

1 **Safety and Efficacy of Dupilumab for the Treatment of Hospitalized Patients with**
2 **Moderate to Severe COVID 19: A Phase IIa Trial**

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21 **ABSTRACT**

22 Background: A profound need remains to develop further therapeutics for treatment of those
23 hospitalized with COVID-19. Based on data implicating the type 2 cytokine interleukin (IL)-13 as
24 a significant factor leading to critical COVID-19, this trial was designed to assess dupilumab, a
25 monoclonal antibody that blocks IL-13 and IL-4 signaling, for treatment of inpatients with
26 COVID-19.

27 Methods: We conducted a phase IIa randomized double-blind placebo-controlled trial to assess
28 the safety and efficacy of dupilumab plus standard of care versus placebo plus standard of care
29 in mitigating respiratory failure and death in those hospitalized with COVID-19. Subjects were
30 followed prospectively for 60 days. The primary endpoint was the proportion of patients alive
31 and free of invasive mechanical ventilation at 28 days.

32 Findings: Forty eligible subjects were enrolled from June to November of 2021. There was no
33 difference in adverse events nor in ventilator free survival at day 28 between study arms.
34 However, for the secondary endpoint of mortality at day 60, subjects randomized to dupilumab
35 had a higher survival rate compared to the placebo group (89.5% vs 76.2%, adjusted HR 0.05,
36 95% CI: 0.0- 0.72, p=0.03). There were fewer subjects admitted to the ICU in the dupilumab
37 group compared to placebo (33.3% vs 66.7%; adjusted HR 0.44, 95% CI: 0.09-2.09, p=0.30).
38 Lastly, we saw downstream evidence of IL-4 and IL-13 signaling blockade in the dupilumab
39 group through analysis of immune biomarkers over time.

40 Interpretation: Dupilumab was well tolerated and improved 60-day survival in patients
41 hospitalized with moderate to severe COVID-19.

42 Trial Registration: This trial is registered with ClinicalTrials.gov, NCT04920916.

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45 **INTRODUCTION:**

46 As in-hospital mortality remains at 10-26%^{1,2} paired with the ongoing threats of new SARS-CoV-
47 2 variants, there remains a substantial need for additional therapeutics for those hospitalized
48 with COVID-19. Current therapies against both the virus and with intention for
49 immunomodulation have demonstrated variable and/or modest benefit. For example, the
50 RECOVERY trial showed a mortality reduction from 26% to only 23% with dexamethasone use
51 in those hospitalized with COVID-19 respiratory failure, with the greatest mortality benefit seen
52 in those requiring mechanical ventilation at randomization³. Clinical trials for remdesivir, an
53 antiviral nucleoside analog, have produced variable results, with the ACTT-1 trial demonstrating
54 a 5 day reduction in clinical recovery time in those on supplemental oxygen⁴. Randomized
55 controlled trials investigating interleukin (IL)-6 inhibitors have shown conflicting results, with
56 some indicating a mortality benefit in those within 24 hours of intensive care unit (ICU)
57 admission and others showing no difference in clinical outcomes between study groups^{5,6}.
58 Janus kinase inhibitors initially showed only a 1 day improvement in clinical recovery time when
59 combined with remdesivir, with later trials since showing reduced mortality from 13% to 8%
60 when combined with usual care in those requiring hospitalization and at least 1 elevated
61 inflammatory marker^{7,8}. Findings from these studies suggest a need for improvement in
62 treatment of those admitted with COVID-19 pneumonia.

63
64 We have discovered that COVID-19 patients with high plasma IL-13 levels have a significantly
65 greater risk of needing mechanical ventilation⁹. IL-13, which signals through the receptor IL-4R α
66 along with the closely related cytokine IL-4, is involved in eosinophilic inflammation, mucous
67 secretion, goblet cell metaplasia and fibrosis, and has been regularly implicated in airway
68 hyperresponsiveness and atopic disease¹⁰. We additionally found that neutralization of IL-13 in
69 K18-hACE2 C57Bl/6J mice protected the animals from severe infection with SARS-CoV-2, as
70 evidenced by reduced clinical score, weight loss and mortality⁹. The association of IL-13 along

71 with other effectors of type 2 immunity with respiratory failure from COVID-19 has also been
72 demonstrated in other observation studies^{11,12}. These findings established mechanistic and
73 biologic plausibility for IL-13 as a driver of pulmonary injury in COVID-19.

