Lead team presentation
Tofacitinib for treating moderate to severe active rheumatoid arthritis after the failure of disease-modifying anti-rheumatic drugs

Clinical effectiveness

1st Appraisal Committee meeting, 26 July 2017

Committee D

Evidence Review Group: School of Health and Related Research (ScHARR), The University of Sheffield

Lead team: Malcolm Oswald, Femi Oyebode

Key issues: Clinical effectiveness

- Is tofacitinib comparable to the bDMARDs in clinical effectiveness in <u>moderate</u> and severe rheumatoid arthritis?

  – Is the network meta-analysis a reliable estimate of the relative effect?

- Is tofacitinib effective as a monotherapy?

- Is the EULAR response derived from DAS 28 acceptable?

- For the EULAR response outcome, does the true treatment effect lie between estimates 1 and 2, but closer to estimate 1 than 2?

- Have the crossover issues been addressed appropriately?

- Is the safety profile of tofacitinib acceptable?

Rheumatoid arthritis

- An inflammatory autoimmune disease that typically affects the synovial tissue of the small joints of the hands and feet but can affect any synovial joint, causing swelling, stiffness, pain and progressive joint destruction.

- Disease severity measured using the composite disease activity score (DAS28), includes assessment of 28 joints for swelling/tenderness, the patient's assessment of health and erythrocyte sedimentation rate or C-reactive protein

- Associated with increased mortality and increasing disability.

- No cure

Relevant NICE technology appraisals

TA	Treatment	Population
415 2016	CTZ + MTX	Adults whose disease has responded inadequately to, or who cannot tolerate, other DMARDs including at least 1 TNF inhibitor, only if: • disease activity is severe and RTX is contraindicated or not tolerated
415 2016	CTZ monotherapy	As above but only if: • RTX therapy cannot be given because MTX is contraindicated or not tolerated
375 2016	ADA, ETN, IFX, CTZ, GOL, TCZ, ABA (all + MTX)	Disease is severe (disease activity score [DAS28] >5.1) and has not responded to intensive therapy with a combination of cDMARDs
375 2016	ADA, ETN, CTZ, TCZ monotherapy	As above but for people who cannot have MTX because of contraindications or intolerance
247 2012	TCZ + MTX	Disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot have RTX because it is contraindicated or not tolerated, and TCZ is used as described for TNF inhibitor treatments in TA195, specifically the recommendations on disease activity or the disease has responded inadequately to 1 or more TNF inhibitor treatments and to RTX
225 2011	GOL + MTX	Adults whose RA has responded inadequately to other DMARDs, including a TNF inhibitor, if it is used as described for other TNF inhibitor treatments in TA195
195 2010	RTX + MTX	Adults with severe active RA with an inadequate response to, or are intolerant of, other DMARDs, including at least 1 TNF inhibitor.
195 2010	ADA, ETN, IFX, ABA (all + MTX)	As for RTX + MTX but for people who cannot have RTX because of contraindications or intolerance
195 2010	ADA, ETN monotherapy	As for RTX + MTX but for people who cannot have RTX because they have a contraindication to, or intolerance of MTX

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Details of the technology	
Technology	Tofacitinib (Xeljanz, Pfizer)
Marketing authorisation	Treatment of moderate to severe active RA in adult patients • who have responded inadequately to, or • who are intolerant to one or more DMARDs − used as monotherapy or in combination with MTX
Mechanism of action	Reversible janus kinase (JAK) inhibitor. Tofacitinib prevents full activation of lymphocytes interrupting the inflammatory process
Administration	Oral, 5 mg twice daily. Continuous treatment (no stopping rule), but dose reduction to 5 mg once daily may be considered for people severe renal impairment (creatinine clearance <30mL/min) or moderate hepatic impairment
Acquisition cost	• List price: 5 mg x 56 tab: £690.03 (6-month treatment: £4,500.60 per patient; subsequent annual cost: £9,001.19 per patient) • **Simple PAS scheme** (discount to the list price) • **Patient funding scheme** in place to provide tofacitinib free-of-charge to the NHS during the period where reimbursement is not yet available in England and Wales
Additional information	Tofacitinib was added to the EMA's list of medicines under additional monitoring in April 2017

