Mavrilimumab Improves Outcomes in Phase 2 Trial in Non-Mechanically-Ventilated Patients with Severe COVID-19 Pneumonia and Systemic Hyperinflammation

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Background – Unmet Need for Treatment Alternatives in COVID-19 Pneumonia

- Granulocyte/macrophage-colony stimulating factor (GM-CSF) is a cytokine that is vital to:
  - Vital to lung homeostasis[1,2,3]
  - Important modulator of inflammation and autoimmunity[1,2,3]
  - Implicated in the mechanism driving excessive/aberrant immune cell infiltration and activation in the lungs
  - May contribute to respiratory failure/death in patients with COVID-19 pneumonia/hyperinflammation[4-6]
- Mavrilimumab (human monoclonal antibody)
  - Binds GM-CSF receptor α, blocks GM-CSF signaling, and downregulates the inflammatory process
  - Previous experience- prospective primary efficacy & safety endpoints achieved:
    - Rheumatoid arthritis (Phase 2, n=550)
    - Giant Cell Arteritis (Phase 2, n=70)
  - Blocking GM-CSFRα may reduce cellular and molecular inflammation (e.g., IL-2Rα, IL-6, CRP)[7-9]

1. Trapnell, Nat Rev Dis Pri, 2019; 2. Wicks, Nat Rev Immunology, 2015; 3. Hamilton, Exp Rev Clin Immunol, 2015; 4. De Luca, Lancet Rheumatol, 2020; 5. Cremer, Lancet Rheumatol, 2021; 6. Zhou, Nature, 2020; ; 7. De Alessandris et al., J Leukoc Biol. 2019; 8. Sterner et al., Blood 2019; 9. Guo et al., Rheumatology 2017;

Prior Early Signals of Mavrilimumab Efficacy and Phase 2 Study Objective

Non-mechanically ventilated patients:

- Open-label treatment protocol in Italy (n=13 patients vs 26 contemporaneous controls)
  - All patients had clinical improvement with mavrilimumab vs 65% by day 28 (p=0.030)[1]
  - No patients died with mavrilimumab versus 27% mortality by day 28 (p=0.086)[1]

- MASH-COVID: double-blind, PBO-controlled, randomized investigator-initiated study (n=40 patients) enrolled at 3 centers in the U.S. on top of corticosteroids
  - 57% alive and off supplemental oxygen therapy with mavrilimumab vs 47% with placebo (odds ratio 1.48 [95%CI 0.43-5.16; p=0.76) [2]
  - Trends toward clinical improvement and lower mortality in mavrilimumab recipients, as well as shorter duration of mechanical ventilation in patients who went on to mechanical ventilation[2]

