A Phase 2 Study of Leronlimab for Mild to Moderate Coronavirus Disease 2019 (COVID-19)

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The pursuit of precision medicine

Leronlimab

- Leronlimab (PRO 140) is a humanized IgG4,κ monoclonal antibody (mAb) to the C-C chemokine receptor type 5 (CCR5).
- Leronlimab is currently under investigation for the treatment of mild to moderate respiratory illness caused by COVID-19 infection.
- Also investigated for severe or critical COVID-19 in an ongoing Phase 2b/3 study.

Clinical Development of Leronlimab

PROGRAM	INDICATION		PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3
HIV	Combination Therapy [1]	FTD-2006				
	Monotherapy					
Cancer	Triple-Negative Breast [2]	FTD-2019				
	Basket trial for solid tumors (including melanoma, brain-glioblastoma, throat, lung, stomach, colon, breast, testicular, ovarian, uterine, pancreas, bladder, among other indications)					
Immunology	GvHD [3]	ODD-2017				
	NASH [4]					
	75 Patients Randomized - Phase 2 Mild to Moderate; Coronavirus [Covid-19]; 390 Patients Randomized - Phase 2b/3 Severe and Critical					
	Autoimmune (mutiple potential indications including Crohn's disease, IBS (inflammatory bowel syndrome), MS (Multiple Sclerosis), Hashimoto's thyroiditis, Vasculitis, Psoriasis, Polymyositis, Autoimmune Hepatitis, Grave's disease, Sjogren's syndrome, Myasthemia gravis)					

FTD = Fast Track Designation; ODD = Orhan Drug Designation

[1] BLA filing in-process

[2] Trial underway with Fast Track designation

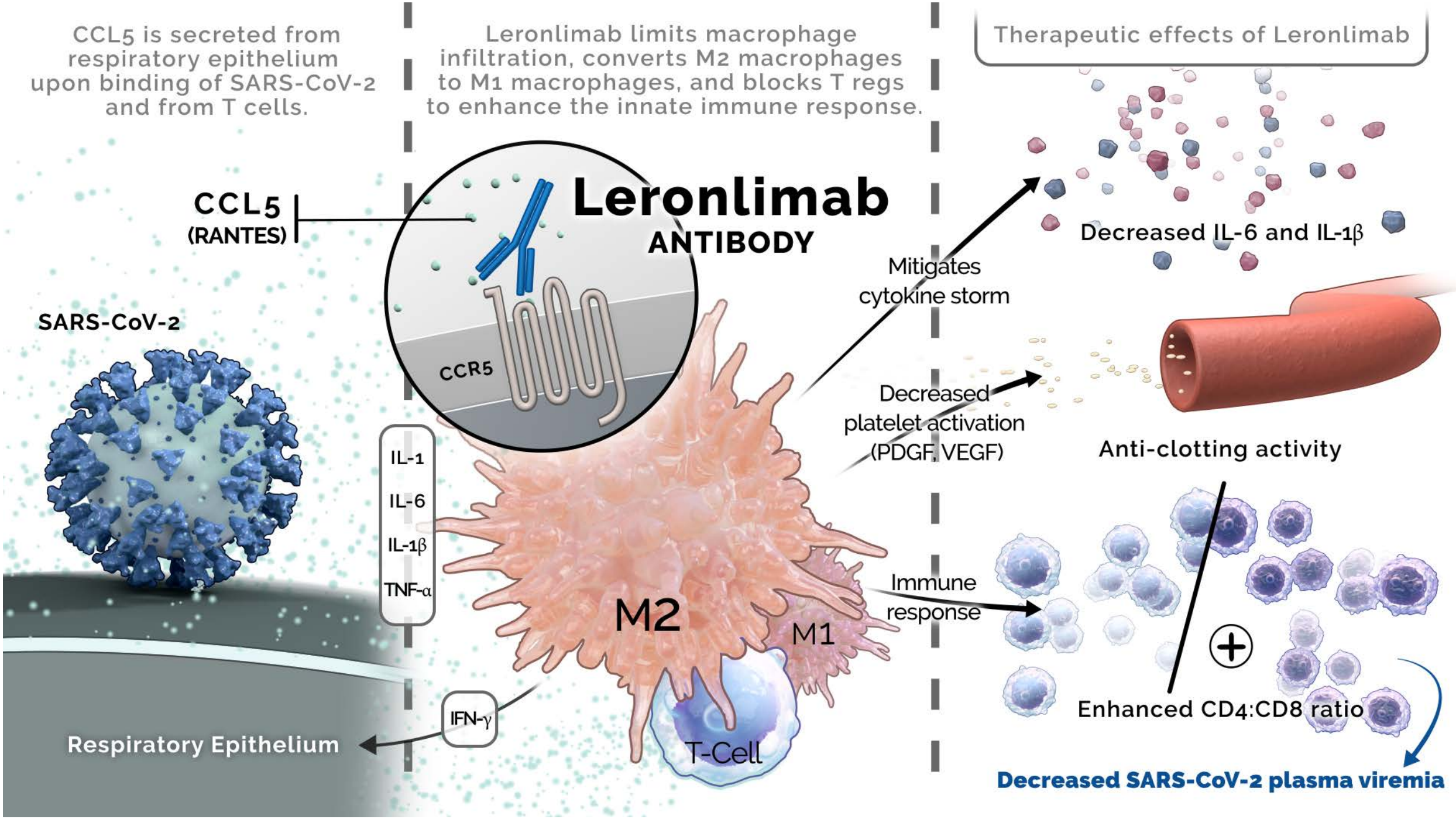
[3] Trial underway with Orphan Drug designation

