Tocilizumab in COVID-19

Update - 8th October 2020

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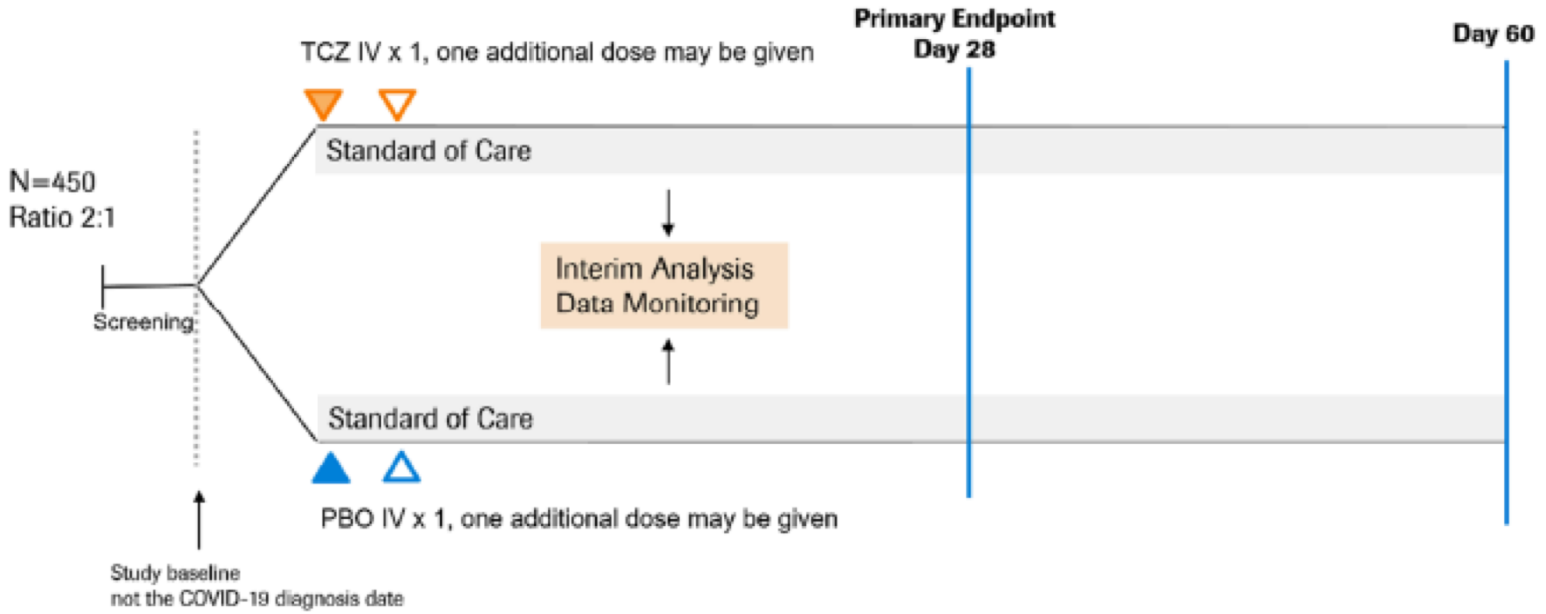
COVACTA Study Design



IV = intravenous; PBO = placebo; TCZ = tocilizumab.

- Primary endpoint: clinical status on 7-category ordinal scale
- 452 patients enrolled, 438 in mITT population
- Patients who received 2 doses: 30% PBO, 22% TCZ

Demographics

- Groups are well balanced
- Approximately ⅔ rds of the patients were male, slightly more patients ≥ 85 years old in TCZ

	PBO (N=144)	TCZ 8 mg/kg (N=294)
Sex		
n	144	294
Male	101 (70.1%)	205 (69.7%)
Female	43 (29.9%)	89 (30.3%)
Age (yr)		
n	144	294
Mean (SD)	60.6 (13.7)	60.9 (14.6)
Median	61.5	63.0
Min - Max	22 - 93	25 - 96
Age group (yr)		
n	144	294
18-64	81 (56.3%)	163 (55.4%)
65-84	60 (41.7%)	117 (39.8%)
>=85	3 (2.1%)	14 (4.8%)
Weight (kg)		
n	143	294
Mean (SD)	88.09 (24.31)	88.90 (23.64)
Median	82.00	84.60
Min - Max	37.3 - 185.9	43.5 - 186.0
Female Fertility Status		
n	43	89
Yes	9 (20.9%)	24 (27.0%)
No	34 (79.1%)	65 (73.0%)
Post-Menopausal	32 (74.4%)	52 (58.4%)
Pre-Menarchal	0	1 (1.1%)
Surgically Sterile	1 (2.3%)	12 (13.5%)

