Itolizumab COVID19 Study Results

Itolizumab Label Expansion for COVID19 complications

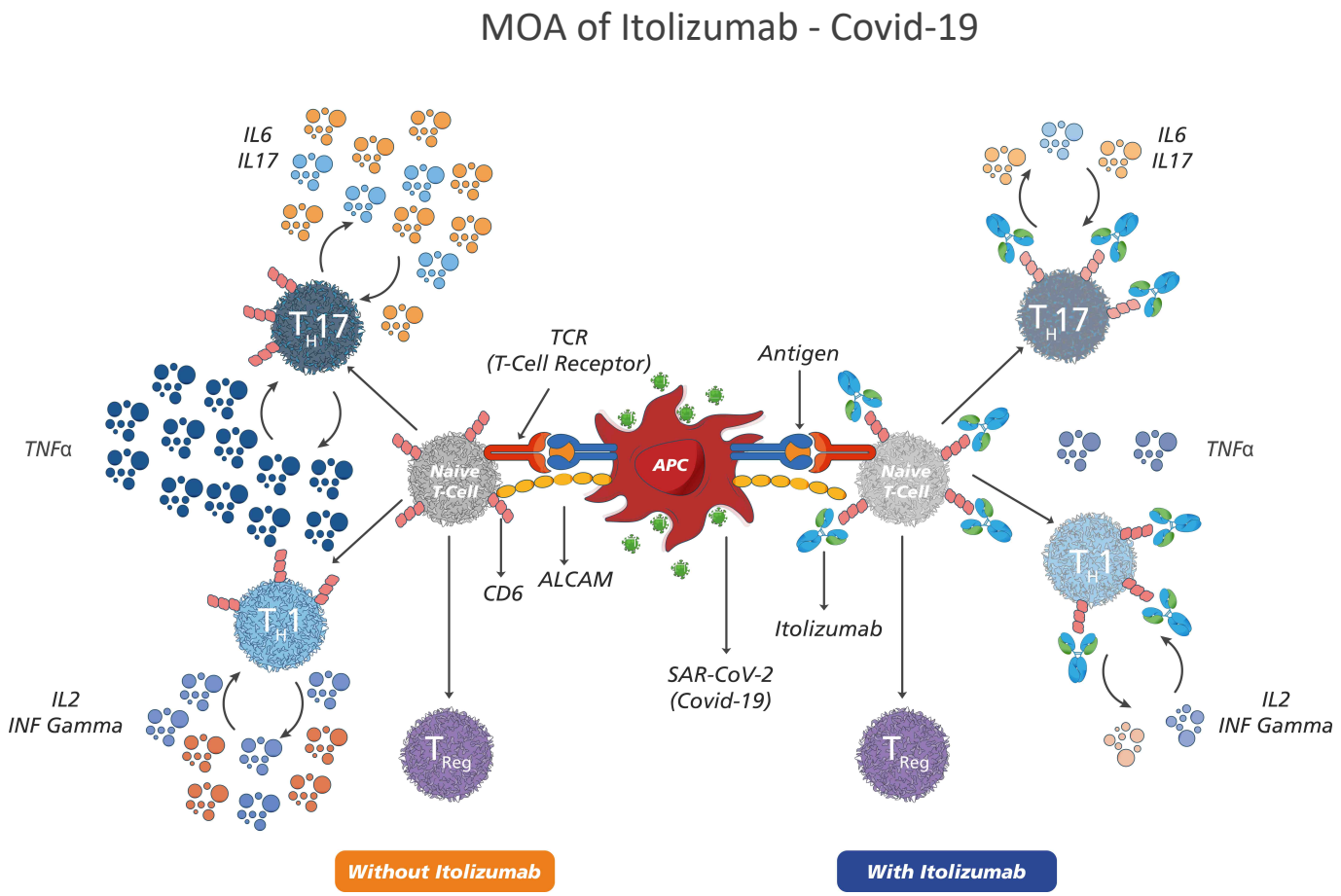
"A Multi-Centric, Open label, Two Arm Randomized Phase 2 Trial to Study the Efficacy and Safety of Itolizumab in COVID-19 Complications".

