F. Hoffmann-La Roche Ltd. (Shareholder)**Genentech, Inc.** (Employee) **Yifeng Chia, PhD**, **F. Hoffmann-La Roche Ltd** (Shareholder)**Genentech, Inc.** (Employee) **Tripthi Kamath, PhD**, **F. Hoffmann-La Roche Ltd** (Shareholder)**Genentech, Inc.** (Employee) **Larry Tsai, MD**, **F. Hoffmann-La Roche Ltd** (Shareholder)**Genentech, Inc.** (Employee)

516. Evaluation of COVID-19 Monoclonal Antibody Therapies for the Treatment of Non-hospitalized Patients with COVID-19

Faiza Morado, PharmD[1]; Neha Nanda, MD, FSHEA[2]; [1]Keck Medical Center of USC, Pasadena, CA; [2]Keck School of Medicine, Los Angeles, CA

Session: P-24. COVID-19 Treatment

Background. In an effort to reduce strain on healthcare systems with patient hospitalizations and deaths due to COVID-19, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for 2 monoclonal antibodies for the treatment of COVID-19 in November 2020: bamlanivimab (BAM) and casirivmab-imdevimab (CAS-IMD). While clinical trial data demonstrated reductions in hospitalization rate, real-world data at the time of approval was vastly limited.

Methods. A retrospective chart review of non-hospitalized patients who received either BAM or CAS-IMD from November 27th, 2020 to February 16th, 2021. Variables included timing of monoclonal antibody infusion, adverse events, and 30-day hospitalization rate. Descriptive statistics were calculated for all data.

Results. 101 patients received either BAM (75.2%) or CAS-IMD (24.8%) at a median of 6 days (IQR 4-7) from reported symptom onset. The most commonly reported symptoms of COVID-19 at time of referral were cough (57.4%), fever (29.7%), and myalgia (27.7%). All patients (100%) had at least 1 documented EUA defined risk factor for severe COVID-19 (Table 1). Following transfusion, 7/101 (6.9%) and 3/101 (3.0%) experienced mild to moderate and severe adverse events, respectively (Table 2). At day 30, 5 patients (5.0%) were hospitalized with COVID-19 at a median of 7 days (IQR 3-8) post monoclonal antibody infusion.

Table. 1 Risk Factors for Severe Disease

Risk Factor	No. (%) (n=101)
BMI ≥ 35 kg.m^2	13 (12.9)
Chronic kidney disease	8 (7.9)
Diabetes	28 (27.7)
Immunosuppressive Disease	41 (40.6)
Acute myeloid leukemia	1 (2.4)
Heart transplant	2 (4.9)
HIV	2 (4.9)
Hematopoietic stem cell transplant	4 (9.8)
Kidney-pancreas transplant	1 (2.4)
Kidney transplant	15 (36.6)
Liver-kidney transplant	1 (2.4)
Liver transplant	14 (13.9)
Lymphocytic lymphoma	1 (2.4)
Receiving Immunosuppressive Treatment	48 (47.5)
≥ 65 years	29 (28.7)
≥ 55 years and cardiovascular disease	5 (5.0)
≥ 55 years and hypertension	9 (8.9)

Table 2. Adverse Events

	No. (%) (N=101)
Mild to moderate	7 (6.9%)
Gastrointestinal upset	2 (28.6)
Elevated blood pressure	1 (1.4)
Chills	2 (28.6)
Headache	2 (28.6)
Severe[a]	3 (3.0)
Systolic blood pressure greater than 200 mmHg	2 (66.6)
Diarrhea and vomiting	1 (33.3)

[a] Serious adverse event defined as an event not present at baseline or was an exacerbation of a preexisting condition occurring during the observation period requiring admission to an evaluation and treatment center

Conclusion. We observed a higher frequency of hospitalization compared to 1.6% for BAM in BLAZE-1 and 3% for CAS-IMD in REGN-COV-2. This observation may reflect our higher risk population as all patients presented with at least 1 risk factor for severe disease compared to 69.6% and 65.0% in BAM and CAS-IMD clinical trials, respectively. Additionally, patients presented with longer durations of symptoms prior to infusion in our study population compared to 3 days reported in BAM and 4 days reported in CAS-IMD trials. Since the conclusion of this study, the FDA revoked the EUA for BAM administered alone based on increased observations of resistant variants to BAM monotherapy. However, our observations highlight the need for further exploration in the prevention of hospitalization in high risk populations as well as the optimal timing of monoclonal antibody therapy.