[4] IND and Phase 2 protocol filed

- **Over 1000 patients have been injected across multiple studies. Leronlimab has been generally well-tolerated and no patterns of drug-related toxicities have been observed.**

Leronlimab in COVID-19

- The “cytokine storm” is believed to play an integral role in the development of acute respiratory distress syndrome (ARDS)
- Chemokines and chemokine receptors play a critical role in the recruitment, activation, and coordination of leukocytes in the pathophysiology of lung inflammation
- ARDS in COVID-19 results from the accumulation of neutrophils within the pulmonary circulation and alveolar spaces
- Leronlimab (PRO 140) inhibits the migration of Tregs into areas of inflammation, which can inhibit the innate immune response against pathogens and, most importantly, the migration of macrophages and release of pro-inflammatory cytokines in lungs
- Leronlimab can potentially mitigate the cytokine storm


CCL5 is secreted from respiratory epithelium upon binding of SARS-CoV-2 and from T cells.
Leronlimab limits macrophage infiltration, converts M2 macrophages to M1 macrophages, and blocks T regs to enhance the innate immune response.
Therapeutic effects of Leronlimab
CCL5 (RANTES)
Leronlimab ANTIBODY
CCR5
SARS-CoV-2
IL-1
IL-6
IL-1β
TNF-α
IFN-γ
Respiratory Epithelium
M2
M1
T-Cell
Mitigates cytokine storm
Decreased IL-6 and IL-1β
Decreased platelet activation (PDGF, VEGF)
Anti-clotting activity
Immune response
Enhanced CD4:CD8 ratio
Decreased SARS-CoV-2 plasma viremia

COVID-19 Clinical Trials

- **CD10_COVID-19:** Phase 2, two-arm, randomized, double blind, placebo controlled multicenter study to evaluate the safety and efficacy of leronlimab (PRO 140) in patients with **mild-to-moderate symptoms of respiratory illness caused by coronavirus 2019 infection.** Patients randomized to receive weekly doses of 700 mg leronlimab (PRO 140), or placebo. Leronlimab (PRO 140) and placebo will be administered via subcutaneous injection.
  - **Completed**
- **CD12 _COVID-19 :** Phase 2b/3, two-arm, randomized, double blind, placebo controlled, adaptive design multicenter study to evaluate the safety and efficacy of leronlimab (PRO 140) in patients with **severe or critical symptoms of respiratory illness caused by coronavirus 2019 infection**. Patients randomized to receive weekly doses of 700 mg leronlimab (PRO 140), or placebo. Leronlimab (PRO 140) and placebo will be administered via subcutaneous injection.
  - In progress: 220 enrolled as of Sep 4, 2020
  - Data Safety Monitoring Board
    - Recommendation given to continue study as planned after review of 150 patient data (July 2020)
    - Upcoming Interim Analysis (IA) for efficacy with 195 patients (October 2020)

COVID-19: Emergency INDs

- Additionally, there have been 65 patients with severe and critical COVID-19 infection treated with 700 mg leronlimab (PRO 140) under individual patient, emergency use INDs.
- >50% intubated at baseline.
- Majority of patients have shown improved or sustained clinical outcome.