74

75 There are medications available to block IL-13 signaling: dupilumab, an anti-IL-4R α monoclonal
76 antibody, was approved for treatment of moderate to severe atopic dermatitis by the FDA in
77 2017. It reduces clinical severity in patients with allergic diseases including atopic dermatitis,
78 asthma and chronic rhinosinusitis¹³. The original clinical trials demonstrated minimal adverse
79 events with dupilumab use, favoring it as a steroid sparing therapy in atopic disease^{14,15}. Post
80 hoc analysis of initial studies saw reduced incidence of respiratory viral infections with its use¹⁶.

81

82 Dupilumab use was associated with greater survival from COVID-19 in retrospective analysis:
83 using the TriNetX international electronic medical record (EMR) database, we previously
84 identified a cohort of 350,004 patients with COVID-19, of whom 81 had been prescribed
85 dupilumab prior to their COVID-19 diagnosis⁹. Patients on dupilumab had a 12.3% absolute risk
86 reduction in mortality compared to a propensity score matched sub cohort of 81 patients with
87 COVID-19 not on dupilumab but with atopic diseases for which dupilumab is routinely used⁹.
88 Dupilumab has since been shown to reduce symptom severity and improve clinical outcomes in
89 other observational studies utilizing large patient databases^{17,18}.

90

91 The association of IL-13 with COVID-19 respiratory failure, the demonstration of survival benefit
92 with IL-13 blockade in a mouse model and the retrospective EMR analysis showing reduced
93 COVID-19 mortality in those receiving dupilumab for atopic disease, provided significant
94 evidence for further exploration of dupilumab use for treatment of COVID-19. This along with the
95 safety of dupilumab and the potential for a targeted approach to therapy led to the design of a
96 clinical trial to test its use in those hospitalized with COVID-19.

97

98 **METHODS**

99 **Design**

100 This was a randomized, double-blind, placebo-controlled trial designed to assess the safety and
101 efficacy of dupilumab use in 40 hospitalized patients from a single center with moderate to
102 severe COVID-19 infection. It was approved by the University of Virginia Institutional Review
103 Board (IRB) in June 2021 (NCT04920916). Eligible subjects were enrolled and randomized at a
104 1:1 ratio to receive either dupilumab or placebo, stratifying on disease severity measured by an
105 oxygen requirement of ≤ 15 L/min or > 15 L/min by nasal cannula. Included were those over the
106 age of 18 who were hospitalized with a positive reverse transcription polymerase chain reaction
107 test (RT-PCR) for SARS-CoV-2 within the last 14 days and evidence of moderate to severe
108 COVID-19 as defined by National Institutes of Health (NIH) COVID-19 Severity Categorization¹⁹.
109 Patients requiring mechanical ventilation at the time of enrollment were excluded. Both arms
110 received standard of care management per current NIH COVID-19 treatment guidelines,
111 including dexamethasone and remdesivir as deemed appropriate by their primary provider¹⁹.
112 Subjects received a loading dose of dupilumab (600 mg, given as two 300 mg subcutaneous
113 injections) or placebo on day 0 with additional maintenance doses of 300 mg or placebo given
114 on days 14 and 28 if the subject remained hospitalized and receiving active care²⁰. Subjects
115 were followed prospectively for 60 days.