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517. Subcutaneous Sarilumab for the Treatment of Hospitalized patients with Moderate to Severe COVID19 Disease: A Pragmatic, Embedded, Multi-Center Randomized Clinical Trial

Westyn Branch-Elliman, MD, MMSc[1]; Ryan Ferguson, ScD[2]; Gheorghe Doros, PhD[3]; Patricia Woods, RN, MSN[2]; Sarah Leatherman, PhD[2]; Judith Strymish, MD[2]; Rupak Datta, MD, PhD[4]; Rekha Goswami, MD[5]; Matthew Jankowich, MD[6]; Nishant Shah, MD[6]; Thomas H. Taylor, MD[7]; Sarah T. Page, MPH[8]; Sara Schiller, MPH[2]; Colleen Shannon, MPH[2]; Cynthia Hau, MPH[2]; Maura Flynn, NP[2]; Erika Holmberg, MPH[2]; Karen Visnaw, RN[2]; Rupali Dhond, PhD[2]; Mary Brophy, MD[2]; Paul Monach, MD,PhD[9]; [1]Veterans Affairs Boston Center for Healthcare Organization and Implementation Research, Boston, MA; [2]VA Boston Healthcare System, Boston, MA; [3]Boston University School of Medicine, Boston, MA; [4]Yale School of Medicine - Yale New Haven Hospital, West Haven, CT; [5]Togus VA Medical Center, Togus, ME; [6]Providence VA Medical Center, Providence, RI; [7]White River Junction VA Medical Center, White River Junction, Vermont; [8]VA Boston, Boston, Massachusetts; [9]VA Boston Healthcare Sustem, Boston, MA

Session: P-24. COVID-19 Treatment

Background. The aim of this pragmatic, embedded adaptive trial was to measure the effectiveness of subcutaneous sarilumab in addition to an evolving standard of care for clinical management of inpatients with moderate to severe COVID-19 disease (NCT04359901). The study is also a real-world demonstration of the realization of a prospective learning healthcare system.

Methods. Two-arm, randomized, open-label controlled 5-center trial comparing standard care alone to standard care (SOC), which evolved over time, with addition of subcutaneous sarilumab (200 mg or 400 mg anti-IL6R) among hospitalized patients with moderate to severe COVID-19 not requiring mechanical ventilation. The primary outcome was 14-day incidence of intubation or death. The trial used a randomized play-the-winner design and was fully embedded within the EHR system, including the adaptive randomization process.

Results. Among 417 patients screened, 162 were eligible based on chart review, 53 consented, and 50 were evaluated for the primary endpoint of intubation or death (>30% of eligible patients enrolled) (Figure 1). After the second interim review, the unblinded Data Monitoring Committee recommended that the study be stopped due to concern for safety: a high probability that rates of intubation or death were higher with addition of sarilumab to SOC (92.6%), and a very low probability (3.4%) that sarilumab would be found to be superior.