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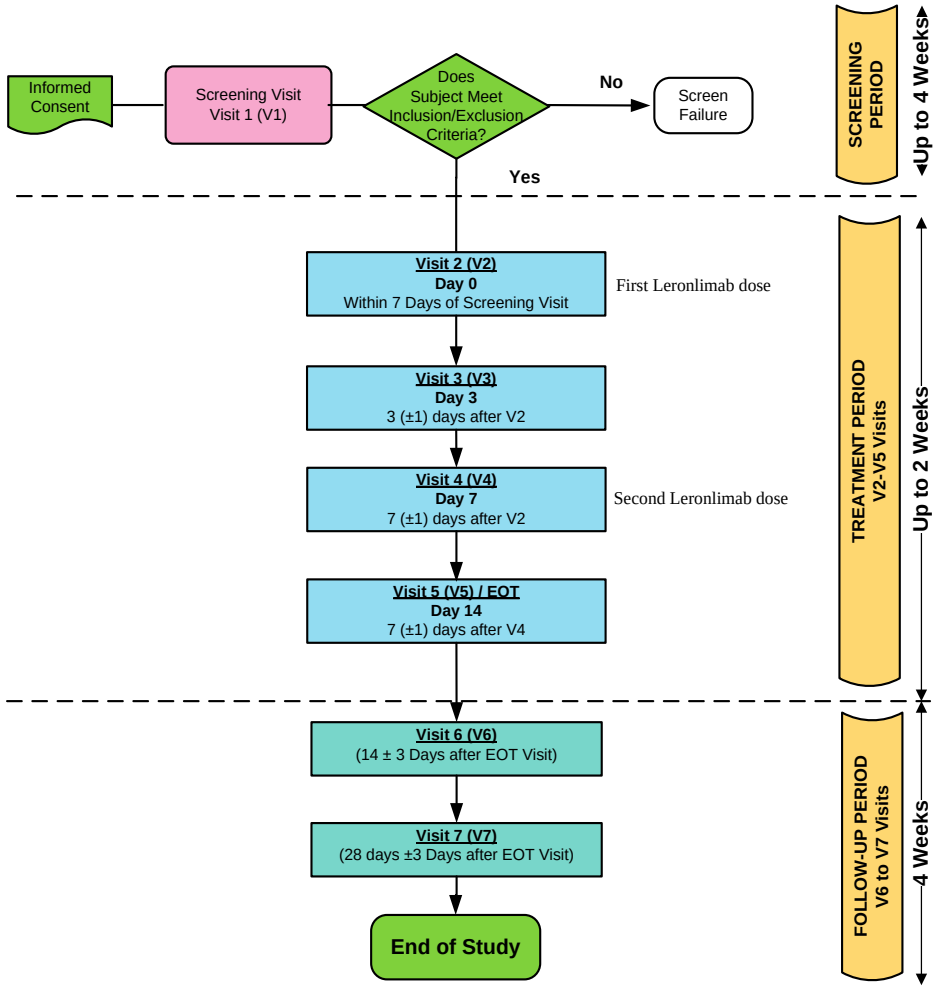
CD10_COVID-19

A Phase 2, Randomized, Double Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Leronlimab for Mild to Moderate Coronavirus Disease 2019 (COVID-19)