116

117 **Outcomes**

118 The primary outcome of the study was the proportion of patients alive and free of invasive
119 mechanical ventilation at day 28. Safety outcomes were assessed via determination of the
120 cumulative incidence of adverse events, including those previously reported to occur with
121 dupilumab use (i.e., injection site reactions, eye/eyelid inflammation, conjunctivitis, herpes viral
122 infection, eosinophilia)²⁰. Additional clinical endpoints included all-cause mortality at day 28 and

123 60, proportion of patients alive and free of invasive mechanical ventilation at 60 days, hospital
124 length of stay (LOS), ICU LOS, change in 8-point ordinal score and change in partial pressure of
125 oxygen (PaO₂) or oxygen saturation (SaO₂) to fraction of inspired oxygen (FiO₂) ratio. Plasma
126 inflammatory markers, including C reactive protein (CRP), ferritin and a 47-plex cytokine panel
127 were measured at various time points during the study. Additional type 2 inflammatory markers
128 including TARC (CCL17), YKL40, eotaxin 3 (CCL26), arginase1 (Arg1), hyaluronan, soluble
129 ST2 and total serum immunoglobulin E (IgE) were also measured. Ferritin, CRP and IgE levels
130 were measured at the University of Virginia Clinical Laboratories while other biomarkers were
131 measured by multiplex immunoassays or ELISAs depending on the analyte. SARS-CoV-2
132 baseline nucleocapsid (N)- protein level was measured from day 0, 2, 5, 7 and 14 available
133 plasma of each subject using a microbead-based immunoassay, a highly sensitive detection
134 method described in previous studies²¹. Day 0 nasopharyngeal (NP) swabs obtained for
135 assessment of SARS-CoV-2 RNA positivity via RT-PCR underwent genomic sequencing to
136 determine the SARS-CoV-2 lineage for samples with sufficient RNA using ARTIC v3 primers on
137 either MiSeq (Illumina) or MinIon (Oxford Nanopore) using the and categorized according to
138 PANGOLIN and World Health Organization^{22,23}.

139

140 **Statistical Analysis**

141 COVID-19 hospitalization data from UVA between March 2020 and April 2021 showed that
142 79.5% of COVID-19 inpatients were alive and free of mechanical ventilation at 28 days under
143 usual care. With a pre-selected sample size of 40 patients and alpha=0.1 (one sided), we would
144 be able to detect a difference of 17.7% in the proportion of subjects alive and free of mechanical
145 ventilation at 28 days with 75% power.

146

147 Primary and secondary outcomes were analyzed under the intention-to-treat (ITT) principle.

148 Safety outcomes were analyzed in the as treated population, including subjects who were

149 enrolled and received at least one dose of study drug. Demographics, clinical and safety
150 outcomes were analyzed initially with the Chi-square or Fisher's exact tests for categorical
151 measures and two-sample t-test or Wilcoxon rank sum for continuous measures, after
152 assessment of normality. Treatment differences in ventilator free survival proportions were
153 analyzed via logistic regression. Mortality differences were evaluated by the log-rank test and
154 further in the Cox regression for time to death outcome. Baseline patient characteristics and
155 known risk factors for severe disease in COVID-19, including age, sex, body mass index (BMI),
156 comorbidities and COVID-19 vaccination status, were adjusted in regression models if initial
157 analyses discovered imbalance in group characteristics²⁴. Differences in the biomarkers
158 between treatment groups were analyzed exploratively by t-test or Wilcoxon rank sum testing at
159 each time point.

160

161 As an exploratory analysis, we included mechanical ventilation as a time varying variable in the
162 Cox regression for further investigation of its influence on survivability. This allowed us to
163 account for the significant change in mortality risk between pre- and post-intubation when a
164 patient was placed on mechanical ventilation. We additionally tested differences in the likelihood
165 of ICU admission between the two groups by the log-rank test. Lastly, after assessment of
166 normality, N-protein levels were split into quartiles and analyzed by treatment group for
167 influence on mortality via log-rank test and Cox regression. Regression models were adjusted
168 for additional medications that were most likely to influence viral load, including monoclonal
169 antibodies and remdesivir. Longitudinal N- protein levels over the first fourteen study days were
170 evaluated by the treatment groups using the linear mixed effects models to account for within-
171 subject correlations.