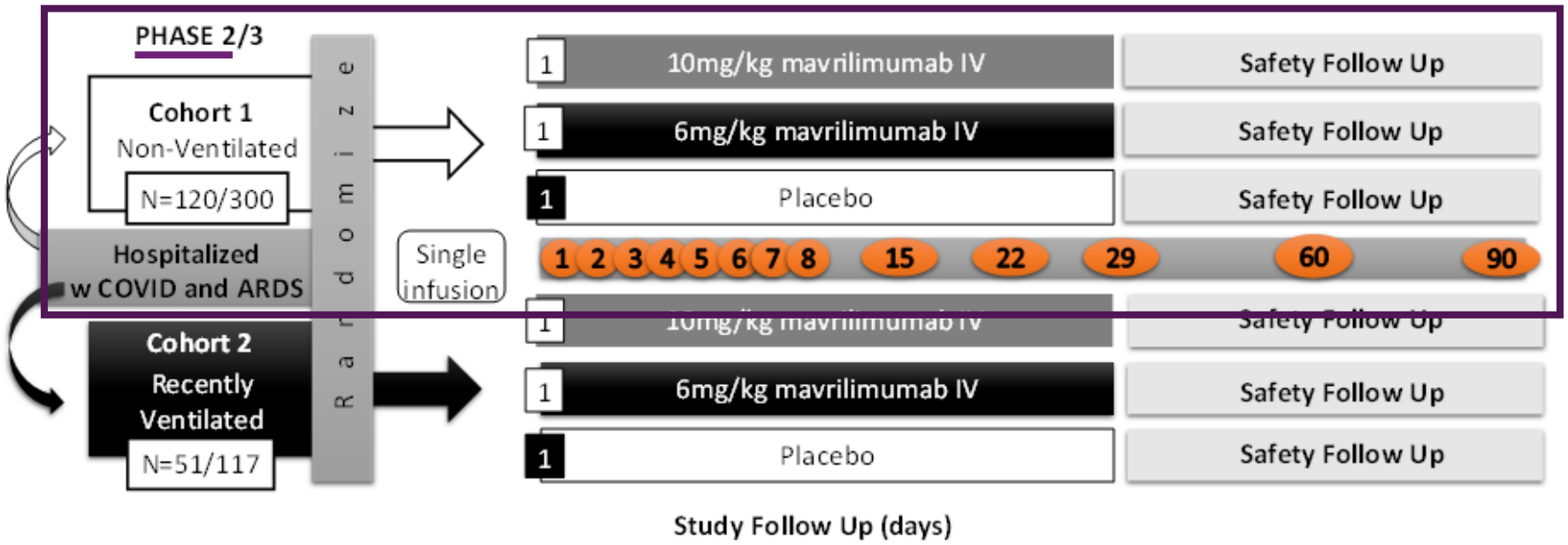
Phase 2 Objective

- To evaluate the efficacy and safety of mavrilimumab for clinical improvement in patients with severe COVID-19 pneumonia and hyperinflammation and not requiring mechanical ventilation (Cohort 1)

1. De Luca, Lancet Rheumatol, 2020; 2. Cremer, Lancet Rheumatol, 2021

Phase 2 Clinical Trial of Mavrilimumab in Severe COVID-19 Pneumonia and Hyperinflammation

Global, randomized, double-blind, placebo-controlled trial



Key Inclusion Criteria:

- Positive COVID-19 test within 14 days prior to randomization
- Hospitalized for COVID-19
- Bilateral pneumonia on chest x-ray or computed tomography
- Clinical laboratory results indicative of hyper-inflammation
- Cohort 1: Non-ventilated; requiring supplemental oxygen to maintain oxygen saturation (SpO2) ≥ 92% and not-intubated
- Cohort 2: Recently ventilated with mechanical ventilation prior to randomization

Cohort 1:

Primary Efficacy Endpoint:

- Proportion of patients alive and without mechanical ventilation at Day 29.

Secondary Efficacy Endpoints:

- Time to 2-point clinical improvement (National Institute of Allergy and Infectious Diseases COVID-19 ordinal scale) by Day 29
- Time to return to Room Air or Discharge by Day 29
- Mortality rate at Day 29

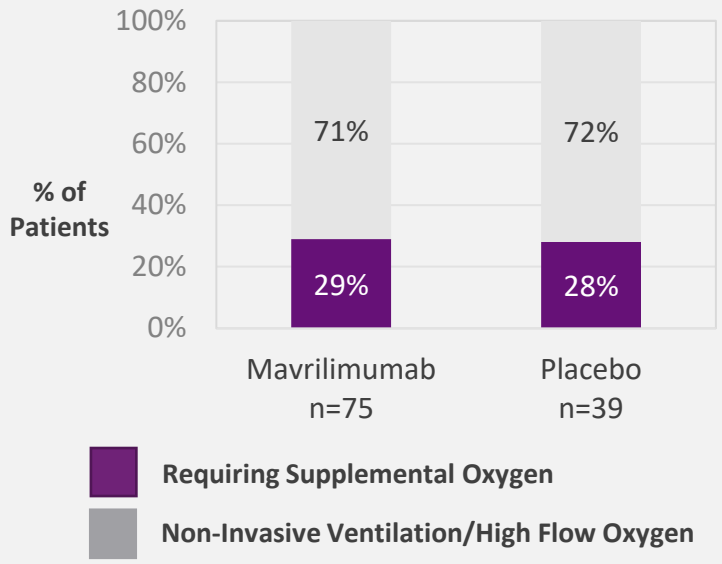
Prespecified evidentiary standard for Phase 2 endpoints was a 2-sided p value of 0.2, without adjustment for multiplicity

Baseline Demographics and Clinical Characteristics

Baseline Demographics (n=114)

Mean Age (years)	57.1
Age Range (years)	29-86
≥ 65 years old	29%
Female	43%
Non-white	43%
Body mass index ≥ 30	49%