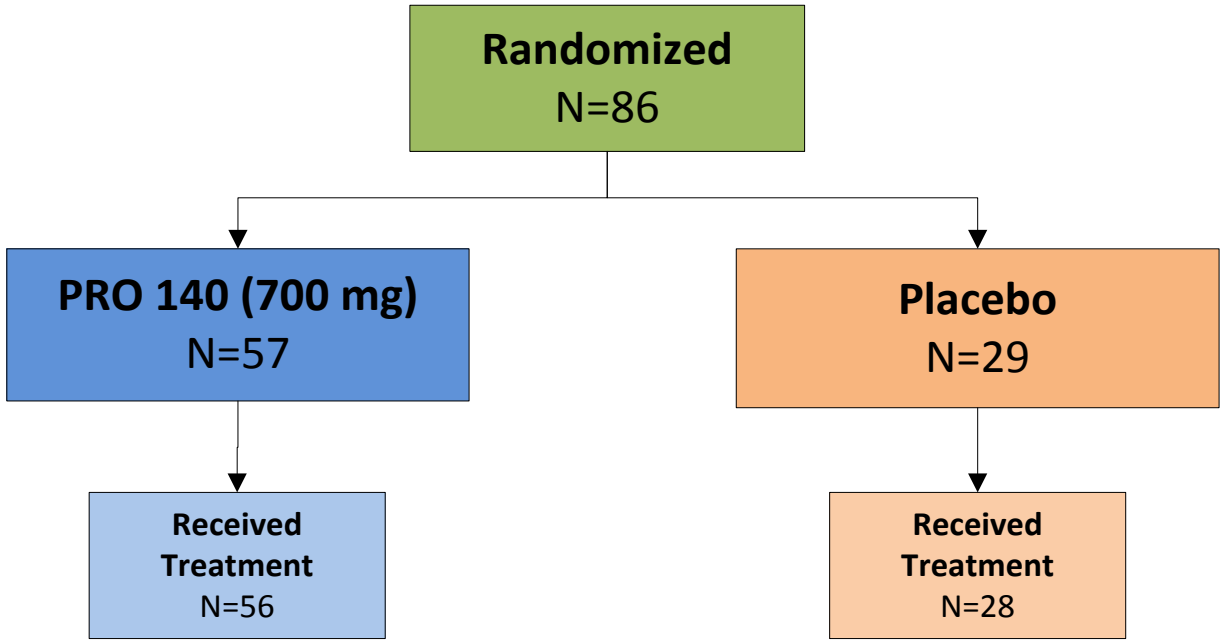
CD10_COVID-19: Study Design

- This was a two-arm, randomized, double blind, placebo controlled multicenter study to evaluate the safety and efficacy of leronlimab (PRO 140) in patients with mild-to-moderate symptoms of respiratory illness caused by coronavirus 2019 infection.

- Patients were randomized to receive weekly doses of 700 mg leronlimab (PRO 140), or placebo (2 total doses). Leronlimab (PRO 140) and placebo were be administered via subcutaneous injection.



CD10_COVID-19: Subject Disposition



CD10_COVID-19: Subject Demographics

Parameter	Characteristic	PRO 140 (700 mg) N=56 n (%)	Placebo N=28 n (%)	Total N=84 n (%)
Gender	Male, n (%)	24 (42.9)	9 (32.1)	33 (39.3)
	Female, n (%)	32 (57.1)	19 (67.9)	51 (60.7)
Age (Years) [1]	n	56	28	84
	Mean (SD)	54.59 (12.38)	55.36 (13.84)	54.85 (12.81)
	Median	55.5	55.5	55.5
	Min - Max	30 - 79	23 - 84	23 - 84
Race	Black/African American, n (%)	15 (26.8)	4 (14.3)	19 (22.6)
	White, n (%)	27 (48.2)	16 (57.1)	43 (51.2)
	Other, n (%)	14 (25.0)	8 (28.6)	22 (26.2)
Ethnicity	Not Hispanic/Latino, n (%)	35 (62.5)	17 (60.7)	52 (61.9)
	Hispanic/Latino, n (%)	18 (32.1)	10 (35.7)	28 (33.3)
	Not Reported, n (%)	1 (1.8)	1 (3.6)	2 (2.4)
	Unknown, n (%)	2 (3.6)	--	2 (2.4)

[1] Age (Years) = Integer of [(Date of Informed Consent - Date of Birth) / 365.25].

Note: All percentages are based on the number of subjects in population and treatment group (N).

CD10_COVID-19: Baseline Characteristics

Parameter	Statistics	PRO 140 (700 mg) N=56 n (%)	Placebo N=28 n (%)	Total N=84 n (%)
Baseline Total Symptom Score Group	≤4	29 (51.8)	16 (57.1)	45 (53.6)
	>4	27 (48.2)	12 (42.9)	39 (46.4)
With Use of any Off-Label COVID-19 Treatments [1]	Yes	14 (25.0)	6 (21.4)	20 (23.8)
	No	42 (75.0)	22 (78.6)	64 (76.2)
Age Group (Years)	<60	35 (62.5)	17 (60.7)	52 (61.9)
	≥60	21 (37.5)	11 (39.3)	32 (38.1)
Consumption of Tobacco Products	Never	37 (66.1)	19 (67.9)	56 (66.7)
	Current	4 (7.1)	0 (0.0)	4 (4.8)
	Former	15 (26.8)	8 (28.6)	23 (27.4)

[1] With use of any off-label COVID-19 treatments including hydroxychloroquine, chloroquine, azithromycin, levofloxacin, ceftriaxone, piperacillin/tazobactam etc. at baseline.

Note: All percentages are based on the number of subjects in population and treatment group (N).

