Double-Blind Study of Tocilizumab Plus Methotrexate vs Tocilizumab Plus Placebo in Patients With Active Rheumatoid Arthritis Despite Prior Methotrexate: Progression of Structural Damage, Quality of Life, and Physical Function at 24 Weeks

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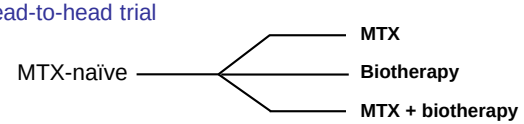
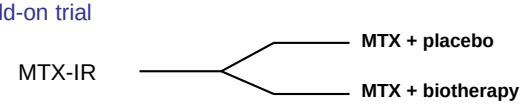
TCZ switch or add-on strategy in RA-MTX-IR

MTX – biologics clinical trial design

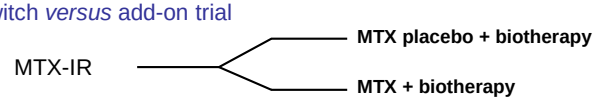
- Head-to-head trial



- Add-on trial

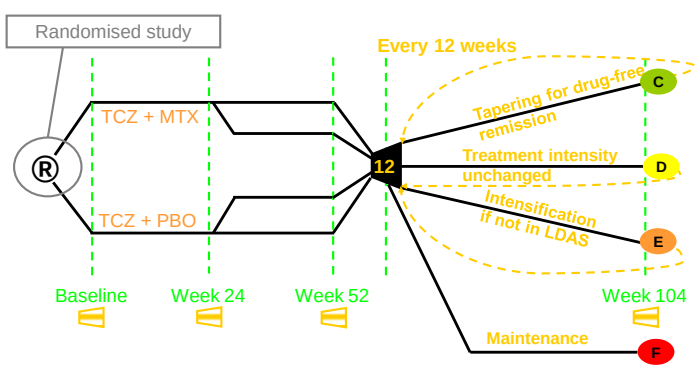


- Switch *versus* add-on trial



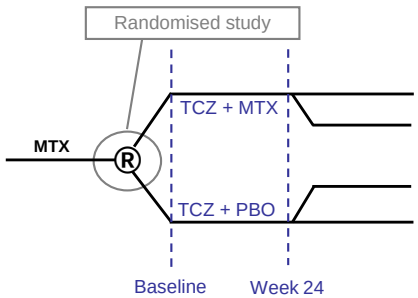
TCZ switch or add-on strategy in RA-MTX-IR

ACT-RAY study design



TCZ switch or add-on strategy in RA-MTX-IR

ACT-RAY study design



TCZ switch or add-on strategy in RA-MTX-IR

ACT-RAY: Study objectives

- Objective at week 24
  To assess the efficacy and safety of **adding TCZ to MTX *versus* switching to TCZ** (placebo-controlled) in MTX inadequate responders with moderate to severe active RA
  - TCZ + placebo vs. TCZ + MTX
  - Clinical endpoints
  - Structural endpoints
  - Safety
- Additional objective at Wk 52
  - Inhibition of progression of structural damage
  - Sustainability of the response
- Additional objective at Wk 104
  - Potential of TCZ to lead to drug-free remission

TCZ switch or add-on strategy in RA-MTX-IR

ACT-RAY Study: Inclusion criteria

- Diagnosis: RA (1987 ACR criteria)
- Active: DAS >4.4
- Severe: at least one radiological erosion
- Refractory: currently receiving MTX

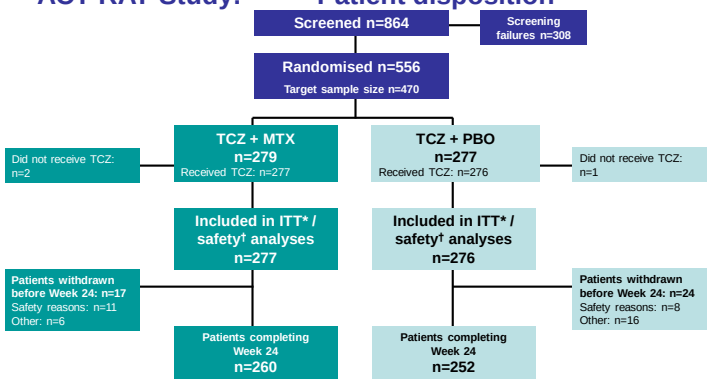
TCZ switch or add-on strategy in RA-MTX-IR