NIAID[1] Score at Randomization

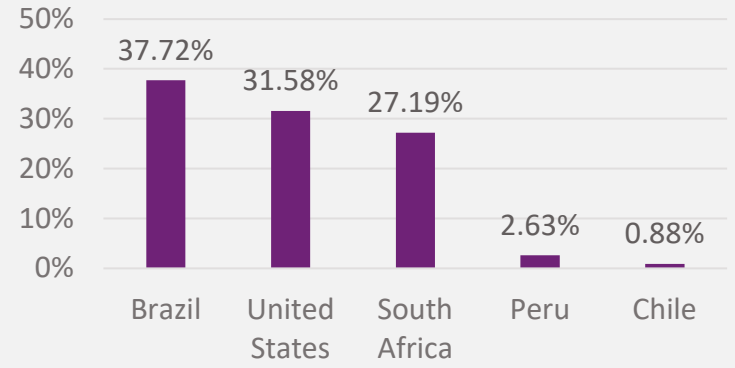


1. National Institute of Allergy and Infectious Diseases

Local Standard of Care by Day 29 (% of patients)

Corticosteroids/Dexamethasone	96%
Antivirals/Remdesivir	29%

Randomized Number of Patients by Country

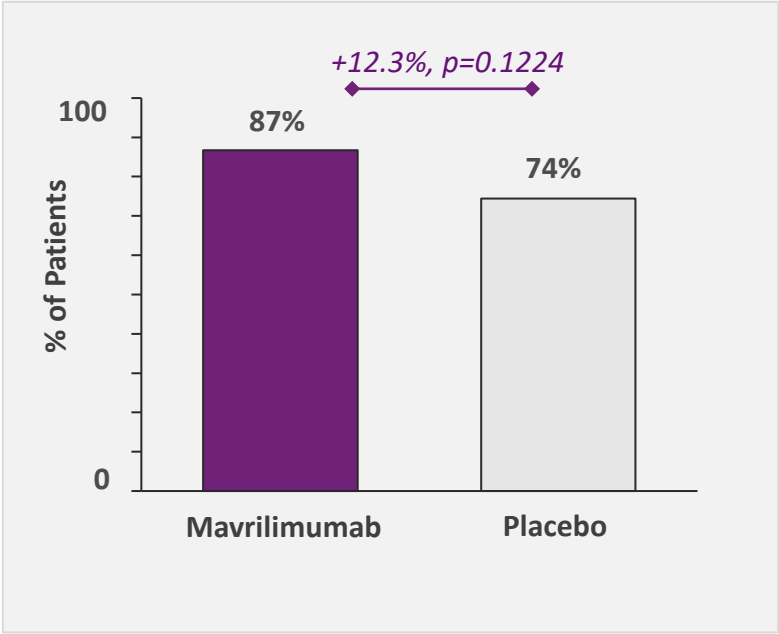


Key Points

- In Cohort 1 (non-mechanically ventilated), 116 patients with hypoxia and severe COVID-19 pneumonia/hyperinflammation were enrolled across sites in the US, Brazil, Chile, Peru, and South Africa
- Baseline demographics were balanced across treatment arms
- A majority of patients received corticosteroids/dexamethasone as standard of care

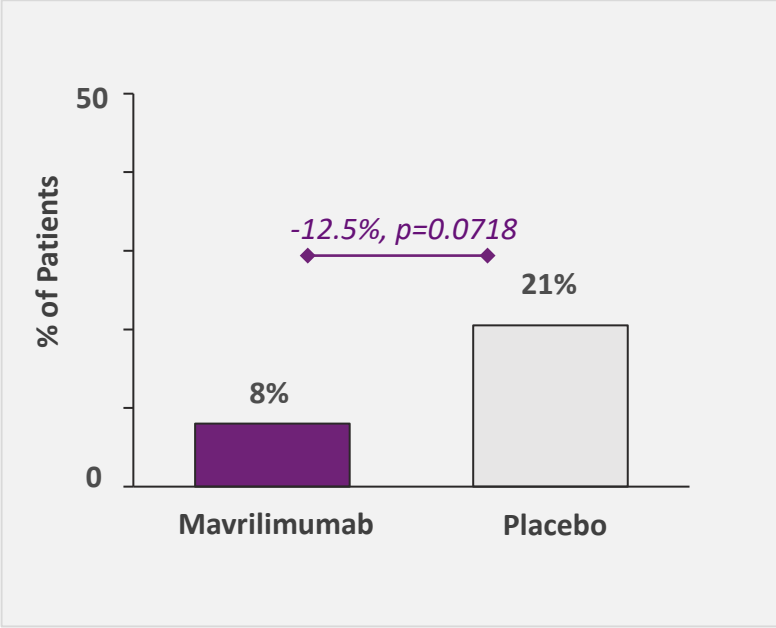
Mavrilimumab Improved Proportion of Patients Alive and Free of Mechanical Ventilation