Baseline Disease Characteristics

- Generally well-balanced. 10% difference in steroid use at baseline (more on PBO)

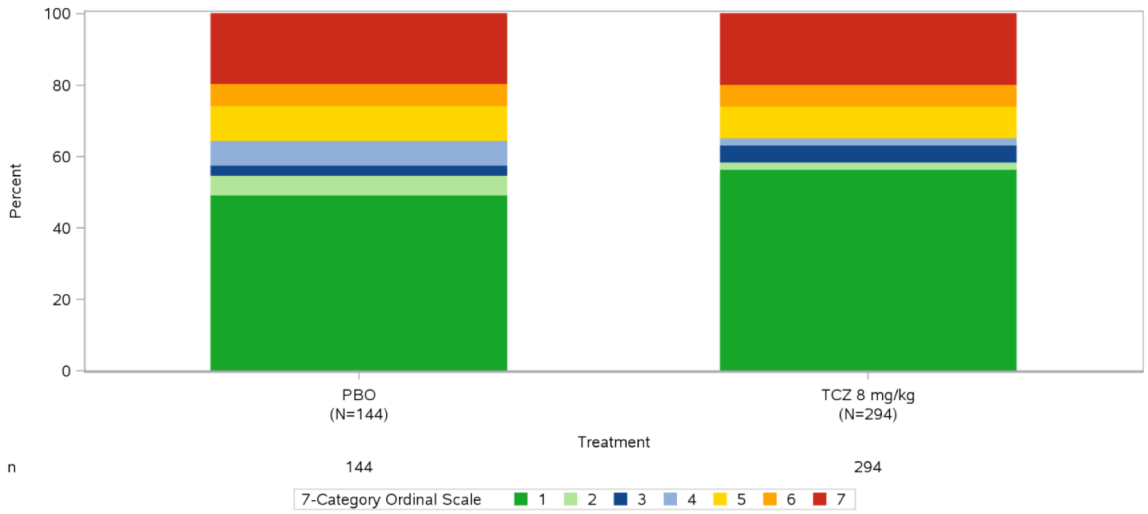
	PBO (N=144)	TCZ 8 mg/kg (N=294)
NEWS2 Score		
n	144	294
Mean (SD)	7.01 (3.03)	7.06 (3.00)
Median	7.00	7.00
Min - Max	0.0 - 14.0	0.0 - 15.0
Ordinal Scale for Clinical Status (a)		
n	144	294
1	0	0
2	6 (4.2%)	9 (3.1%)
3	44 (30.6%)	78 (26.5%)
4	39 (27.1%)	94 (32.0%)
5	15 (10.4%)	45 (15.3%)
6	39 (27.1%)	68 (23.1%)
7	1 (0.7%)	0
IL-6 Level (ng/L) (b)		
n	100	233
Mean (SD)	195.42 (368.19)	201.94 (418.41)
Median	71.15	88.10
Min - Max	3.1 - 2810.0	3.1 - 4020.0
CRP Levels (mg/L)		
n	125	237
Mean (SD)	172.64 (113.97)	168.35 (101.36)
Median	150.30	157.20
Min - Max	1.6 - 499.6	1.1 - 446.6
Ferritin Levels (pmol/mL)		
n	128	241
Mean (SD)	4027.27 (45430.66)	6891.07 (106735.92)
Median	2.17	2.30
Min - Max	0.1 - 514000.0	0.0 - 1657000.0
Mechanical Ventilation (c)		
n	144	294
Yes	54 (37.5%)	111 (37.8%)
No	90 (62.5%)	183 (62.2%)
Steroid Use (d)		
n	144	294
Yes	41 (28.5%)	57 (19.4%)
No	103 (71.5%)	237 (80.6%)