172

173 **RESULTS**

174 **Patient and Virus Characteristics**

175 Forty patients were enrolled from June 23, 2021 through November 11, 2021 (Fig S1). The
176 groups were well matched with regard to age, BMI, race, ethnicity, comorbidities, vaccination
177 status and days from COVID-19 symptom onset to enrollment (Table 1). Patients in the placebo
178 arm were more likely to be male compared to the dupilumab arm (76.2% vs. 36.8%). There
179 were no significant differences in non-study COVID-19 therapies received between the
180 treatment groups (Table 1). Of those NP samples available for SARS-CoV-2 sequencing, 30 of
181 31 (96.8%) subjects had the delta variant and one subject in the placebo group had the iota
182 variant (Table S1).
183

	Placebo (n=21)	Dupilumab (n=19)
Age	63.0 (23.0)	69 (26.0)
Sex		
Male	16 (76.2%)	7 (36.8%)
BMI	32.3 (10.1)	33.6 (14.9)
Ethnicity		
Hispanic	3 (14.3%)	3 (15.8%)
Race		
White	14 (66.7%)	13 (68.4%)
Black	6 (28.6%)	4 (21.1%)
Asian	0 (0.0%)	1 (5.3%)
Other	1 (4.8%)	1 (5.3%)
Comorbidities		
Obesity	15 (71.4%)	14 (73.7%)
Chronic Kidney Disease	7 (33.3%)	3 (15.8%)
Asthma	4 (19.1%)	4 (21.1%)
Respiratory Disease (COPD, emphysema)	3 (14.3%)	2 (10.5%)
Diabetes	8 (38.1%)	7 (36.8%)
Coronary Artery Disease	6 (28.6%)	3 (15.8%)
Cardiac Valvular Disease	3 (14.3%)	2 (10.5%)
Hypertension	10 (47.6%)	8 (42.1%)
Congestive Heart Failure	5 (23.8%)	2 (10.5%)
Cardiac Arrhythmia	4 (19.1%)	1 (5.3%)
Depression or psychotic disorder	3 (14.3%)	8 (42.1%)
Malignancy	4 (19.1%)	3 (15.8%)
Autoimmune disease	2 (9.5%)	2 (10.5%)
Organ or stem cell transplant recipient	3 (14.3%)	1 (5.3%)
Other immune deficiency	1 (4.8%)	0 (0.0%)
Smoking History		
Never	12 (57.1%)	15 (79.0%)
Current	3 (14.3%)	0 (0.0%)
Past	6 (28.6%)	4 (21.1%)
Days from symptom onset to study treatment	8.0 (4.0)	7.0 (5.0)
Received COVID-19 vaccine		
Moderna	4 (19.1%)	1 (5.3%)
Pfizer	5 (23.8%)	4 (21.1%)
J&J	0 (0.0%)	2 (10.5%)
None	12 (57.1%)	12 (63.2%)
Other COVID-19 therapeutics received		
Steroids	20 (95.2%)	19 (100%)
Remdesivir	10 (47.6%)	16 (84.2%)
IL-6 inhibitor	0 (0.0%)	0 (0.0%)
Janus kinase inhibitor	4 (19.1%)	1 (5.3%)
Monoclonal antibodies	3 (14.3%)	2 (10.5%)

Table 1: Patient characteristics. Continuous variables expressed as median (interquartile range). Categorical variables expressed as total n (percentage). Age expressed in years. Body Mass Index (BMI, kg/m²), Chronic Obstructive Pulmonary Disease (COPD), Johnson and Johnson (J&J).

185 **Safety**

186 There were no significant differences in cumulative adverse events observed between the
187 treatment groups (Table 2). In the dupilumab group, five subjects developed asymptomatic
188 eosinophilia compared to one subject in the placebo group (Fisher's exact p=0.09). There were
189 no clinical consequences, including dermatologic, gastrointestinal, pulmonary, cardiac or
190 neurologic, attributed to the peripheral eosinophilia seen in these subjects.

