the first 6 months) and data from long-term extension trials (for later periods).

Serious adverse event (SAE) information derived from literature.

The estimation of total cost for sequences included: drugs acquisition (public ex-factory prices with mandatory deduction or reference prices) and parenteral administration, disease progression and SAE management.

Local unitary costs (€, 2018) were applied. Additional comparisons were explored testing other potential sequences.

Results: The base case results showed that sequences initiating with tofacitinib provided greater outcomes than the correspondent sequences excluding tofacitinib. In scenario 1 tofacitinib+MTX→Rituximab+MTX→sc Tocilizumab+MTX→Etanercept+MTX→Certolizumab+MTX provided 13.99 QALYs versus 13.92 QALYs for adalimumab+MTX→Rituximab+MTX→sc Tocilizumab+MTX→Etanercept+MTX→Certolizumab+MTX. In scenario 2 tofacitinib+MTX→Adalimumab+MTX→Rituximab+MTX→sc Tocilizumab+MTX→Etanercept+MTX provided 13.75 QALYs versus 13.62 QALYs for Baricitinib+MTX→Adalimumab+MTX→Rituximab+MTX→sc Tocilizumab+MTX→Etanercept+MTX.

Tofacitinib-containing sequences provided lower total costs than the alternative sequences (−€5,783 and −€13,975 for the pairwise comparisons previously described), resulting, therefore, dominant options versus sequences excluding tofacitinib.

On the probabilistic sensitivity analyses, sequences initiating with tofacitinib resulted cost-effective in 64.0% (scenario 1) and 56.9% (scenario 2) of the 1,000 iterations performed, because incremental cost-effectiveness ratio fell below a €25,000/QALY gained willingness to pay threshold.

Conclusion: These results suggest that the inclusion of tofacitinib could be a dominant strategy for treatment of moderate to severe RA patients after DMARDs failure in Spain.

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THU0188 INHIBITION OF STRUCTURAL JOINT DAMAGE WITH UPADACITINIB AS MONOTHERAPY OR IN COMBINATION WITH METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS: 1 YEAR OUTCOMES FROM THE SELECT PHASE 3 PROGRAM

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Background: Long-term prevention of structural joint damage is a key treatment goal in the management of RA¹. Upadacitinib (UPA), a JAK1-selective inhibitor, inhibited the progression of structural joint damage at 6 months as monotherapy in methotrexate (MTX)-naïve RA patients (pts)² and in combination with MTX in pts with inadequate response (IR) to MTX³.

Objectives: To evaluate the progression of structural joint damage (radiographic) through Week 48 in pts with moderately to severely active RA treated with UPA monotherapy or in combination with MTX.

Methods: Radiographic progression was assessed in 2 phase 3 randomized controlled trials (RCTs), as previously described^{2,3}. MTX-naïve pts were randomized to UPA 15 or 30mg QD or MTX monotherapy [SELECT-EARLY, N=945], while MTX-IR pts were randomized to UPA 15mg QD or adalimumab (ADA) 40 mg eow or placebo (PBO), with continuous background MTX [SELECT-COMPARE, N=1629]. Both RCTs specifically enrolled pts at high risk for progression of joint damage (high disease activity including elevated hsCRP, presence of baseline erosions and ACPA and/or RF positivity^{2,3}). The mean changes (Δ) from baseline

(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.

	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)
LSM 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
LSM 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)												
	MTX-naïve (SELECT-EARLY)						MTX-IR (SELECT-COMPARE)					
	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)
LSM 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
LSM 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, %	76.4	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 randomized group. In SELECT-EARLY, non-progressors (CDR improvement ≥ 1 in EULAR EULAR) were included from both monotherapy and UPA monotherapy to UPA-MTX at Week 26. In SELECT-COMPARE, non-progressors were included from PBO to UPA, UPA to ADA and ADA to UPA at Week 26 (and all remaining non-progressors 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.

Δ mTSS, change from baseline in modified total sharp score; ADA, adalimumab; QD, every other week; LSM, least-square means; MTX, methotrexate; 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.

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

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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.

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