Protocol Number: ITOLI-C19-02-I-00

Trial Centers

Mumbai	New Delhi
KEM Hospital	LNJP Hospital
Nair Hospital	AIIMS

Itolizumab Mechanism Of Action

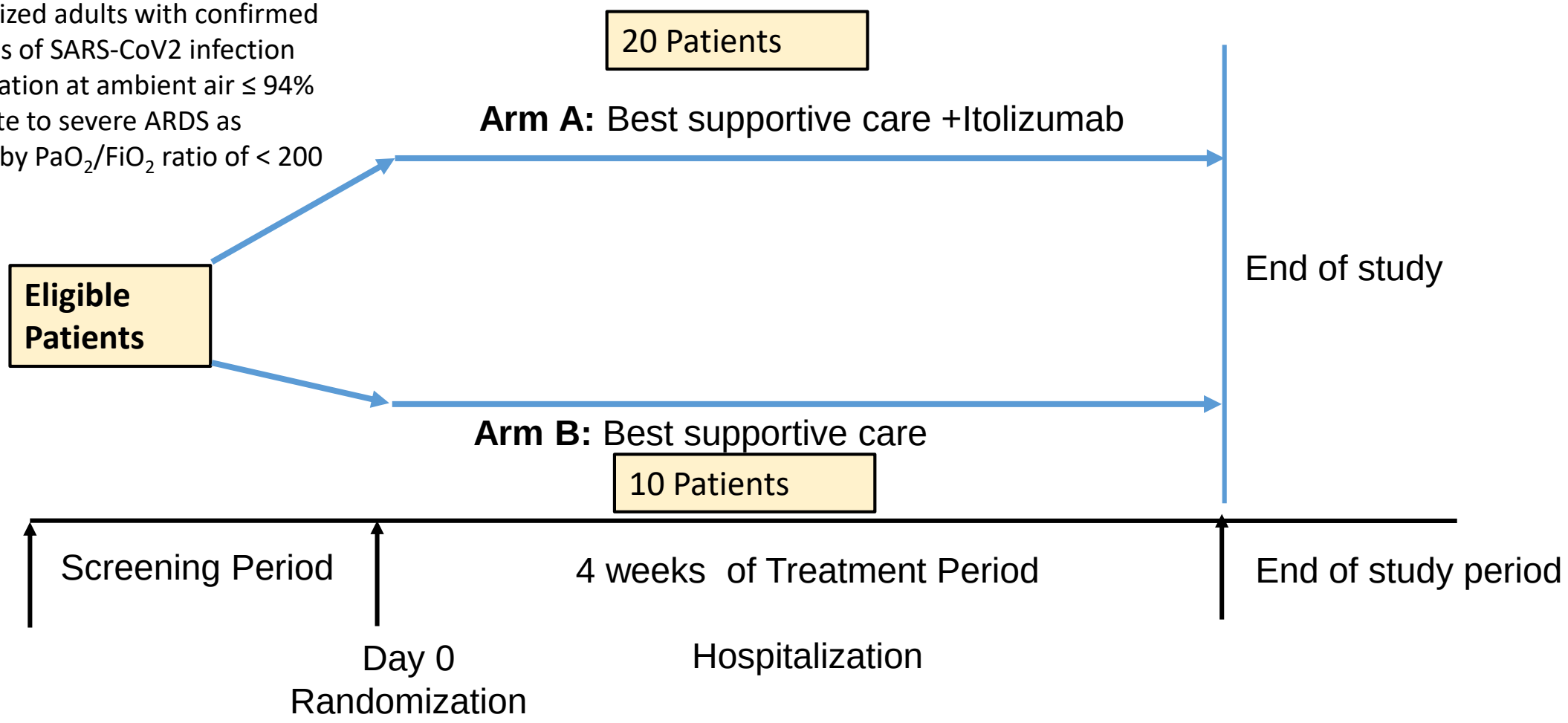


CD6 is expressed mainly on effector T cells (Teff). CD6 stimulates ALCAM mediated T cell activation and subsequently pro-inflammatory cytokines release. Itolizumab, inhibits T-cell activation and lowers major pro-inflammatory cytokines of the Th1/Th17 pathways.