Positioning of tofacitinib in the treatment pathway
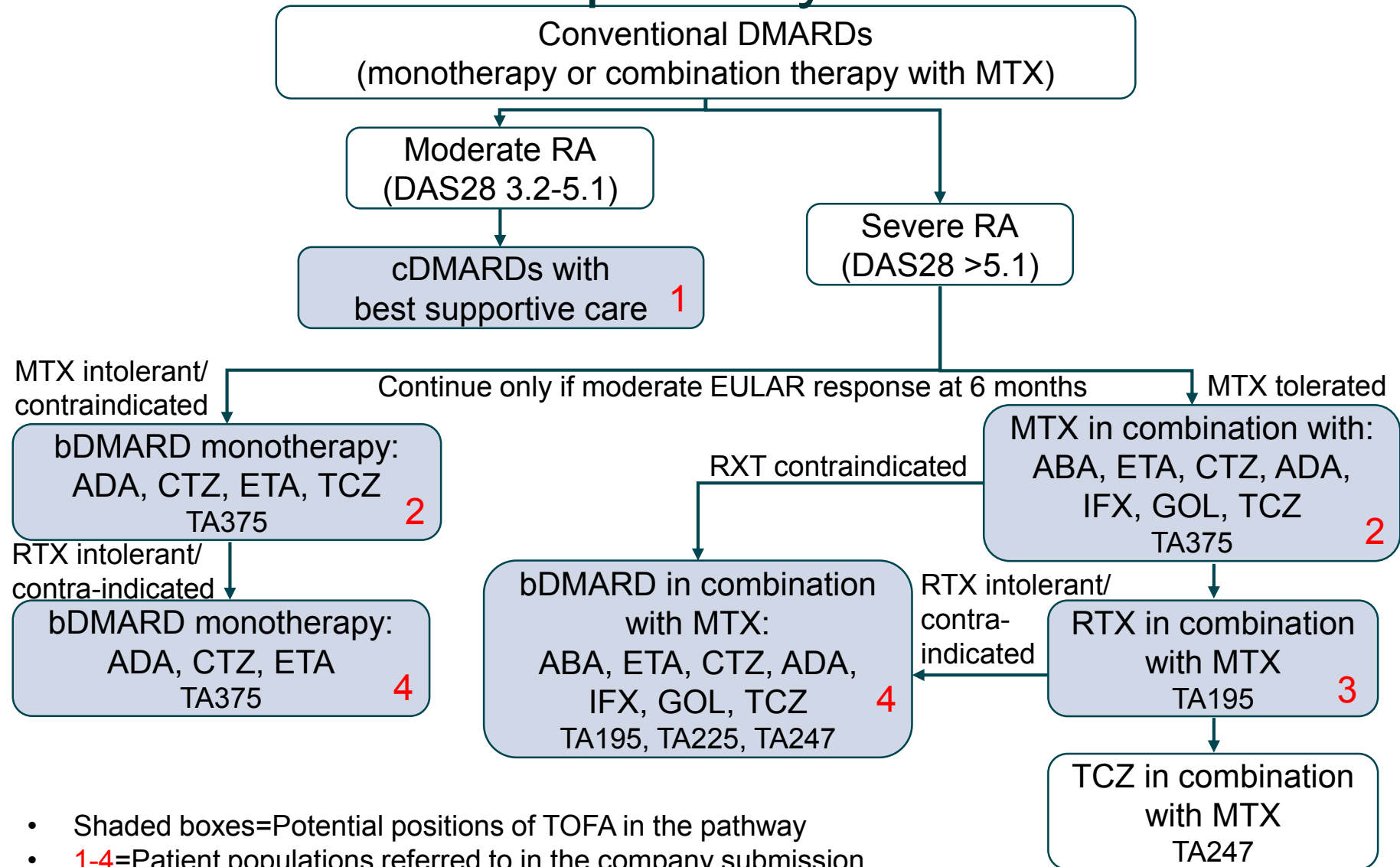
- Shaded boxes=Potential positions of TOFA in the pathway
- 1-4=Patient populations referred to in the company submission
- BARI is currently being appraised by NICE at the same positions as TOFA in the treatment pathway (FAD available June 2017, guidance to be published August 2017)