CD10_COVID-19: Total Symptom Score

- The primary endpoint was assessed by the measurement of clinical improvement as assessed by change in total symptom score.
  - *Symptoms assessed were fever, myalgia, dyspnea, and cough.*
  - *Each symptom was graded from 0 to 3 [0=none, 1=mild, 2=moderate, and 3=severe].*
  - *The total score per patient ranges from 0 to 12 points.*
- In patients with Total Symptom Score of ≥ 4 at baseline (Note: Higher score indicating a worse health state)
  - At Day 3, **90%** of subjects treated with leronlimab were reported with improvement in total clinical symptom score compared to **71%** of subjects in the placebo group.
- In all treated patients (mITT population)
  - At Day 3, **63%** of patients in the leronlimab group showed clinical improvement compared to **56%** of subjects in the placebo group.

CD10_COVID-19: National Early Warning Score 2 (NEWS2)

- NEWS2 score is based on clinical parameters such as respiration rate, oxygen saturation, any supplemental oxygen, temperature, systolic blood pressure, heart rate, and level of consciousness.
- Modified Intent-to-Treat Population
  - At the End of Treatment (or Day 14), **50%** of patients in the leronlimab group experienced improved scores compared to **20.83%** of patients in placebo. The difference was statistically significant (**p=0.0223**).
- Per Protocol Population
  - At Day 3, **42%** of patients in the leronlimab group experienced improved scores compared to **14%** of patients in placebo. The difference was statistically significant (**p=0.0282**).
  - At the End of Treatment (or Day 14), **55%** of patients in the leronlimab group experienced improved scores compared to **23%** of patients in placebo. The difference was statistically significant (**p=0.0185**).

CD10_COVID-19: Adverse Events (AEs)

Parameter	PRO 140 (700 mg) N=56		Placebo N=28		Total N=84	
	n (%)	Events	n (%)	Events	n (%)	Events
Total Number of Subjects with Any AE	**19 (33.9)**	**43**	**14 (50.0)**	**53**	**33 (39.3)**	**96**
Severe [1]	5 (8.9)	6	3 (10.7)	3	8 (9.5)	9
Moderate	2 (3.6)	3	6 (21.4)	18	8 (9.5)	21
Mild	12 (21.4)	34	5 (17.9)	32	17 (20.2)	66

[1] Severe AEs are those adverse events that were considered severe or life-threatening or causing death.

Note1: All percentages are based on the number of subjects in the safety population and treatment group (N).

Note2: A subject is counted only once within each category, using the event with the maximum severity.

- The incidence, frequency, and severity of AEs were lower in the leronlimab group compared to the placebo group.

CD10_COVID-19: Serious Adverse Events (SAEs)

Parameter	PRO 140 (700 mg) N=56		Placebo N=28		Total N=84	
	n (%)	Events	n (%)	Events	n (%)	Events
Total Number of Subjects with Any Serious TEAE	**5 (8.9)**	**8**	**6 (21.4)**	**11**	**11 (13.1)**	**19**
Possibly Related	0 (0.0)	0	2 (7.1)	5	2 (2.4)	5
Unrelated	5 (8.9)	8	4 (14.3)	6	9 (10.7)	14

Note: All percentages are based on the number of subjects in the safety population and treatment group (N).

- Only 8 SAEs in 56 Patients (14%) treated with leronlimab compared to 11 SAEs in 28 Patients (39%) in placebo arm.

Conclusion

- In this study leronlimab demonstrated a reduction in NEWS2 score at Day 14. This may suggest that leronlimab (PRO 140) can prevent progression to severe or critical COVID-19 illness; however, there were no differences in oxygen use or hospitalizations in the placebo arm.

- This study is limited by its exclusion of patients with pre-existing medical conditions including severe pulmonary, liver, and renal disease who have been shown to be at higher risk for COVID-19 progression and overall mortality.

Conclusion

- Leronlimab (PRO 140) has been previously shown to concurrently downregulate pathologic inflammatory responses, and restore immune homeostasis in patients with severe COVID-19 infection.
- Although the therapeutic benefit of leronlimab (PRO 140) on healthy patients with mild to moderate COVID-19 infection may be limited, additional studies will be required to broaden eligibility criteria to patients with higher risk of disease progression. To this end, no significant adverse effects attributed to leronlimab (PRO 140) were reported in the study treatment population.
- The utilization of leronlimab in conjunction with adjuvant treatments, e.g. remdesivir or convalescent plasma, remains to be investigated. Additional data will be available relating to the treatment of patients with severe and critical illness following the release of our subsequent randomized clinical trial, CD12 (NCT04347239).