Study Design Overview

Inclusion Criteria:

- Hospitalized adults with confirmed diagnosis of SARS-CoV2 infection
- O_2 saturation at ambient air ≤ 94%
- Moderate to severe ARDS as defined by PaO_2/FiO_2 ratio of < 200



Enrollment & Demography

Randomized patients

Arm A (Itolizumab + BSC)	Arm B (BSC)	Total
22	**10**	**32**

2 patients randomized to Arm A were discontinued from trial due to an infusion reaction shortly after initiation and did not complete the initial dose. Per study protocol subjects who did not complete a full dose on first infusion were not considered randomized and were replaced in the study using the same randomization code for the subsequent subject at that site.

Baseline Demography

	Arm A	Arm B
Number of patients	20	10
Age (Yrs)		
Mean	49.55	48.3
Median	50.5	49.5
Min, Max	28, 65	29, 73
<60	15	8
>60	5	2
Gender		
Male	19	7
Female	1	3
Comorbidities		
Diabetes	3	2
Hypertension	4	2
Hypothyroidism	2	-
COPD	-	1

Efficacy: One-month Mortality Rate

3 deaths reported in Arm B; no deaths reported in Arm A

Status	Arm A	Arm B
Recovered	20	7
Death	-	3
Total	20	10

Two sided test of difference for proportion (H0: P1 = P2 vs. Ha: P1 ≠ P2)						
Outcome	ARM A (p1)	ARM B (p2)	Diff. (p1 - p2)	95% CI (Exact Method)	p-value (Wald Z)	p-value (Fisher Exact)
Mortality	0	0.3	- 0.3	[-0.61,-0.08]	**0.0098**	**0.0296**

Significant statistical difference was seen in favor of Arm A with a p value < 0.05

Efficacy: Stable/Improved SpO2 Without Increasing FiO2

Stable SpO2: Defined as absence of increase in FiO2 to maintain Spo2 ≥ 92%
Improvement of SpO2: Defined as decrease in FiO2 to maintain SpO2 >92%

	Day 7		Day 14		Day 21		Day 30	
	Arm A	**Arm B**	**Arm A**	**Arm B**	**Arm A**	**Arm B**	**Arm A**	**Arm B**
Total N	20	10	20	10	20	10	20	10
Patients with stable/improved SpO2	17	5	19	7	20	7	20	7
Proportion (%)	**85%**	**50%**	**95%**	**70%**	**100%**	**70%**	**100%**	**70%**
p-value (Fisher Exact Test)	0.0778		0.0952		**0.0296**		**0.0296**	
P-value (Wald Z Test)	0.0410		0.0576		**0.0098**		**0.0098**	

- Patients improved/ weaned off O2, the observation was carried forward .
- 3 patients in arm B died on day 4, 5 and 12
- **p-value<0.05 is considered significant**

3 Patients worsened and died in Arm B by Day 12

Statistically Significant Difference Day 21 Onwards

Efficacy: Stable PaO2 Without Increasing FiO2

Stable PaO2: Defined as up to 10% change in PaO2/FiO2 ratio from baseline
Improvement of PaO2: Defined as > 10% improvement in PaO2/FiO2 ratio from baseline (including patients weaned off oxygen)

	Day 7		Day 14		Day 21		Day 30	
	Arm A	**Arm B**	**Arm A**	**Arm B**	**Arm A**	**Arm B**	**Arm A**	**Arm B**
Total N	20	10	20	10	20	10	20	10
Patients with stable/improved PaO2	18	6	19	7	20	7	20	7
Proportion (%)	**90%**	**60%**	**95%**	**70%**	**100%**	**70%**	**100%**	**70%**
p-value (Fisher Exact Test)	0.1413		0.0952		**0.0296**		**0.0296**	
p-value (Wald Z method)	0.0528		0.0576		**0.0098**		**0.0098**	