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Decision problem

	Final scope issued by NICE	Company submission	ERG's comment
Comparator(s)	<u>Severe RA **cDMARD-IR**</u>: • bDMARDs in combination with MTX (ADA, ETN, INF, CZP, GOL, TOC, ABA) • ADA, ETN, CZP, or TOC (each as monotherapy) <u>Severe RA **bDMARD-IR** RTX-eligible</u>: • RTX in combination with MTX <u>Severe RA **bDMARD-IR** RTX-ineligible</u>: • ABA, ADA, CZP, ETN, INF, TOC, or GOL, each in combination with MTX • ADA, ETN or CZP (each as monotherapy) <u>Moderate RA **cDMARD-IR**</u>: • Combination therapy with cDMARDs (including MTX and ≥1 DMARD) • cDMARD monotherapy with dose escalation • Best standard of care (only where cDMARDs are not appropriate due to intolerance)	As per the final scope issued by NICE. ***BARI appraisal: no analyses are presented for severe RA cDMARD-IR who cannot take MTX and for whom BARI would be used as monotherapy***	Currently unlicensed, unapproved or yet to be assessed by NICE were excluded in the CS (anakinra, baricitinib, sarilumab, sirukimab). Baricitinib is currently under assessment by NICE* for treating moderate to severe RA and, like tofacitinib, is an orally administered JAK inhibitor (4mg once per day).

➢ Population, intervention, outcomes and economic analysis were in line with the final scope

* FAD available, publication due August 2017

Patient perspectives
Living with rheumatoid arthritis

- 2 Submissions: National Rheumatoid Arthritis Society CEO, patient

- A chronic and painful disease with no cure

- "distressing...life-changing ...3/4 of people diagnosed when of working age...anxiety over job loss"

- "hard on your family who have to witness your pain, accommodate your lack of energy and help you when you cannot manage to do even basic tasks"

- "Pain and fatigue are the two most common symptoms...major barriers to being able to live independently"

Patient perspective
Advantages of tofacitinib

- "with the introduction of biosimilars...with local procurement deals ...that what is available in one area, may not be the same as the next"

- "Even with all the new treatments available, the heterogeneity of this disease means that there remains unmet need"

- "drugs can become less effective...the more effective alternatives, the better for every patient"

- "JAKs offer a completely new class of innovative therapy"

- "very exciting especially for patients...who have refractory disease and who have been through all the biologics"

- Oral treatment
  - Potential cost-saving for the NHS (by not having to bring people into day case care for infusions or have home healthcare companies delivering drugs)
  - Preferred by patients (who do not need to inject themselves or be infused in hospital)

Clinician perspectives

- 3 submissions: UK Clinical Pharmacy Association, British Society for Rheumatology, consultant specialist

- "The burden of rheumatoid arthritis upon individuals and society remains substantial. Developing alternative strategies to manage the disease is essential"

- "Most trials...undertaken for limited time periods in a life long disorder... cardiovascular events and raised lipids may be of concern in the long term sustained use of the drug"

- Studies focus on DAS28; "ACR20 outcomes should be given more weight"

Clinician perspectives
Tofacitinib in practice

- Differences in local treatment pathways for RA because lack of recommendations on the choice of therapy (NICE TA375: "it should be guided by cost-effectiveness")

- Tofacitinib + MTX should normally be reserved for patients showing an inadequate response to TNF-inhibition and other biologic therapies

- Use of Tofacitinib:
  - Not currently used in the NHS
  - "not for patients with severe hepatic impairment"
  - "may necessitate more frequent drug monitoring for toxicity"
  - "secondary care clinics specialising in musculoskeletal/ rheumatology"
  - no additional training or equipment required
  - "no cold-storage requirements...significantly reduces the burden to patients and risk of wasted or ineffective pharmaceuticals"