Figure 1. Key Study Milestones, Outcomes, and Adaptations

Time	Study Milestone	Sarilumab (Events/Subjects)	Standard of Care (Events/Subjects)
		Randomization Ratio 1:1	
	Study Start Until N=30 Enrolled	5/14	1/15
		First Interim Analysis	
		Probability Sarilumab Superior = 7.9%	Probability Sarilumab Inferior = 86.8%
		Updated Randomization Ratio = 21.9% Sariumab/ 78.1% SOC	
	First Interim Analysis (Additional N=15 Enrolled)	0/5	0/9
		Second Interim Analysis	
		5/19 Total Probability Sarilumab Superior = 5.78%	1/24 Total Probability Sarilumab Inferior = 87.6%
		Updated Randomization Ratio = 19.4% Sarilumab/ 80.6% SOC	
	Follow up After Second Interim Analysis	0/0	0/6
		Third Interim Analysis	
		5/19 total/final	1/30 total/final
		Probability Sarilumab Superior = 3.36%	Probability Sarilumab Inferior = 92.6%
		Study Stopped	
	Limited to Dose Increase to 400 mg (N=41)	2/15	0/25
		Probability Sarilumab Superior = 11.2%	Probability Sarilumab Inferior = 78.6%

Conclusion. This randomized trial of patients hospitalized with COVID-19 and requiring supplemental oxygen but not mechanical ventilation found no evidence of benefit from subcutaneous sarilumab in addition to an evolving standard-of-care. The numbers of patients and events were too low to allow independent conclusions to be drawn, but this study contributes valuable information about the role of subcutaneous IL-6 inhibition in the treatment of patients hospitalized with COVID-19. The major innovation of this trial was the advancement of embedded, point-of-care clinical trials for FDA-approved drugs; this represents a realization of the learning healthcare system. Methods developed and piloted during the conduct of this trial can be used in future investigations to speed the advancement of clinical science.

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518. Model-informed Dose Selection of Dual Toll-like Receptor 7/8 Inhibitor Enpatoran (M5049) for the Treatment of COVID-19 Pneumonia

Lena Klopp-Schulze, PhD[1]; Jamie Shaw, BS[2]; Jennifer Dong, PhD[2]; Akash Khandelwal, PhD[3]; Elizabeth Adams, MD[4]; Dongzi Yu, MD[2]; Kosalaram Goteti, PhD[2]; [1]The healthcare business of Merck KGaA, Darmstadt, Germany, Darmstadt, Hessen, Germany; [2]EMD Serono, Billerica, MA, USA, Billerica,

Massachusetts; [3]The healthcare business of Merck KGaA, Darmstadt, Hessen, Germany; [4]EMD Serono, Billerica, MA, USA; Current affiliation: BioNTech SE, Germany, Billerica, Massachusetts

Session: P-24. COVID-19 Treatment

Background. Enpatoran, formerly known as M5049, is a potential first-in-class small molecule antagonist of toll-like receptors (TLR) 7 and 8, which may prevent viral-associated hyperinflammatory response and progression to 'cytokine storm' in coronavirus disease 2019 (COVID-19) patients. The objective of this study was to leverage existing population pharmacokinetic/pharmacodynamic (popPK/PD) models for enpatoran to inform dose selection for an accelerated Phase II study in COVID-19 patients with pneumonia.

Methods. The popPK/PD models were based on plasma PK and PD biomarker (ex vivo-stimulated interleukin [IL]6 and interferon α [IFNα] secretion) data from the enpatoran first-in-human Phase I study in healthy participants (Port A, et al. Lupus Sci Med 2020;7(Suppl. 1): Abstract P135). A two-compartment model describing PK used a sigmoidal E_{max} model with proportional decrease from baseline characterizing the PD response across the investigated single and multiple daily dose range of 1–200 mg (N=72). Concentrations that inhibited 50% and 90% (IC_{50}/IC_{90}) of cytokine secretion were estimated and stochastic simulations were performed to assess target coverage under different dosing regimens.

Results. Simulations suggested that, to achieve maximal inhibition of IL-6 over time, enpatoran PK concentrations would be maintained above the IC_{90} throughout the dosing interval with doses of 100 mg and 50 mg twice daily in 90% and 30% of participants, respectively. In comparison, IFNα inhibition was predicted to be lower, with IC_{90} coverage in 60% and 8% of participants with twice daily doses of 100 mg and 50 mg enpatoran, respectively.

Conclusion. Utilization of existing popPK/PD models allowed for the accelerated development of enpatoran in COVID-19 to address an unprecedented global pandemic. Rational model-informed dose selection was supported by data from a Phase I study in which there were no safety concerns.