(a) Ordinal Scale for Clinical Status 1. Discharged (or "ready for discharge") 2. Non-ICU hospital ward (or "ready for hospital ward") not requiring supplemental oxygen 3. Non-ICU hospital ward (or "ready for hospital ward") requiring supplemental oxygen 4. ICU or non-ICU hospital ward, requiring non-invasive ventilation or high-flow oxygen 5. ICU, requiring intubation and mechanical ventilation 6. ICU, requiring ECMO or mechanical ventilation and additional organ support 7. Death
(b) Any values reported as BLQ were set to the lower limit of detection for the assay (3.12 pg/mL).
(c) as listed in IxRS
(d) Between Day -7 and Day 1. Steroid use only includes systemic use. Anti-viral treatment includes Lopinavir;Ritonavir, Remdesivir, Lopinavir, Ritonavir, Chloroquine, Hydroxychloroquine and Hydroxychloroquine Sulfate.

Primary Endpoint

Clinical Status assessed using 7-category Ordinal Scale at Day 28 (Week 4)

	PBO (N=144)	TCZ 8 mg/kg (N=294)
Number of patients in each category		
Week 4		
n	144	294
1	71 (49.3%)	166 (56.5%)
2	8 (5.6%)	6 (2.0%)
3	4 (2.8%)	14 (4.8%)
4	10 (6.9%)	6 (2.0%)
5	14 (9.7%)	26 (8.8%)
6	9 (6.3%)	18 (6.1%)
7	28 (19.4%)	58 (19.7%)



Day 28 (Week 4) outputs displaying data post LOCF (Last Post-Baseline Observation Carried Forward) imputation.

Primary Endpoint

Clinical status assessed using a 7-category ordinal scale at Day 28 (Week 4)

No Statistical Significance was found for the Difference between TCZ and PBO Clinical Status assessed using 7-category Ordinal Scale at Week 4, with medians of TCZ = **1.0**; PBO = **2.0**, a Difference in Medians [95% CI] = **-1.0 [-2.5 , 0.0]** and a P-Value* of **0.3600.** The Odds Ratio* [95% CI] was **1.19 [0.81 , 1.76]**

	PBO (N=144)	TCZ 8 mg/kg (N=294)
Clinical Status		
n	144	294
Median	2.0	1.0
95% CI	(1.0, 4.0)	(1.0, 1.0)
25th Percentile	1.0	1.0
95% CI	(1.0, 1.0)	(1.0, 1.0)
75th Percentile	6.0	6.0
95% CI	(5.0, 7.0)	(5.0, 6.0)
Difference in Medians		-1.0
95% CI (a)		(-2.5, 0.0)
P-Value (Van Elteren Test)		0.3600

LOCF (Last Post-Baseline Observation Carried Forward) Imputation used for Withdrawals.
*P-Value and Odds Ratio from the Van Elteren test and Ordinal Logistic Regression respectively, both stratified by region and mechanical ventilation at baseline

Key Secondary Endpoints

Difference in Mortality at Day 28 (Week 4)

No Statistical Significance was seen for the Difference between TCZ and PBO in the % of patients that died by Week 4; TCZ = **19.7%** and PBO = **19.4%** with a Weighted Difference [95% CI] of **0.3% [-7.6%, 8.2%]** and a P-Value* of **0.9410**