Clinical effectiveness systematic review and network meta-analysis

- Company systematic review identified 4 RCTs
  - <u>ORAL Standard (n=717)</u>: cDMARD experienced, MTX-IR *vs* MTX + ADA *vs* MTX + placebo (combination)
  - <u>ORAL Scan (n=797)</u>: cDMARD experienced, MTX-IR *vs* placebo + MTX (combination)
  - <u>ORAL Sync (n=792)</u>: DMARD-IR* *vs* placebo + MTX (combination)
  - <u>ORAL Solo (n=610)</u>: DMARD-IR* *vs* placebo (monotherapy)

- The primary outcomes for these studies were:
  - Proportion of patients who met ACR20 at Month 6 (Month 3 for ORAL Solo)
  - Mean change from baseline in HAQ-DI at Month 3
  - Proportion of patients with DAS28<2.6 at Month 6 (Month 3 for ORAL Solo)
  - *Only for ORAL Scan*: Mean change from baseline in mTSS score at Month 6

- Network meta-analysis (NMA) assessed the relative efficacy of TOF in the cDMARD-IR and bDMARD-IR populations

- Clinical effectiveness data feeding into the model: ORAL trials (probabilities of EULAR response for TOF) and NMA (probabilities of EULAR response for the comparators)

*c-DMARD include MTZ or bDMARD

Early escape design
A way to adjust for cross over

- **ORAL Scan, Sync and Standard trials:** <u>patients receiving placebo that did not respond at Month 3</u> crossover to receive TOF after early escape

- **ORAL Step and Solo trials:** <u>all patients receiving placebo</u> were switched to TOF at Month 3, <u>regardless of response</u>

2 non-responder imputation (NRI) approaches

Estimate 1

NRI <u>without</u> advancement penalty: NRI applied to Month 3 placebo non-responders

Estimate 2

NRI <u>with</u> advancement penalty: NRI applied to Month 3 placebo non-responders $\pm$ Month 3 TOF non-responders

Company favoured Estimate 1 & used in base case for all trials in the NMA

ERG believes that the true treatment effect lies between these two estimates, but closer to estimate 1 than to estimate 2 .

- The primary analysis for the ORAL Standard, Scan and Sync trials was based on NRI with advancement penalty (Estimate 2).

- In the BARI appraisal, no crossover issues were discussed.

EULAR response
EULAR response derived from DAS28 scores

➢ EULAR response was not collected from ORAL trials, therefore it was derived from DAS28

➢ The CS estimated EULAR response criteria from DAS28 scores as a good or moderate EULAR response (described in the CS as an improvement in DAS28 from baseline) for ORAL Standard, ORAL Scan and ORAL Sync at 6 months and for ORAL Solo at 3 months.

DAS28 at time point	Improvement in DAS28 from baseline		
	>1.2	≤1.2 and >0.6	≤0.6
≤3.2	Good	Moderate	No response
≤5.1 and >3.2	Moderate	Moderate	No response
>5.1	Moderate	No response	No response

➢ In the BARI appraisal, EULAR response was collected directly from RCTs therefore it did not have to be derived from DAS28

EULAR response data
ORAL Standard, Standard, Sync, Solo

Trials	EULAR response		
	TOF 5 mg	Combined PBO	P value
ORAL Standard	■	■	■
ORAL Scan	■	■	■
ORAL Sync	■	■	■
Oral Solo	■	■	■

Preliminary ACR50 results
ORAL Strategy: MTX-IR, cDMARD-experienced

Outcome		TOF 5 (N=384)	TOF 5 + MTX (N=376)	ADA 40+ MTX (N=386)
ACR50 response rate at Month 6, n (%)		147 (38.28)	173 (46.01)	169 (43.78)
Differences in ACR50 response rate				
Comparing with ADA 40 mg + MTX	Absolute difference (TOF – ADA), %	-5.50	2.23	-
	98.34% CI*	-13.98, 2.98	-6.40, 10.86	-
	Non-inferiority criteria met?	No	Yes	-
	p-value†	0.0512	<0.0001	-
Comparing with TOF 5 mg + MTX	Absolute difference (TOF mono – TOF+MTX), %	-7.73	-	-
	98.34% CI*	-16.29, 0.83	-	-
	Non-inferiority criteria met?	No	-	-
	p-value†	0.2101	-	-