	Placebo (n=21)	Dupilumab (n=19)
Injection site reactions	0 (0.0%)	0 (0.0%)
Conjunctivitis	2 (9.5%)	0 (0.0%)
Bacterial pneumonia	1 (4.8%)	2 (10.5%)
Herpes viral infection	0 (0.0%)	0 (0.0%)
Eosinophilia*	1 (4.8%)	5 (26.3%)
Hyper eosinophilic syndrome	0 (0.0%)	0 (0.0%)
Other infections	2 (9.5%)	4 (21.1%)
Cumulative	6	11

191 **Table 2:** Adverse events observed throughout the study period by treatment group. Other
192 infections included *Clostridioides difficile* infection (1), bacteremia (2), urinary tract
193 infections (2) and oral candidiasis (1). Categorical variables expressed as total n
194 (percentage). Eosinophilia was defined as an absolute eosinophil count >0.6 k/uL at ≥ 1
measurement throughout the study period. *Difference between treatment groups was not
statistically significant with Fischer's exact p=0.09.

195 **Clinical Efficacy**

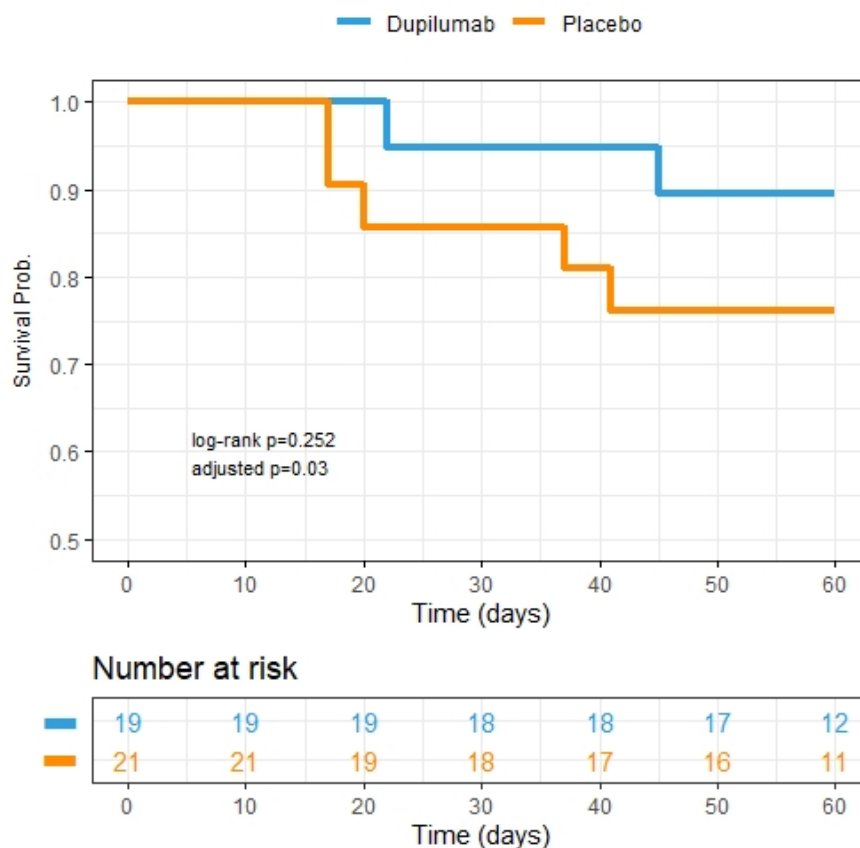
196 There was no significant difference in the primary endpoint of proportion of patients alive and
197 free of mechanical ventilation at day 28 between the two groups (Table 3). However, by
198 secondary endpoint at 60 days, 89.5% of subjects in the dupilumab group were alive compared
199 to 76.2% for the placebo group as no patients remained on mechanical ventilation by day 60 in
200 either group (Table 3). After adjustment for sex and mechanical ventilation as a time varying
201 predictor, the risk of death over 60-day follow-up period was significantly lower in dupilumab
202 group compared to placebo (Table 3; Fig 1).