Primary Efficacy Endpoint: Proportion of Patients Alive and Free of Mechanical Ventilation at Day 29



~1/4 of placebo recipients required mechanical ventilation or died by day 29; this risk was reduced by 12.3 percentage points in mavrilimumab recipients

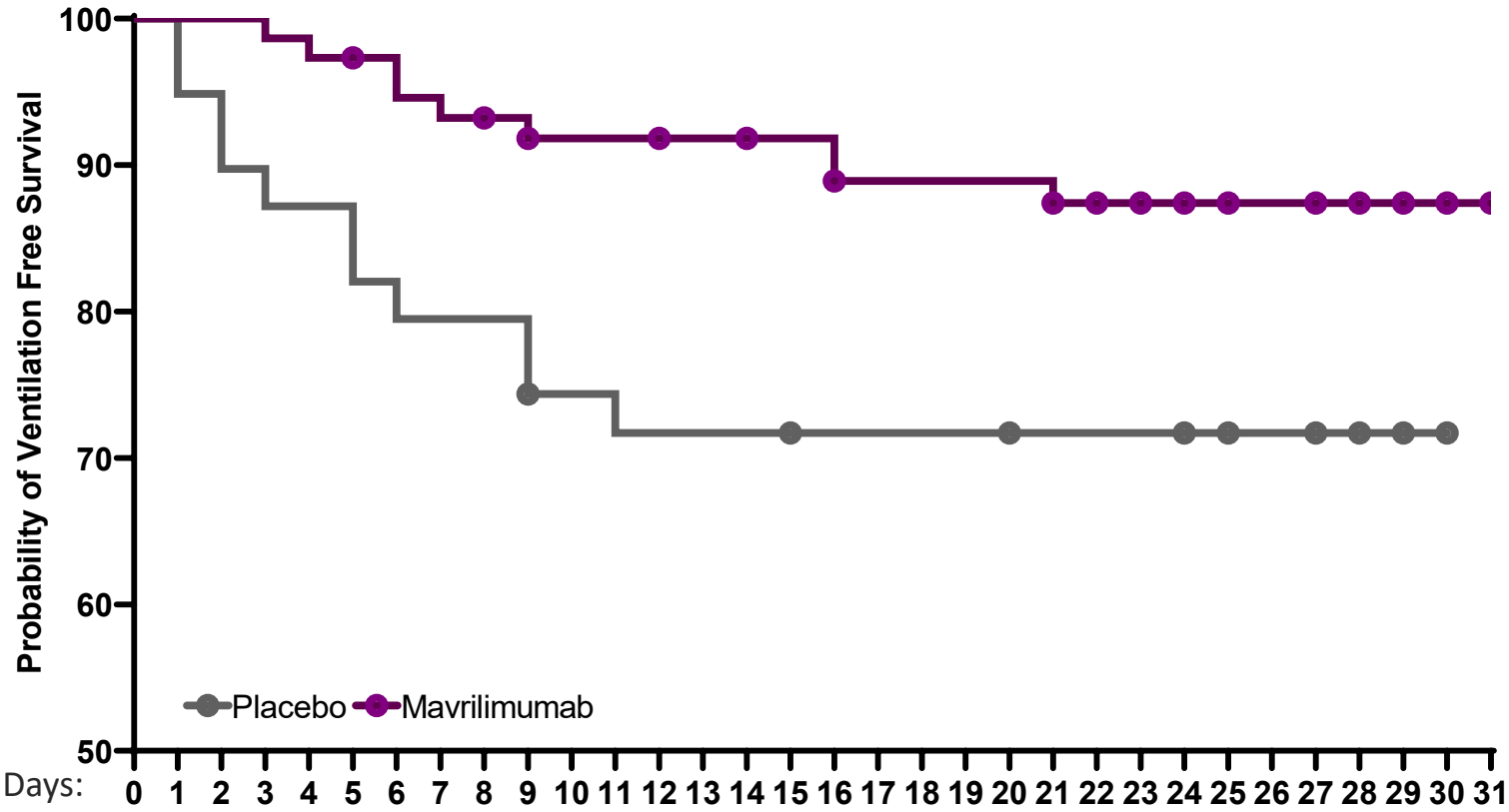
Key Secondary Efficacy Endpoint: Mortality at Day 29