Abbreviations: ACR, American College of Rheumatology; ADA, adalimumab; CI, confidence interval; MTX, methotrexate; TOF, tofacitinib.
†p-values are from non-inferiority hypothesis testing. The p-values are multiplicity-adjusted and should be compared with 0.05.
* Non-inferiority between groups was shown if the lower bound of the 98·34% CI of the difference between comparators was larger than –13·0%

➢ TOF + MTX is non-inferior to ADA + MTX
➢ TOF monotherapy was shown not to be non-inferior to TOF + MTX and ADA + MTX

ERG critique on adverse events

- Initial CS: insufficient literature searches, lack of full and transparent safety due to pooling both combination and monotherapy trials, no information of all AEs vs. the control arm

- Updated CS: highest incidence rates of AEs for serious infections and herpes zoster

  – TOF infection rate: ▮▮▮▮ per 100 patient years (company) *vs* 4.3 per 100 patient years (ERG*); substantially higher within Asia (7.7 per 100 patient years)

  – No data on comparator's infection rates whereas ERG* found data estimating higher rates than bDMARDs (adalimumab: 2.8 per 100 patient years) and for placebo (1.5 per 100 patient years)

  – NMA by Curtis *et al.* (2016): incidence of herpes zoster was significantly higher in TOF than in bDMARDs

- BARI appraisal: majority of herpes zoster cases were mild to moderate in severity and complicated cases were uncommon

- SPC of BARI and TOF report the same frequency estimate of Herpes Zoster (common: ≥ 1/100 to < 1/10)

- ERG conducted their own search (2015 to 2017): no relevant primary studies were identified

*Based on Winthrop *et al.*, (2014) reviewed the tofacitinib RA development programme from the phase II, III and long-term extension studies; use a data cut from 2011.

ERG critique of the NMA

- NMAs were performed separately for the cDMARD-IR and bDMARD-IR populations

- Several issues with company approaches including:
  - Use of different models for EULAR response in the 2 populations (binomial and multinomial)
  - Use of a random effects (RE) model for the cDMARD-IR population and a fixed effects model was used for the bDMARD-IR population
  - Statistical assessments of heterogeneity I^2 suggested that a RE model would be more appropriate for EULAR response and HAQ-DI (cDMARD-IR population)
  - Use of LARA trial (may underestimate the treatment effect of ETN)
  - Use of a uniform prior in the RE model when data are sparse lead to implausible posterior uncertainty in the results
  - Unclear how odd ratios were calculated in bDMARD-IR population (because of use of probit model)

- Estimate 1 (NRI approach without penalty) was used in the base case NMA to calculate the relative treatment effect of TOF in ORAL trials, which overestimate the result. Conclusions for efficacy ranking of TOF among the bDMARDs varies markedly depending on the NRI approach (with or without penalty) applied to the TOF trials with early escape. NMA results should be interpreted with caution.

ERG request for NMA additional analysis

Analysis	Original CS	Change requested by ERG
NMA	Different models for both populations	Same model for both populations (multinomial, fixed effect)
Prior used for the treatment effect relative to the reference treatment	Vague prior, uniform [0,5]	Informative prior, truncated log normal (-2.56, 1.74[2])
Non-responder imputation	Estimate 1	Estimate 2
Studies included in NMA	Include all studies following exclusion criteria	• Exclude studies which only reported DAS from the NMA and did not report EULAR[1] • Exclude studies with patients with prior bDMARD use[2]
Inclusion of etanercept	LARA trial (assuming intensified cDMARD was the same as cDMARD)	SWEFOT trial and LARA trial (without assuming intensified cDMARD was the same as cDMARD)
Reference treatment	placebo + cDMARD/cDMARD	No change

[1]In response to the clarification letter, the company stated that "these original papers appear to have been using the term DAS when EULAR would have been more accurate. On the basis of both the review of the original publications, and their inclusion in previous technology appraisals in RA, it should be considered that all 7 of the publications have EULAR data readily available, and do not need to be excluded from the analysis." Hence, there were no changes to the data used regarding this point. [2]A sensitivity analysis of not excluding these studies was also requested. The results were similar.