203

204

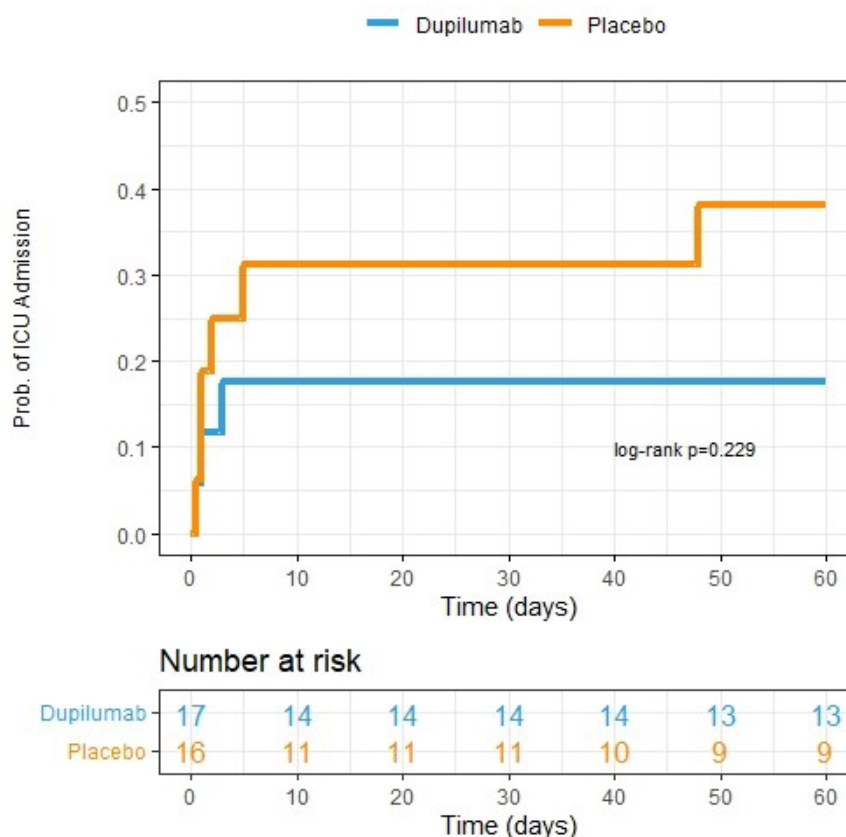
	Placebo (n=21)	Dupilumab (n=19)	OR (95% CI) or HR (95% CI)	P value
Proportion of patients alive and free of mechanical ventilation by day 28	18 (85.7%)	15 (78.9%)	Unadjusted OR: 1.60 (0.31, 8.30)	0.57
			Adjusted OR: 2.45 (0.40, 15.10)	0.34
Proportion of patients alive and free of mechanical ventilation by day 60	16 (76.2%)	17 (89.5%)	Unadjusted OR: 0.38 (0.06, 2.22)	0.28
			Adjusted OR: 0.44 (0.07, 2.96)	0.40
Mortality by day 28	3 (14.3%)	1 (5.3%)	Unadjusted HR: 0.35 (0.04, 3.32)	0.36
			Adjusted HR: 0.06 (0.003, 1.59)	0.09
Mortality by day 60	5 (23.8%)	2 (10.5%)	Unadjusted HR: 0.40 (0.08, 2.05)	0.27
			Adjusted HR: 0.05 (0.004, 0.72)	0.03

205 **Table 3:** Primary and key secondary endpoints by treatment group. Primary endpoint was ventilator free survival by
 206 day 28. Secondary endpoints were ventilator free survival by day 60, mortality by day 60 and mortality by day 28.
 207 Proportions are listed as total n (%). The differences in the ventilator free survival proportions were evaluated using
 208 logistic regression, adjusted for sex. The differences in mortality risk were evaluated in the Cox regression, adjusted
 209 for sex and time varying mechanical ventilation.



208 **Figure 1:** Kaplan Meier survival curves depicting 60-day mortality between two
 209 treatment groups. Dupilumab group is represented by blue line. Placebo group
 210 is represented by the orange line. Adjusted p value indicative of adjustment for
 211 sex and time varying ventilation in the Cox regression. Patient study visits
 212 occurred within an allotted range of exact study days and therefore the number
 at risk in the table is representative of patient data availability up until those
 exact days (i.e., if study visit was conducted on day 59 and no event had
 occurred, then the subject was included in the at-risk pool up until day 59 but
 not in that for day 60).