Mavrilimumab recipients experienced a 61% reduction in the risk of death (HR= 0.39; p=0.0726)

The prespecified evidentiary standard for Phase 2 endpoints was a 2-sided alpha value of 0.2, without adjustment for multiplicity.
Patients were pooled across dose levels (10 and 6 mg/kg), as there were no apparent differences in outcomes observed between dose levels.

Mavrilimumab Reduced Risk of Mechanical Ventilation or Death by 65% Versus Placebo



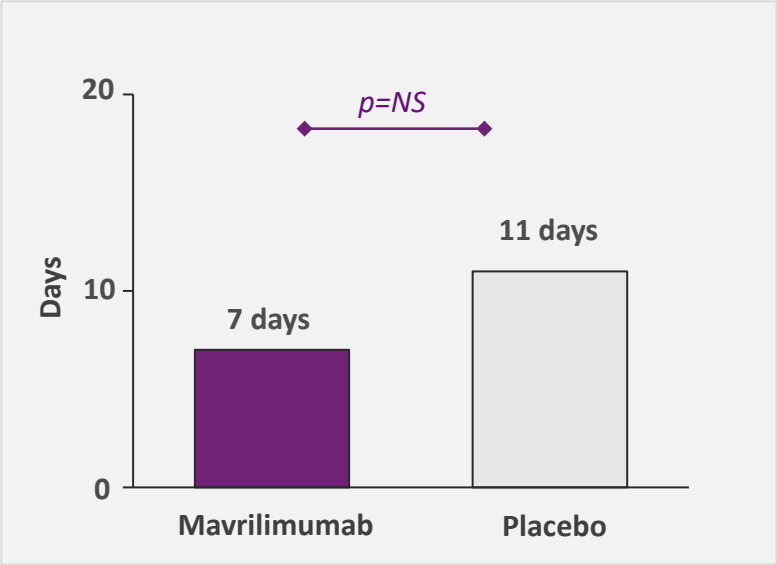
Hazard Ratio = 0.35
Log-rank p-value = 0.0175
Risk Reduction = 65%

No. at Risk	Days: 0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Mavrilimumab	75	75	75	75	74	73	71	69	68	67	65	65	65	64	64	63	63	59	59	59	59	59	55	52	50	49	47	47	45	38	18	3
Placebo	39	39	37	35	34	34	32	31	31	31	28	28	27	27	27	27	26	26	26	26	26	25	25	25	25	24	22	22	17	14	4	

The prespecified evidentiary standard for Phase 2 endpoints was a 2-sided alpha value of 0.2, without adjustment for multiplicity.
Patients were pooled across dose levels (10 and 6 mg/kg), as there were no apparent differences in outcomes observed between dose levels.

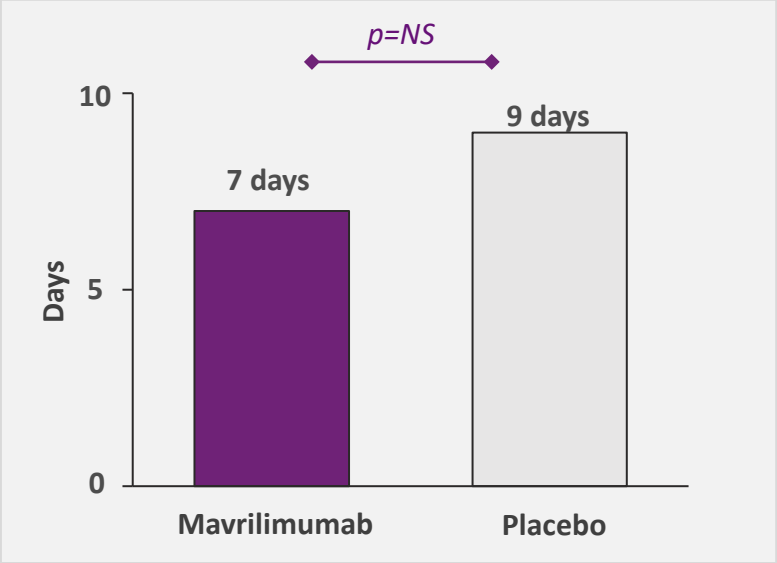
Mavrilimumab Improved Time to Clinical Improvement and Time to Room Air