Disclosures. **Lena Klopp-Schulze, PhD**, Merck KGaA, Darmstadt, Germany (Employee) **Jamie Shaw, BS**, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA, Darmstadt, Germany) (Employee) **Jennifer Dong, PhD**, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA, Darmstadt, Germany) (Employee) **Akash Khandelwal, PhD**, Merck KGaA, Darmstadt, Germany (Employee, Shareholder) **Elizabeth Adams, MD**, BioNTech SE, Germany (Employee)EMD Serono Research & Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA, Darmstadt, Germany)(employer at the time of study) (Employee) **Dongzi Yu, MD**, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA, Darmstadt, Germany) (Employee) **Kosalaram Goteti, PhD**, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA, Darmstadt, Germany) (Employee)**Pfizer** (Shareholder)

519. Risk Factor Analysis for Hospital Admission Following *Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)* Monoclonal Antibody Treatment

Lana Abusalem, MD[1]; Cole Wood, MD[1]; Juan Carlos Rico Crescencio, MD[1]; Ryan K. Dare, MD, MS[1]; [1]University of Arkansas for Medical Sciences, Little Rock, Arkansas

Session: P-24. COVID-19 Treatment

Background. The FDA has issued emergency use authorization (EUA) for neutralizing monoclonal antibodies (mAb) for the treatment of mild-moderate coronavirus disease 2019 (COVID-19) in patients who are at high risk of disease progression. The EUA allows for COVID-19 mAb infusion to occur up to 10 days from symptom onset and due to logistics, mAb treatment typically occurs later in this 10 day window. Efficacy of early versus late mAb treatment is unknown

Methods. In this single center, retrospective case-control study, we performed a risk factor analysis of patients with mild COVID-19 infection treated with mAb on the composite outcome of subsequent evaluation in the Emergency Department (ED) or inpatient admission December 2020 through May 2021. Multivariate analysis of variables found to be significant in univariate analysis was performed using STATA 15 statistical software

Results. Two-hundred eighty-eight patients who received mAb treatment were included in analysis. The mean age was 58.6 years and 59.7% were female, 64.9% white, and 27.1% African American. Following mAb infusion, 31 (10.8%) had disease progression resulting in an ED encounter or inpatient admission. Patients who received early (days 1-5 of symptoms) mAb infusion were less likely to have progressive disease than patients with late (days 6-12 of symptoms) infusion; (6.1% vs 13.2%; P= 0.048). Zero of 21 patients who received mAb infusion on day 1-3 of symptoms had disease progression. Patients with CHF (7.4% vs 19.4%; P=0.038), cirrhosis (9.3% vs 25.8%; p=0.012), CKD (12.5% vs 35.5%; p=0.001) and hypertension (70.8% vs 90.3%; p=0.021) were more likely to have disease progression. There were no differences in sex, race, BMI, or symptoms between groups. Multivariate analysis revealed cirrhosis (OR 3.0; 95% CI 1.1-7.9) and CKD (OR 2.6; 95% CI 1.0-6.4) increased risk of disease progression while early mAb infusion was protective (OR 0.38; 95% CI 0.14-1.0)

Conclusion. Infusion of mAb for the treatment of mild to moderate Covid-19 within 5 days of symptom onset reduces rate of disease progression compared to delayed (day 6-12 of symptoms) infusion. This finding was significant when controlling for comorbidities. Efforts should be made to infuse high risk patients with COVID-19 mAb therapy within 5 days of symptom onset

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520. Pharmacokinetic and Safety Phase 1 Study and Microneutralization Assay Results with BRII-196/BRII-198, a Novel Antibody Cocktail Active Against a Wide Range of SARS-CoV-2 Variants