ACT-RAY Study: Statistical methodology

- Primary end-point: % patients on DAS28 remission at week 24
- Superiority trial (hypothesis)
  - Switch strategy: 30% remission rate
  - Add-on strategy: 42.5% remission rate
- Sample size: $\alpha = 5\%$, $\beta = 20\%$, $\Delta = 12.5\%$
  ⇨ 235 patients per arm

TCZ switch or add-on strategy in RA-MTX-IR

ACT-RAY Study: Patient disposition



*Intent-to-treat (ITT) population: all patients who received at least 1 dose of TCZ and had at least 1 post-baseline efficacy assessment.
†Safety population: all patients who received at least 1 dose of study medication and who had post-baseline safety assessments.

TCZ switch or add-on strategy in RA-MTX-IR

ACT-RAY Study: Baseline characteristics (1/2)

Mean (SD) unless otherwise stated	TCZ + MTX n=277	TCZ + PBO n=276
Female, % (n)	81.9% (227)	78.6% (217)
Age, years	53.0 (±13.40)	53.6 (±11.91)
Patients aged 65 and older, % (n)	53% (19.1)	51% (18.8)
Body weight, kg	70.5 (±14.71)	71.8 (±15.92)
BMI, kg/m^2	26.3 (±5.19)	26.5 (±5.14)
Duration of RA, years	8.2 (±8.04)	8.3 (±8.37)
Categorical duration of RA in years, % (n)		
<2	18.4% (51)	23.9% (66)
≥2 to <5	27.4% (76)	24.6% (68)
≥5 to <10	23.8% (66)	22.8% (63)
≥10	30.3% (84)	28.6% (79)

Population: ITT

TCZ switch or add-on strategy in RA-MTX-IR

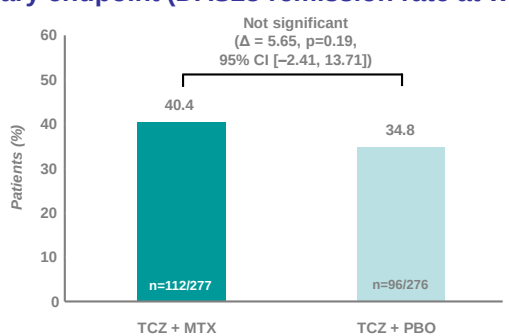
ACT-RAY Study: Baseline characteristics (1/2)

Mean (SD) unless otherwise stated	TCZ + MTX n=277	TCZ + PBO n=276
DAS28-ESR	6.33 (±0.98)	6.36 (±1.00)
Swollen joint count	14.4 (±8.9)	15.3 (±10.2)
Tender joint count	25.8 (±13.9)	26.6 (±15.2)
Physician's Global (100 mm VAS)	61.8 (±16.3)*	61.8 (±16.9)‡
Patient's Global (100 mm VAS)	65.4 (±19.3)	66.1 (±18.8)
VAS Pain (100 mm)	58.6 (±20.6)	61.3 (±20.1)
ESR, mm/hr	39.9 (±24.2)	39.6 (±24.5)
hsCRP, g/l	15.8 (±22.3)	17.3 (±22.4)
HAQ-DI	1.34 (±0.66)*	1.35 (±0.61)†
Genant-modified Sharp Score	30.4 (±31.8)	37.1 (±40.5)
Corticosteroid use, % (n)	48.4% (134)	48.9% (134)*
No. of previous DMARDs§	1.9 (±1.1)	1.9 (±1.0)

Population: ITT
Baseline for ACR core set measures is the last assessment before the start of study medication.
n represents the number of patients contributing to summary statistics; *n=274; †n=271; ‡n=273
§Including MTX received prior to study entry

TCZ switch or add-on strategy in RA-MTX-IR

ACT-RAY: Primary endpoint (DAS28 remission rate at week 24)