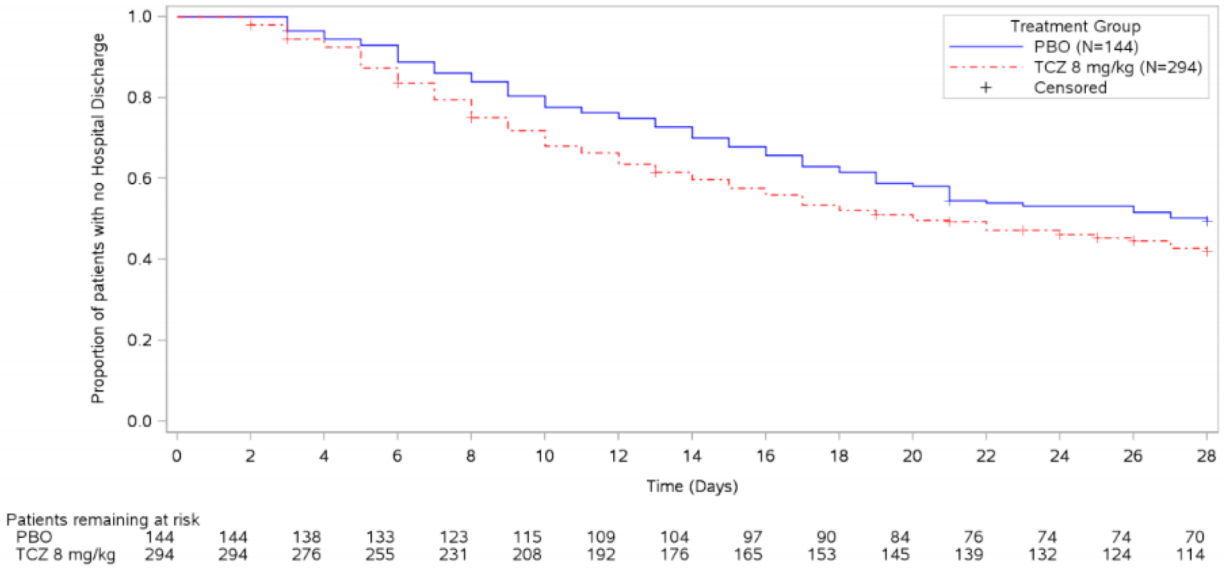
	PBO (N=144)	TCZ 8 mg/kg (N=294)
Mortality	28 (19.4%)	58 (19.7%)
95% CI	(13.0%, 25.9%)	(15.2%, 24.3%)
Weighted Difference in % (a)		0.3%
95% CI		(-7.6%, 8.2%)
P-Value (CMH Test)		0.9410

*P-Value from Extended Cochran–Mantel–Haenszel Test stratified by region and mechanical ventilation at baseline

Key Secondary Endpoints

Time to Hospital Discharge or "Ready for Discharge" to Day 28 (Week 4)

Nominal Statistical Significance was found for the difference in Time to Hospital Discharge or "Ready for Discharge", with median times [95% CI] (days) of TCZ = **20.0 [17.0 , 27.0]** , PBO = **28.0 [20.0 , NE],** a P-Value* of **0.0370**, and Hazard Ratio* [95% CI] (ref=PBO) = **1.350 [1.02 , 1.79]**