EULAR response for cDMARD-IR (combination)
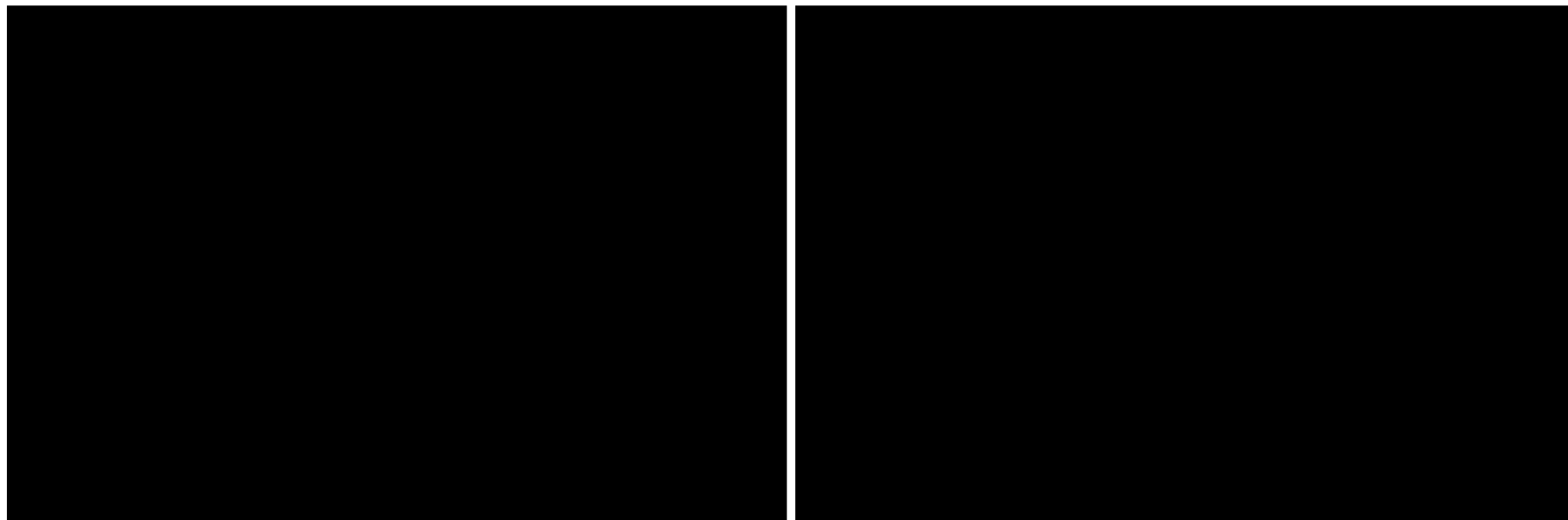
ESTIMATE 1

ESTIMATE 2
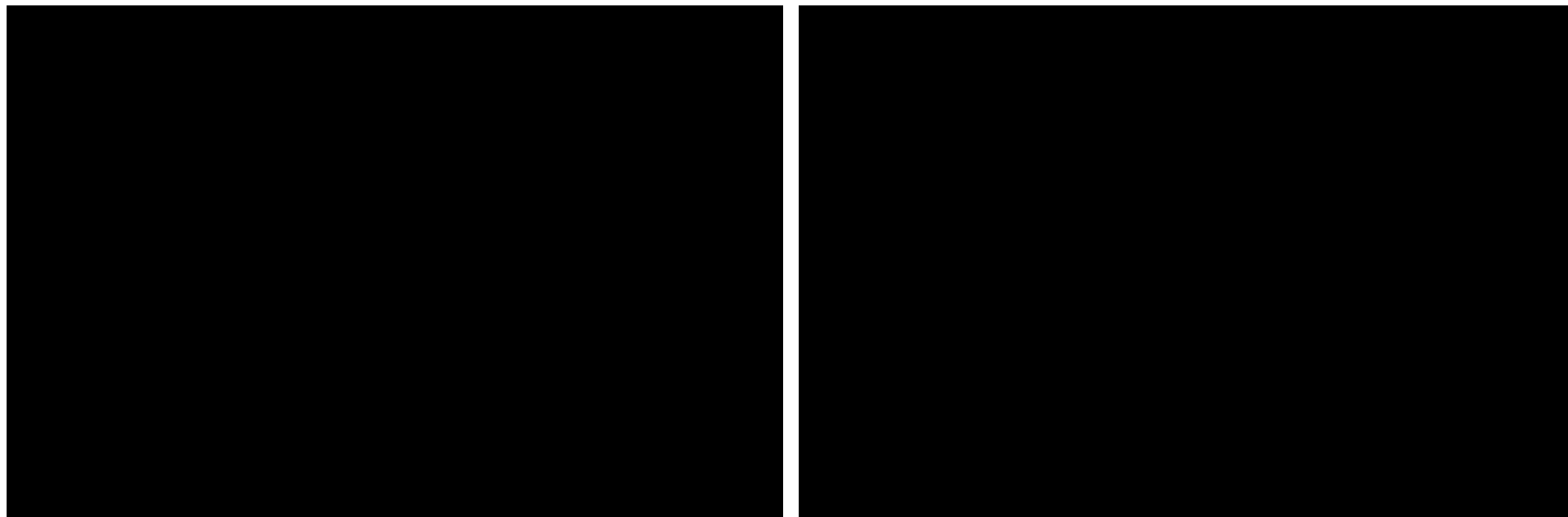
The analyses including patients with and without prior biologics provide very similar results for the cDMARD-IR population, except that the treatment effect of TCZ + cDMARD *vs* cDMARD reduced noticeably using the studies without prior biologics.