Analysis population: ITT

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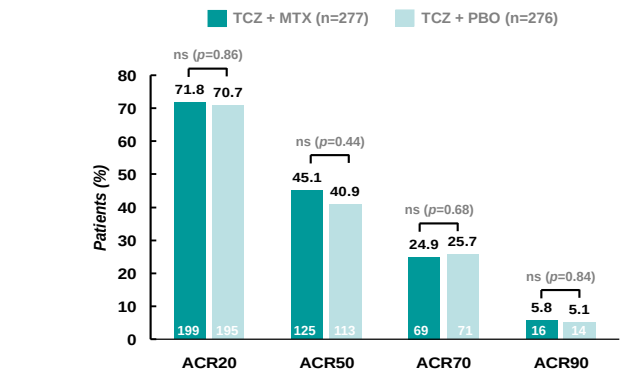
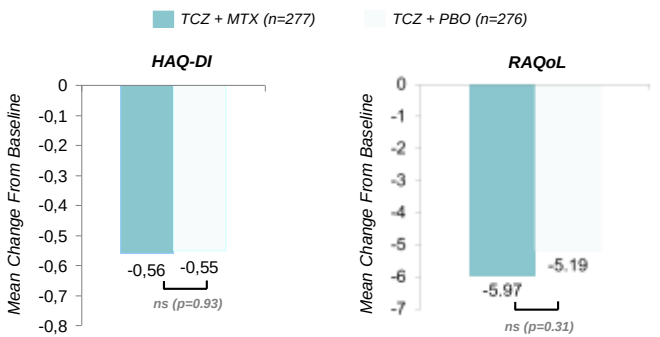
ACT-RAY: Secondary endpoint (ACR responses at week 24)



Analysis population: ITT

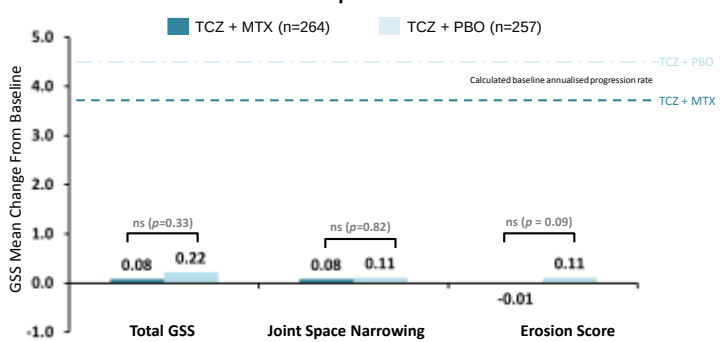
TCZ switch or add-on strategy in RA-MTX-IR

Change From Baseline in QoL Measures



NS, not significant.
P values are for between-group differences from a two-sided Wilcoxon rank-sum test of no difference between the 2 treatment groups in change from baseline

Mean Change From Baseline in Genant-modified Sharp Score



GSS, Genant-modified Sharp Score; gTSS, Genant-modified total Sharp Score; NS, not significant.
Adjusted p-values compare TCZ + MTX to TCZ + PBO; analysis of covariance model included BL DAS28 and baseline score as a covariate; n = number of evaluable patients
Analysis population: ITT (all patients who received at least 1 dose of study medication).

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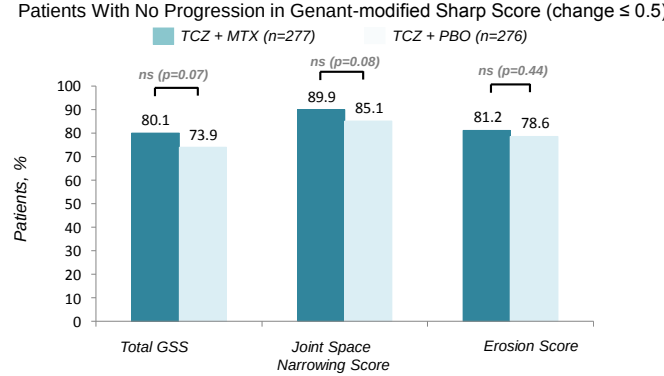
Patients With No Progression in Genant-modified Sharp Score (change ≤ 0.5)



GSS, Genant-modified Sharp Score; NS, not significant.
P values are for between-group differences from a two-sided Cochran-Mantel-Haenszel test stratified for site and baseline DAS28.
"No progression" defined as change in GSS score ≤ 0.5.
Patients without radiographic assessment at baseline or Week 24 were considered as progressors.