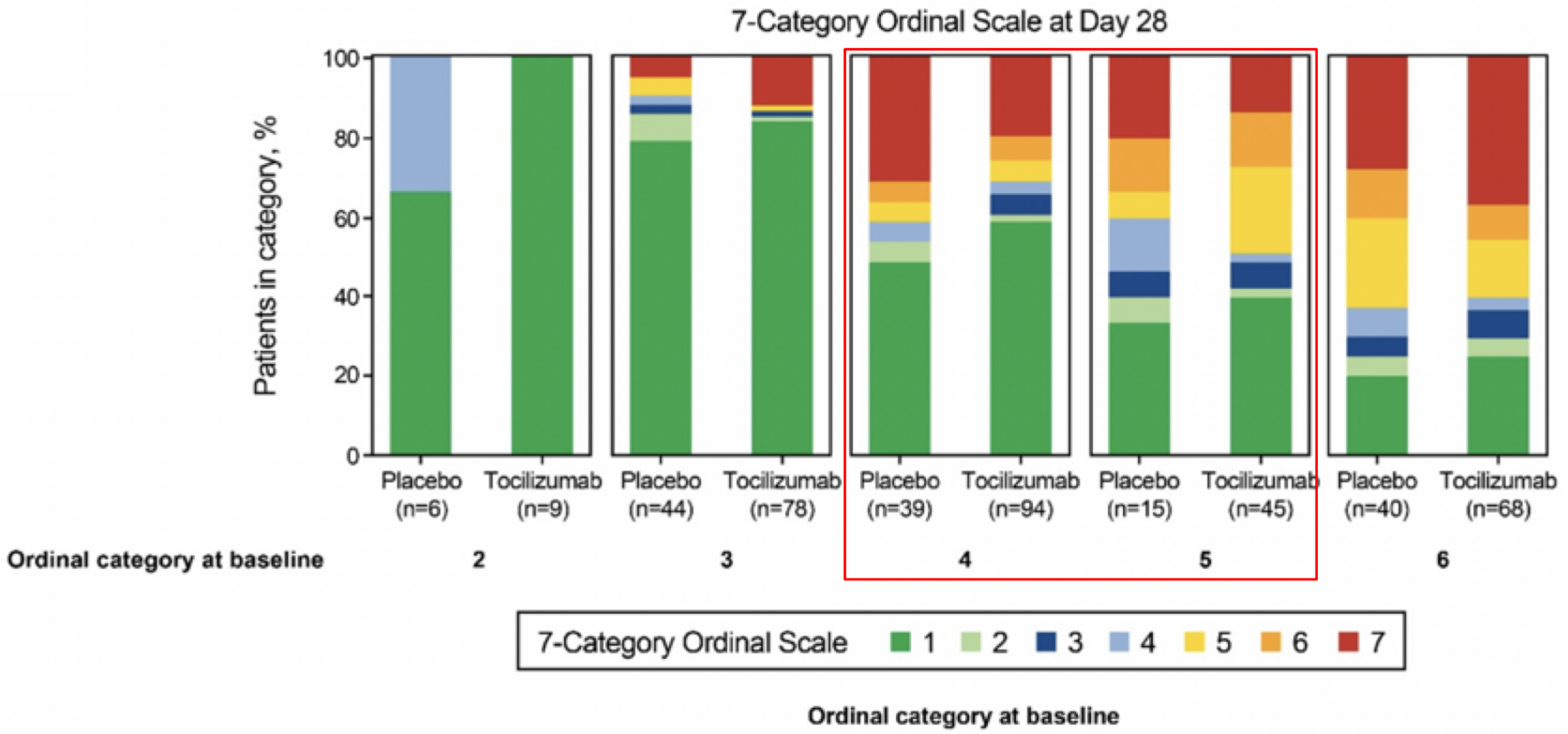


*P-Value from Log-Rank Test and HR from Cox Proportional Hazards Model both stratified by region and mechanical ventilation at baseline

Cumulative incidence function plot produced using the nonparametric Aalen–Johansen estimator.

Subgroup Analyses

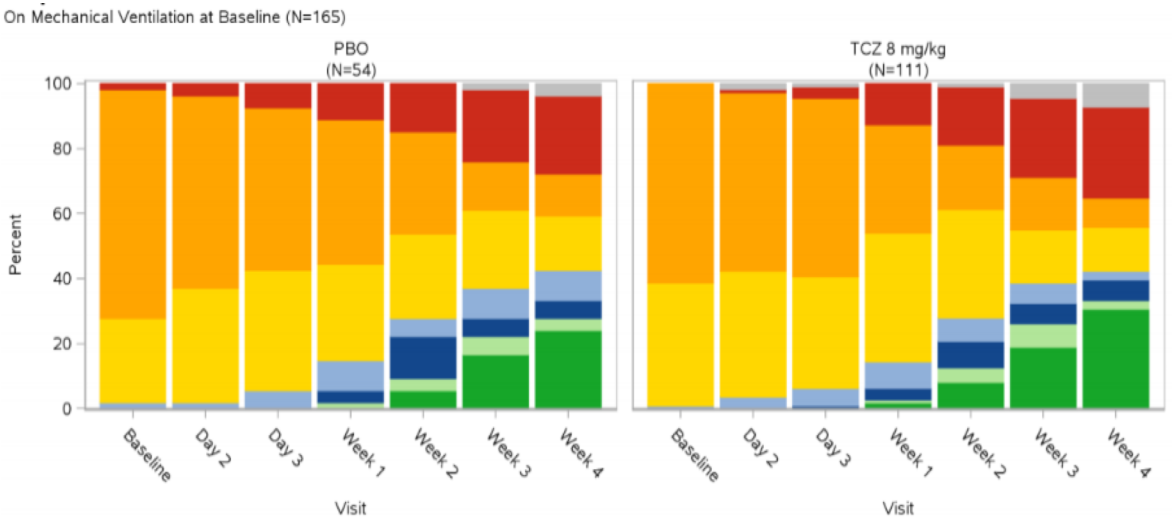
Clinical status at day 28 by baseline ordinal category