Note:

- Patients improved/ weaned off O2, the observation was carried forward.
- 3 patients in arm B died on day 4, 5 and 12
- **p-value<0.05 is considered significant**

Arm A: All patients improved or were stable after Day 14 onwards

Arm B: 3 Patients died; 2 needed Invasive Mechanical Ventilator before they died

Efficacy: Weaning Off O_2 Therapy & IMV Intervention

IMV: Invasive Mechanical Ventilator
NIV: CPAP/BiPAP

Days	Arm A N=20			Arm B N=10		
	Off Oxygen	IMV/Death	NIV	Off Oxygen	IMV/Death	NIV
Baseline	0	-	5	0	-	4
Day 7	5	-	5	2	2*/2	2
Day 14	14	-	0	4	0/3	0
Day 21	18	-	0	6	0/3	0
Day 30/EOS	20	-	0	7	0/3	0

*2 patients on NIV worsened and were on ventilator before death.
Patients not on IMV or NIV had improved and shifted to NRBM, FM, NC

All patients on Arm A weaned off oxygen on the trial by Day 30, none progressed to IMV

Inflammatory markers and ALC- Change from Baseline

Ferritin – Mean change from baseline (ng/mL)

	n	Day 7	n	Day 14	n	Day 21	n	Day 30
Arm A	18	**- 117.8**	15	**- 713.9**	11	**- 780.9**	3	**- 479.3**
Arm B	7	**-87.05**	5	**-209.6**	3	**4238**	2	**-234.4**

LDH – Mean change from baseline (U/L)

	n	Day 7	n	Day 14	n	Day 21	n	Day 30
Arm A	18	**- 134.6**	15	**- 195.8**	11	**- 308.1**	3	**- 212.7**
Arm B	7	**- 44.29**	5	**- 195.2**	3	**155.33**	2	**- 97**

D-dimer – Mean change from baseline (mcg/mL FEU)

	n	Day 7	n	Day 14	n	Day 21	n	Day 30
Arm A	18	**- 1.43**	12	**- 0.45**	11	**- 4.35**	3	**- 2.63**
Arm B	7	**2.3**	4	**- 0.68**	2	**8.54**	2	**- 0.35**

CRP – Mean change from baseline (mg/L)

	n	Day 7	n	Day 14	n	Day 21	n	Day 30
Arm A	18	**- 61.69**	16	**- 81.65**	11	**- 90.99**	3	**- 103.2**
Arm B	8	**- 103.6**	5	**- 107.2**	3	**- 127.5**	2	**- 127.6**

ALC – Mean change from baseline (cells/cu.mm)

	n	Day 7	n	Day 14	n	Day 21	n	Day 30
Arm A	20	**118.95**	16	**421.25**	11	**701.55**	4	**719.75**
Arm B	8	**45.88**	5	**142.6**	3	**10.00**	2	**85.00**

Mean IL-6 Levels and TNF –alpha levels

IL-6 (pg/mL)

Arm A	Pre 1st Dose	Post 1st Dose	P value	Pre 2nd Dose	Post 2nd Dose	P value
N	18	18		13	13	
Mean	159.09	42.98	**0.0269**	311.32	91.04	0.2349
Median	39.28	25.51		23.24	22.17	
SD	293.06	52.93		660.48	245.65	

Arm B	Pre 1st Dose	Post 1st Dose	P value	Pre 2nd Dose	Post 2nd Dose	P value
N	10	10		4	4	
Mean	162.16	211.52	0.50	310.44	316.85	0.4375
Median	55.50	84.11		64.77	213.22	
SD	185.95	297.23		528.22	373.76	

TNF alpha (pg/mL)