Key Secondary Efficacy Endpoint:
Median Time to 2-Point Clinical Improvement*



Trend toward faster median time to 2-point clinical improvement in mavrilimumab recipients

Key Secondary Efficacy Endpoint:
Median Time to Room Air



Trend toward faster median time to room air in mavrilimumab recipients

***National Institute of Allergy and Infectious Diseases COVID-19 ordinal scale**

Mavrilimumab Was Well-Tolerated

n (%)	Mavrilimumab 10 mg/kg (N=35)	Mavrilimumab 6 mg/kg (N=41)	Placebo (N=40)
Treatment Emergent Adverse Events	19 (54.3)	19 (46.3)	26 (65.0)
By Maximum Severity [1]			
Mild	10 (28.6)	8 (19.5)	6 (15.0)
Moderate	5 (14.3)	5 (12.2)	6 (15.0)
Severe	4 (11.4)	6 (14.6)	14 (35.0)
Related to Mavrilimumab or Placebo [2]	2 (5.7)	3 (7.3)	4 (10.0)
Serious Treatment Emergent Adverse Events	4 (11.4)	5 (12.2)	13 (32.5)
Related to Mavrilimumab or Placebo [2]	0	0	1 (2.5)
Treatment Emergent Adverse Events Resulting in Death	3 (8.6)	4 (9.8)	9 (22.5)
Treatment Emergent Adverse Events Leading to Dose Interruption	0	0	1 (2.5)
Treatment Emergent Adverse Events of Special Interest	3 (8.6)	2 (4.9)	6 (15.0)
Infections	4 (11.4)	4 (9.8)	9 (22.5)
Thrombotic events	0	0	5 (12.5)

Key Points

- No drug-related SAEs occurred in mavrilimumab-treated patients
- Adverse events occurred less frequently in mavrilimumab recipients compared to placebo
- Infections were uncommon, and occurred at higher percentages in placebo (22.5%) compared with mavrilimumab (9.8-11.4%)
  - One patient in an endemic area for tuberculosis reported active tuberculosis ~10 days after 10 mg/kg dose of mavrilimumab; the patient received high-dose corticosteroids prior to this event
- Thrombotic events, a known complication of COVID-19, occurred in the placebo arm only

Pts with multiple events in the same category are counted only once in the category. Pts with events in more than one category are counted once in each of those categories. TEAE of Special Interest include: hepatic function abnormality/induced liver injury, acute or delayed hypersensitivity reactions, neutropenia, serious infection, worsening of cytokine release syndrome.
[1] Each pt has only been represented with the maximum severity.
[2] Possibly or definitely related, as assessed by the investigator.

Summary and Conclusions

- **Mavrilimumab reduced mechanical ventilation and death at Day 29 versus placebo in non-mechanically ventilated patients (Cohort 1) with severe COVID-19 pneumonia and hyperinflammation:**
  - The proportion of patients alive and free of mechanical ventilation at Day 29 was 12.3 percentage points higher in mavrilimumab recipients (86.7%) compared to placebo recipients (74.4%) (Primary efficacy endpoint; p=0.1224)
    - Mavrilimumab recipients experienced a 65% reduction in the risk of mechanical ventilation or death (Hazard Ratio (HR) = 0.35; p=0.0175)
  - Day 29 mortality was 12.5 percentage points lower in mavrilimumab recipients (8%) compared to placebo recipients (20.5%) (p=0.0718)
    - Mavrilimumab recipients experienced a 61% reduction in the risk of death (HR= 0.39; p=0.0726)
  - No apparent differences were observed between the 10 mg/kg and 6mg/kg IV treatment arms

- **Mavrilimumab was well-tolerated and exhibited a favorable safety profile:**
  - Adverse events occurred less frequently in mavrilimumab recipients compared to placebo, including secondary infections and thrombotic events (known complications of COVID-19)
  - There were no drug-related SAEs in patients treated with mavrilimumab, and there were no notable dose-related adverse events