213 Numerically fewer subjects in the dupilumab group required ICU care (33.3%) compared to the
 214 placebo group (66.7%) though this difference was not statistically significant (log-rank $p=0.23$,
 215 HR 0.44, CI: 0.09-2.09, $p=0.30$ adjusted for sex, Fig 2). There was no difference in additional
 216 secondary endpoints between the two treatment groups (Table 4, Fig S2, Fig S3).



217 **Figure 2:** Kaplan Meier curve depicting need for escalation to ICU over 60-
 218 day study period. Patients already admitted to the ICU on day of enrollment
 219 ($n=7$) were excluded from analysis. Dupilumab group is represented by
 220 blue line. Placebo group is represented by the orange line. Patient study
 221 visits occurred within an allotted range of exact study days and therefore
 the number at risk in the table is representative of patient data availability
 up until those exact days (i.e., if study visit was conducted on day 59 and
 no event had occurred, then the subject was included in the at-risk pool up
 until day 59 but not in that for day 60).

222 **Biomarker Analysis**

223 In both treatment groups, CRP, ferritin and IgE levels declined in the first two weeks with no
 224 significant difference in the change in measures from day 0 to 14 between groups (Fig S4).

225 When looking at the change in absolute cell counts over time, there was an increase in

226 eosinophils by day 14 in the dupilumab group compared to the placebo group ($p=0.01$ by
227 Wilcoxon rank sum, Fig S5). Analysis of patient cytokine, chemokine and growth factors in
228 serum at various study time points showed a decreased monocyte chemoattractant protein-1
229 (MCP-1) at day 7 in the dupilumab treatment group compared to placebo ($p=0.04$ by Wilcoxon
230 rank sum, Fig S6). By day 14, there was a larger decrease in eotaxin-3 levels in the dupilumab
231 group compared to the placebo ($p=0.08$ by Wilcoxon rank sum, Fig S6). Additionally, there was
232 a trend towards decreased levels of YKL40 in the dupilumab group compared to the placebo by
233 day 14 ($p=0.26$ by Wilcoxon rank sum, Fig S6). There was no statistically significant difference
234 in baseline N-protein levels in the dupilumab group (median 671 ng/mL) compared to the
235 placebo group (median 580 ng/mL; $p=0.75$ by Wilcoxon rank sum). When comparing the top
236 quartile vs. the bottom three quartiles (i.e., bottom 75th percentile) of baseline N-protein level
237 within each treatment group, we found significant survival difference among the four groups
238 (log-rank $p=0.022$, Fig S7). The 60-day mortality risk for those in the top quartile of baseline N-
239 protein was 3.8 times of those in the bottom three quartiles after adjusting for treatment group,
240 remdesivir use and monoclonal antibody use (95% CI: 0.78-18.7, $p=0.098$). N-protein levels in
241 log-scale declined significantly from baseline to day 14 levels ($p<0.0001$), however, no
242 difference was found in the rate of decline between the two treatment groups ($p=0.17$).

243

244 **DISCUSSION**

245 In this randomized double-blind placebo-controlled trial, although there was no difference
246 between study groups regarding the primary endpoint of 28-day ventilator free survival, the
247 secondary endpoint of increased 60-day survival in the dupilumab group was achieved.

248 Additionally, there were no safety signals seen with dupilumab use.

249

250 Although most deaths occurred in the placebo arm (5) compared to dupilumab (2), the overall
251 mortality of subjects enrolled in this study (17.5%) was higher than expected, suggesting

252 enrollment of a population with relatively higher disease severity. ICU mortality was 20% in the
253 dupilumab group versus 36% in placebo, and ventilator mortality was 50% in the dupilumab
254 group compared to 100% in placebo. Severity of illness seen in our study reflected that
255 enrollment occurred during the delta surge and that the majority of those enrolled were
256 unvaccinated, consistent with national data at the time²⁵. For example, the National Hospital
257 Care Survey (NHCS) data from the US Centers for Disease Control and Prevention (CDC),
258 showed 11.9-13.1% in-hospital mortality in select hospitals throughout the United States during
259 the month of August 2021 with ventilatory mortality rates ranging from 47.9%-74.1%, a time
260 period during which this study enrolled subjects²⁶. Furthermore, baseline N-protein levels were
261 the same between the two groups and comparable to baseline N-protein levels of patients
262 enrolled in the ACTIV3 trials²⁷. As high N-protein levels are predictive of COVID-19 disease
263 progression, a finding also demonstrated in this study, this suggests patients enrolled in our
264 study were of comparable baseline disease severity²⁷.