*The company identified a "*copy and paste*" error in their submission related to the analysis of patient level data for Estimate 2 in the Oral Sync trial. Corrected results were provided by the company in an addendum.

EULAR response for cDMARD-IR (monotherapy)
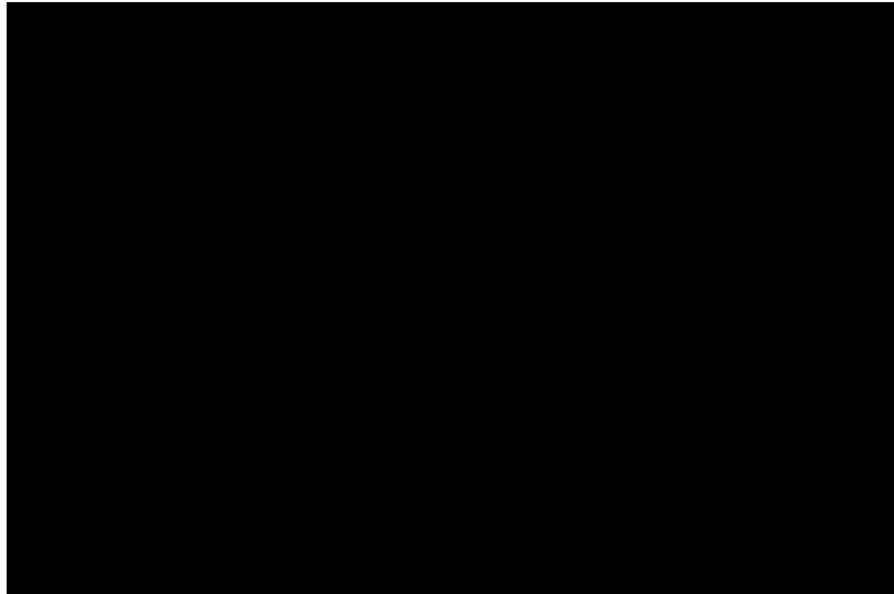
ESTIMATE 1

ESTIMATE 2

The analyses including patients with and without prior biologics use provide very similar results for the cDMARD-IR population, except that the treatment effect of ADA monotherapy became statistically significant without prior biologics.

*The company identified a "*copy and paste*" error in their submission related to the analysis of patient level data for Estimate 2 in the Oral Sync trial. Corrected results were provided by the company in an addendum.

EULAR response for bDMARD-IR (Estimate 2*)

*The company did not provide the results using Estimate 1

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- Is tofacitinib effective as a monotherapy?

- Is the EULAR response derived from DAS 28 acceptable?

- For the EULAR response outcome, does the true treatment effect lie between estimates 1 and 2, but closer to estimate 1 than to estimate 2?

- Has crossover been addressed appropriately?

- Is the safety profile of tofacitinib acceptable?