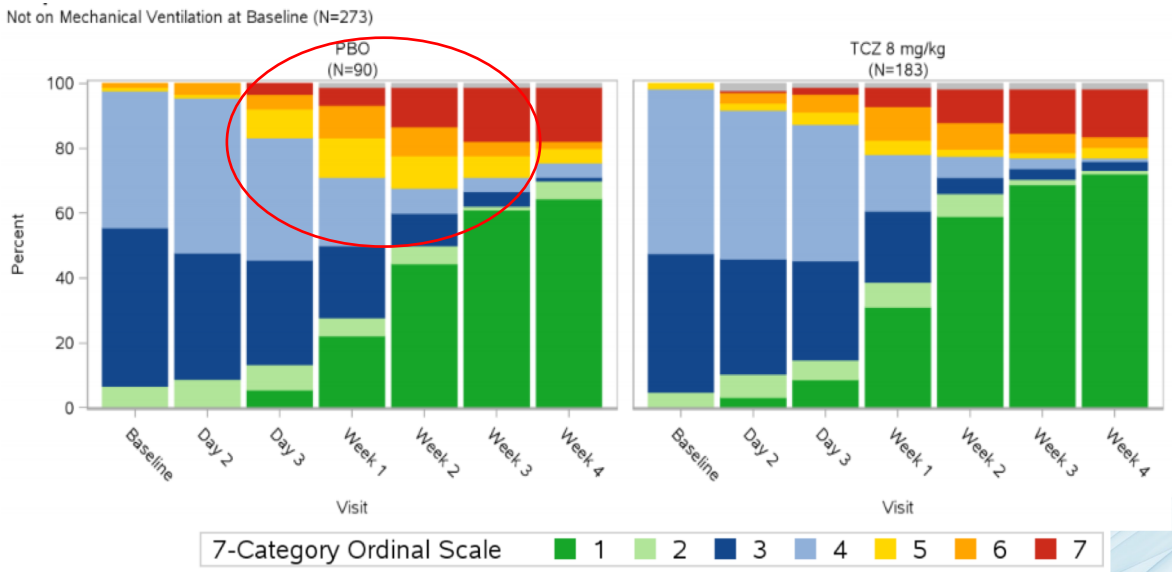
Subgroup Analyses

Clinical status assessed using a 7-category ordinal scale at Day 28 (Week 4)

On Mechanical Ventilation at Baseline



Not on Mechanical Ventilation at Baseline



Other Secondary Endpoints

Time to clinical failure (death, mechanical ventilation, ICU transfer, or withdrawal) among patients not on MV at baseline

	PBO N=90	**TCZ** N=183
With event (%)	38 (42.2%)	53 (29.0%)
Time to event (days) Median 95% CI	NE (11.0, NE)	NE NE
Stratified analysis P value HR (cox proportional hazard model, ref=PBO) (95% CI)	0.0253 0.614 (0.40, 0.94)	

Other Secondary Endpoints

Incidence of mechanical ventilation or death among patients not intubated at baseline

	PBO N=90	**TCZ** N=183
Pts with MV or death	33 (36.7%)	51 (27.9%)
95% CI	(26.7%, 46.6%)	(21.4%, 34.4%)
Weighted difference in % 95% CI	-8.9% (-20.7%, 3.0%)	
P value (CMH test)	0.1355	

Other Secondary Endpoints

Incidence of ICU transfer or death among patients not in ICU at baseline

	PBO N=64	**TCZ** N=127
Pts with ICU admission or death	26 (40.6%)	30 (23.6%)
95% CI	(28.6%, 52.7%)	(16.2%, 31.0%)
Weighted difference in % 95% CI	-16.0% (-30.2%, -1.8%)	
P value (CMH test)	0.0229	

Other Secondary Endpoints

Duration of ICU stay shorter among TCZ patients (mITT population)

	PBO N=144	**TCZ** N=294
Median ICU stay (days)	15.5	9.8
95% CI	(8.7%, 25.5%)	(7.0%, 15.7%)
Weighted difference (days) 95% CI	-5.8 (-15.0%, 2.9%)	
P value (CMH test)	0.0454	

Safety Overview

No new safety signals. Safety profile is similar in both arms.