Arm A	Pre 1st Dose	Post 1st Dose	P value	Pre 2nd Dose	Post 2nd Dose	P value
N	18	18		13	13	0.5000
Mean	43.64	8.87	**0.0253**	68.03	50.18	
Median	6.03	1.52		9.69	11.11	
SD	72.96	12.36		109.58	140.20	

Arm B	Pre 1st Dose	Post 1st Dose	P value	Pre 2nd Dose	Post 2nd Dose	P value
N	10	10		4	4	0.0625
Mean	11.26	39.19	0.248	107.79	185.05	
Median	7.49	4.74		29.87	60.57	
SD	13.63	104.59		175.29	275.80	

Treatment Emergent Serious Adverse Events

#	Patient No (Age /Gender)	Rx Arm	SAE	Causality to Study Drug	Outcome	Comments
1	01-010 27 y male	Arm A	Pericardial effusion (underlying Uncontrolled Hypothyroidism)	Not related	Recovered	Elevation of TSH: 59µIU/mL. Signs of severe uncontrolled hypothyroidism
2	03-010 51 y male	Arm A	Anaphylaxis (Infusion reaction)	Related	Recovered	Upon slowing the infusion it was well tolerated
3	03-006 50 y Female	Arm B	ARDS	NA	Death	-
4	04-010 73 y Male	Arm B	Type 1 Respiratory Failure	NA	Death	-
5	03-007 49 y female	Arm B	Type 1 Respiratory Failure	NA	Death	-

As defined in the protocol, patients who do not complete one full dose were considered unevaluable and were replaced. One patient (1009) randomized to Arm A ,experienced an infusion reaction shortly after initiation of drug and did not complete the first dose. The patient was withdrawn from the study. The event of infusion reaction resolved on the same day. Subsequently the patient recovered from Covid 19 after approximately 2 weeks and was discharged from the hospital

Incidence of Treatment Emergent Adverse Events other than SAEs

Preferred Term	Arm A (N=22)	Causality	Arm B (N=10)	Causality
Sinus tachycardia	1(4.55%)	Not Related	--	--
Hypothyroidism	1 (4.55%)	Not Related	--	--
Constipation	1 (4.55%)	Not Related	--	--
Chills	5 (22.72%)	**Related**	--	--
Fungal infection	--	Not Related	1 (10%)	Not Related
Urinary tract infection	1 (4.55%)	Not Related	--	--
Grade 3 Lab AEs				
Alanine aminotransferase increased	1 (4.55%)	Not Related	--	--
Fibrin D dimer increased	1 (4.55%)	Not Related	--	--
Low density lipoprotein increased	1 (4.55%)	Not Related	--	--
Lymphocyte count decreased	11 (50%)	**Related**	2 (20%)	Not Related
Non-HDL- cholesterol increased	1 (4.55%)	Not Related	--	--
Platelet count decreased	1 (4.55%)	**Related**	--	--
Hyperglycemia	4 (18.18%)	Not Related	1 (10%)	Not Related
Hypertriglyceridemia	2 (9.09%)	Not Related	1 (10%)	Not Related

As defined in the protocol, patients who do not complete one complete dose were considered unevaluable and were replaced. One patient (3001) randomized to Arm A, experienced chills shortly after initiation of drug and did not complete the first dose. The patient was withdrawn from the study. The event of infusion reaction resolved on the same day. Subsequently the patient developed further complications of COVID19 and died 9 days after discontinuation and event was deemed not related to study drug.

Conclusions

- Primary endpoint of one month mortality was statistically significant in favor of Itolizumab arm
- Other key endpoints of lung function such as improvement in PaO2 and O2 saturation were statistically significant in favor of Itolizumab arm
- Key inflammatory markers IL-6 and TNFα are significantly reduced by Itolizumab thereby preventing hyper-inflammation
- Itolizumab is safe in COVID19 patients, Infusion reactions are manageable with slowing infusion rate
- Itolizumab effectively controls hyper-activation of the immune system in response to Covid19 virus and reduces morbidity and mortality related to cytokine storm