David A. Margolis, MD MPH[1]; Fujie Zhang, MD[2]; Xiaohua Hao, PhD[2]; Yanyan Li, Masters[1]; Mingming Wang, PhD[1]; Chunming Li, Masters[1]; Yao Zhang, MD[1]; Ji Ma, PhD[1]; Yun Ji, PhD[1]; Qing Zhu, PhD[1]; [1]Brii Biosciences, Chapel Hill, NC; [2]Beijing Ditan Hospital, Beijing, China

Session: P-24. COVID-19 Treatment

Background. BRII-196 and BRII-198 are human monoclonal antibodies (mAb) with an extended half-life targeting distinct epitopes of the spike protein on SARS-CoV-2. Mutations in these epitope regions are continuously emerging, potentially conferring resistance to COVID-19 therapeutics in development. Individual phase I studies showed that BRII-196 or BRII-198 alone were safe and well tolerated in healthy subjects. The BRII-196 and BRII-198 cocktail is currently under evaluation in Phase 2/3 studies for the treatment of COVID-19.

Methods. Preclinical study: BRII-196 and BRII-198 were evaluated in the microneutralization assay using pseudo-viruses encoding mutations identified in the spike protein of a panel of SARS-CoV-2 variants of concerns, including strains originating in UK, SA, BR, CA, and India. The fold-change in neutralization IC_{50} titers relative to wild-type virus was calculated. Phase 1 study: healthy adults received sequential IV BRII-196 and BRII-198 (n=9) or placebo (n=3); and were followed for 180 days. Two dose levels (750mg/750mg and 1500mg/1500mg) were evaluated for safety, pharmacokinetics and immunogenicity. Interim analysis results are presented.

Results. Preclinical: BRII-196 and BRII-198 exhibited neutralizing activity against pseudo-virus variants that contained spike mutations of a panel of variants including B.1.1.7 (UK), B.1.351(SA), P.1(BR), B.1.427/429 (CA), B.1.526 (NY), and B.1.617 (IN), comparable to that against wild-type virus. Phase I study: BRII-196 plus BRII-198 was well tolerated with no dose-limiting adverse events (AEs), deaths, serious adverse events, or infusion reactions. The majority of AEs were isolated asymptomatic grade 1-2 laboratory abnormalities. (Table 1). Each mAb displayed pharmacokinetic characteristics expected of extended half-life YTE-antibodies.

Table 1 Overall Summary of Treatment-Emergent Adverse Events (Safety Population)

	750/750 mg (N=3) n (%)	1500/1500 mg (N=6) n (%)	Placebo (N=3) n (%)
All TEAEs	3 (100)	4 (66.7)	1 (33.3)
Grade 3 or above TEAEs	1 (33.3)*	0	0
SAEs	0	0	0
Treatment-related TEAEs	0	1 (16.7)	0
BRII-196 related TEAEs	0	1 (16.7)	0
BRII-198 related TEAEs	0	1 (16.7)	0
Infusion-related TEAEs	0	0	0

TEAE: treatment-emergent adverse event; SAE: serious adverse event.

*: There was one grade 3 creatine phosphokinase increased experienced by a subject receiving 750/750 mg BRII-196/BRII-198 after excessive exercise. It was isolated laboratory abnormality without concomitant symptoms which resolved within 8 days without any clinical intervention.

Conclusion. The BRII-196 and BRII-198 cocktail was well-tolerated, and maintains neutralization against currently reported circulating variants of concern. These preclinical and clinical results support further development of BRII-196 and BRII-198 as a therapeutic or prophylactic option for SARS-CoV-2.

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521. Predictors of Hospitalization Due to Coronavirus Disease 2019 (COVID-19) at a Veterans Affairs Medical Center

Macy Ho, PharmD[1]; Sarah Le, PharmD[2]; Rajkumar J. Sevak, PhD, RPh[3]; Jamie G. Chapman-Bueno, MT(ASCP)[1]; Stephen M. Berman, MD, PhD[1]; Patricia Chun, PharmD, BCPS[1]; Yong S. Moon, Pharm.D.[4]; [1]VA Long Beach Healthcare System, Manhattan Beach, CA; [2]VA Long Beach HCS, Long Beach,