Number (%)	to Week 4		to Clinical Cutoff Date	
	PBO N = 143	TCZ N = 295	PBO N = 143	TCZ N = 295
Total Pts with at least one AE Total AEs	116 (81.1%) 360	228 (77.3%) 778	118 (82.5%) 423	237 (80.3%) 906
Total Pts with at least one SAE Total SAEs	55 (38.5%) 101	103 (34.9%) 160	62 (43.4%) 117	113 (38.3%) 183
Total Pts with at least one Infection and infestation AE	58 (40.6%)	113 (38.3%)	62 (43.4%)	126 (42.7%)
Total Pts with at least one Infection and infestation SAE	37 (25.9%)	62 (21.0%)	41 (28.7%)	70 (23.7%)
Total Pts who withdrew treatment due to an AE	1 (0.7%)	0	1 (0.7%)	0
Deaths	28 (19.6%)	58 (19.7%)	33 (23.1%)	70 (23.7%)
Total number of patients withdrawn from study due to an AE (excluding deaths)	0	0	0	0

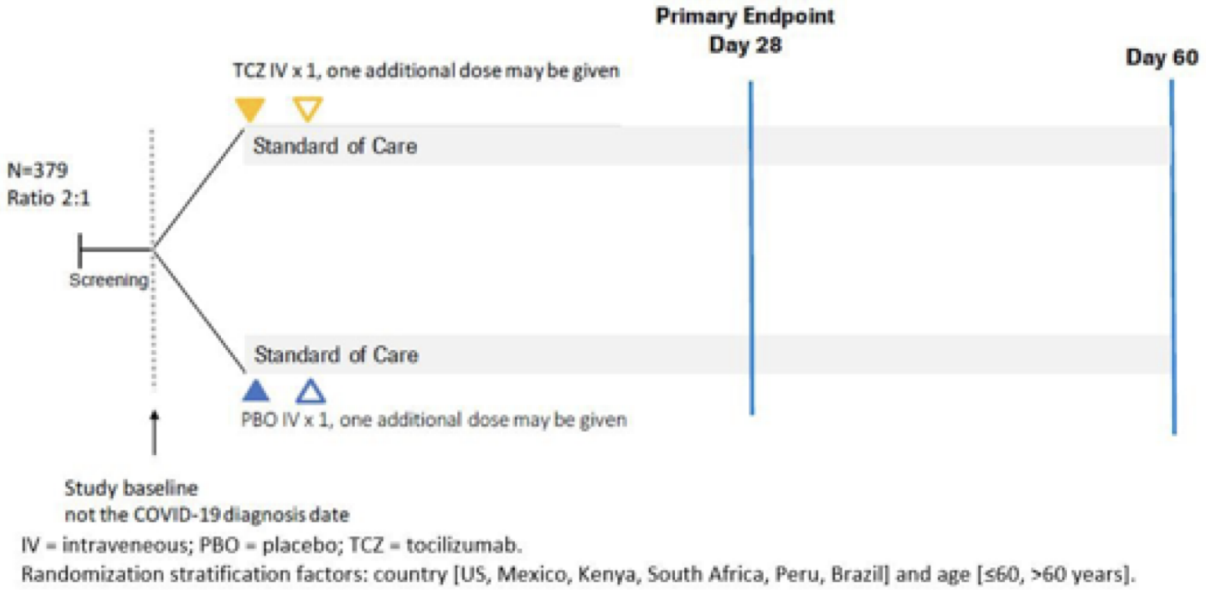
Conclusions

- Efficacy
  - Primary endpoint was not met
  - No difference in mortality
  - 8 day improvement in time to discharge or ‘ready for discharge’ was nominally significant
  - Decreased risk of clinical failure (death, MV, or ICU) was nominally significant (HR 0.614)
  - 5.8 day improvement in ICU stay was nominally significant

- Safety
  - No new safety signals were identified
  - The safety profile was comparable across the treatment groups
  - Infections and serious infections occurred less frequently in TCZ arm

https://www.medrxiv.org/content/10.1101/2020.08.27.20183442v2

EMPACTA - Topline results released



PRIMARY ENDPOINT MET:

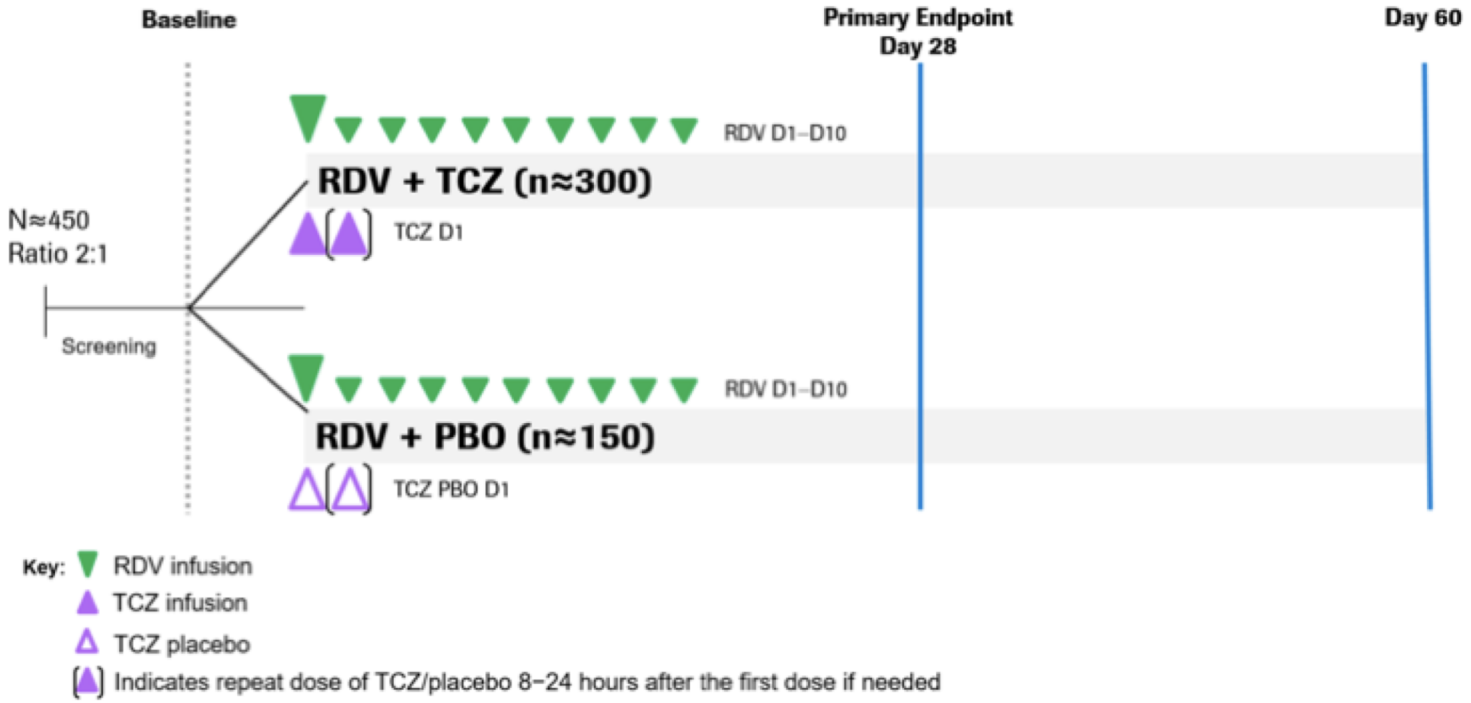
- Statistically significant reduction in risk of MV or death (log-rank p-value = 0.0348; HR [95% CI] = 0.56 [0.32, 0.97]).
- No statistical difference in mortality

Key differences from COVACTA:

- Patients on MV/NIV excluded
- 80% corticosteroids, 50% remdesivir

https://www.roche.com/media/releases/med-cor-2020-09-18.htm

REMDACTA - Recruitment continuing



Key differences from COVACTA:

- Combination treatment with remdesivir
- Patients requiring ≤ 6 LPM supplemental oxygen excluded
- Patients with renal failure excluded

Currently enrolling in US, Brazil, Russia

- Planning expansion in Europe and Latin America

Topline data end of 2020

https://clinicaltrials.gov/ct2/show/NCT04409262?term=REMDACTA&draw=2&rank=1

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