265
266 The detection of survival and mechanical ventilation differences at 60 days rather than at 28
267 days is consistent with reports of immunologic dysfunction from COVID-19 extending out to 8
268 months for mild to moderate COVID-19, with deaths from severe COVID-19 occurring out to 12
269 months^{28,29}. Although the small size of our study limits broad conclusions about the mortality
270 benefit of dupilumab, these findings combined support a late clinical benefit of blockade of a
271 type 2 immune process in COVID-19. The response to dupilumab in asthma is also protracted
272 with improvements in FEV1 first being observed 2 weeks after initiation of treatment³⁰. Thus, the
273 time to clinical effect of dupilumab in the acute COVID-19 setting may have limited our ability to
274 see early clinical differences between the treatment groups. For example, subjects in our study
275 who ultimately required mechanical ventilation did so within the first 8 days of the study, some
276 within 1-2 days of enrollment, during a time in which drug concentration may have been lower,
277 particularly in the context of a rapidly evolving clinical process.

278

279 Although biomarker trends seen in both groups were likely influenced by the steroids that almost
280 all subjects received, we did see a reduction of the Type 2 immune markers YKL40 and eotaxin-
281 3 in the dupilumab arm when compared to the placebo arm, indicative of the IL-4R α blockade
282 with inhibition of downstream mediators of the type 2 immune response. Increased peripheral
283 eosinophil counts in the dupilumab group occurred by day 14, consistent with previous
284 observations of dupilumab use in patients with atopic disease, likely due to decreased
285 eosinophil uptake in tissue^{30,31}. While we did not see IgE decrease at 2 weeks of dupilumab
286 treatment, this is consistent with prior studies showing gradual decline of IgE levels compared to
287 other biomarkers after dupilumab initiation³¹. We also saw reduction in MCP-1, a potent
288 chemoattractant molecule of monocytes/macrophages, in the dupilumab group, high levels of
289 which have been associated with COVID-19 disease severity^{32,33}. Lastly, although recent invitro
290 studies have shown that high IL-13 levels are associated with reduction in ACE2 receptor
291 expression and decreased SARS-CoV-2 viral load, this is inconsistent with our study which
292 shows similar rates of decline in N-protein levels in those who received IL-4R α blockade
293 compared to placebo³⁴.

294

295 The study had several limitations. These included the lack of achievement of the primary
296 endpoint of proportion of patients alive and free of mechanical ventilation at day 28, and the
297 wide confidence intervals in the survival benefit of dupilumab at day 60. Additional limitations
298 included unequal gender distribution between groups, patients were almost exclusively infected
299 by the Delta variant of SARS CoV-2 and a higher-than-expected overall mortality rate.

300

301 The study also had several notable strengths including having as a foundation the preclinical
302 data on the mechanism of disease exacerbation by IL-13 in COVID-19, originality in the study of
303 type 2 immune inhibition, the use of a prospective placebo-controlled randomized and double-

304 blind design, and demonstration of the safety of dupilumab. Importantly, there was evidence for
305 mortality reduction and reduced ICU escalation with dupilumab use as we had predicted from
306 animal models and retrospective human studies, despite sample size limitations. In light of the
307 ongoing need for additional therapies for COVID-19 associated respiratory failure and the
308 modest clinical benefits seen with other anti-viral and immunotherapies currently being used,
309 the results of this study advance dupilumab as a promising treatment option for those
310 hospitalized with COVID-19.

311

312 **COMPETING INTERESTS STATEMENT:** The authors have no competing interests to report.

313

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325

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353

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