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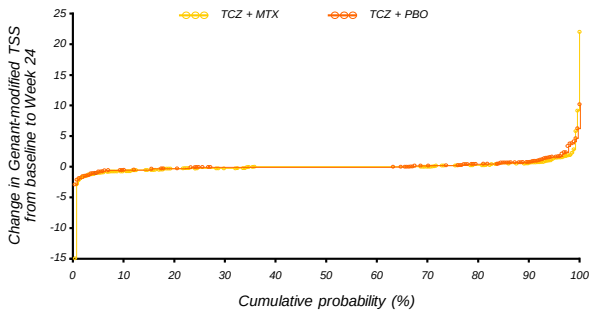
Change in Genant-modified TSS from baseline to Week 24



Analysis population: ITT
Data source: F39abc F40abcdef Cum ProbPlot.doc: F39a_gei_cumprob

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TCZ switch or add-on strategy in RA-MTX-IR

ACT-RAY: Safety profile (overview)

	TCZ + MTX n=277	TCZ + PBO n=276
Total exposure to TCZ, patient-years	**118.31**	**116.40**
Adverse events		
Total patients with at least 1 AE, % (n)	**70.0% (194)**	**72.5% (200)**
Total no. of AEs	**581**	**544**
Rate of AEs (per 100 PY)	**491**	**467**
Serious adverse events		
Total patients with at least 1 SAE, % (n)	**6.1% (17)**	**5.8% (16)**
Total no. of SAEs	**25**	**21**
Rate of SAEs (per 100 PY)	**21**	**18**
Serious infections		
Total patients with at least 1 SIE, % (n)	**2.2% (6)**	**2.2% (6)**
Total no. of SIEs	**7**	**7**
Rate of SIEs (per 100 PY)	**6**	**6**
Total no. of deaths	**1**	**2**

TCZ switch or add-on strategy in RA-MTX-IR

ACT-RAY: Safety profile (hepatic enzymes)

	% (n)	TCZ + MTX Baseline n=265	TCZ + MTX Week 24 n=235	TCZ + PBO Baseline n=266	TCZ + PBO Week 24 n=229
ALT	Normal	92.1% (244)	73.2% (172)	91.4% (243)	86.0% (197)
	1–1.5 x ULN	6.4% (17)	16.2% (38)	6.8% (18)	9.2% (21)
	1.5–3 x ULN	0.8% (2)	8.5% (20)	1.9% (5)	4.4% (10)
	3–5 x ULN	0.4% (1)	1.7% (4)	–	0.4% (1)
	>5 x ULN	0.4% (1)	0.4% (1)	–	–

	% (n)	TCZ + MTX Baseline n=265	TCZ + MTX Week 24 n=235	TCZ + PBO Baseline n=266	TCZ + PBO Week 24 n=229
AST	Normal	97.0% (257)	82.5% (193)	94.3% (250)	91.7% (210)
	1–1.5 x ULN	2.3% (6)	15.4% (36)	4.9% (13)	7.4% (17)
	1.5–3 x ULN	0.4% (1)	1.3% (3)	0.8% (2)	0.9% (2)
	3–5 x ULN	–	0.9% (2)	–	–
	>5 x ULN	0.4% (1)	–	–	–

TCZ switch or add-on strategy in RA-MTX-IR

ACT-RAY: Conclusions

- The study did not demonstrate superiority of the add-on strategy over the switch to TCZ monotherapy strategy
- No overt differences in the safety profile were observed between the two treatments
- Unlike traditional RA biologics, background MTX might not be needed with TCZ to achieve clinically meaningful responses
  - Data on sustainability of the symptomatic effect (1 year) is pending
  - Data on progression of structural damage (1 and 2 yrs) is pending
  - Data on drug free remission possibility is pending (2 years)

TCZ switch or add-on strategy in RA-MTX-IR

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