Bamlanivimab+etesevimab for the treatment of COVID-19 in pediatric patients

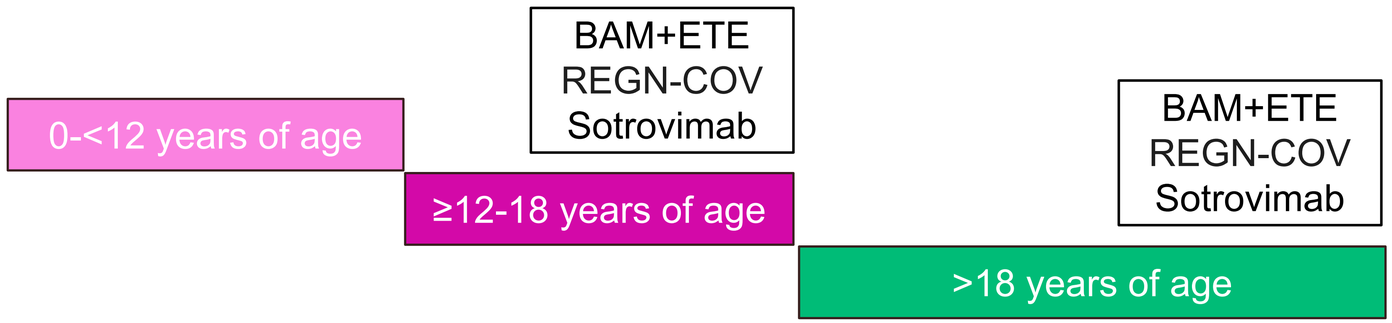
Himanshu Upadhyaya, MBBS, MS, MBA[1]; Jenny Chien, PhD[1]; Martin Bohm, DO[1]; Lisa Macpherson, PhD[1]; Dipak R. Patel, MD, PhD[1]; Matthew M. Hufford, PhD[1]; **Mark Williams, MD[1]**

[1]Eli Lilly and Company, Indianapolis, IN, USA

BACKGROUND

- Bamlanivimab and etesevimab are monoclonal antibodies derived from COVID-19 patients that bind to the receptor binding domain of the SARS-CoV-2 virus spike protein.
- Bamlanivimab and etesevimab together (BAM+ETE) reduce COVID-19 related hospitalization and all-cause mortality in patients ≥12 years of age with mild to moderate COVID-19[1].
- Pediatric (<18 years of age) COVID-19 cases are rising in the United States and constitute 17.7% of positive cases, as of December 30, 2021.
- On December 3rd 2021, BAM+ETE became the first authorized treatment in the US for mild to moderate COVID-19 in patients <12 years of age. Results supporting this authorization* will be presented.

mAb treatments in the US for mild to moderate COVID-19 prior to BAM/ETE authorization for <12 years of age



*Due to the high frequency of the Omicron variant, bamlanivimab and etesevimab are not currently authorized in any U.S. region[2].

STUDY DESIGN

Primary Objective:
Characterize the pharmacokinetics (N=88) of BAM in combination with ETE after intravenous infusion.

Bamlanivimab + etesevimab

Weight-Based Dosing (WBD) (N = 88)

Pediatric Patient's Weight	BAM+ETE Dose
≥ 40kg	700 mg + 1400 mg
> 20 kg to < 40 kg	350 mg + 700 mg
>12 kg to ≤ 20 kg	175 mg + 350 mg
≥ 1.5 kg to ≤ 12 kg	15 mg/kg + 30 mg/kg

WBD (participants <40kg) were exposure matched to authorized adult dose of 700 mg BAM + 1400 mg ETE.

Secondary Objective:
Assess the safety (N=125) and efficacy (N=124*) of BAM in combination with ETE after intravenous infusion.

Bamlanivimab + etesevimab

- 350 mg + 700 mg (N = 5)
- 700 mg + 1400 mg (N = 10)
- 2800 mg + 2800 mg (N = 4)
- Weight-Based Dosing (WBD) (N = 91)
- Placebo (N = 14)

*One participant was excluded from the efficacy analysis (N = 124) due to no post-baseline swab measurements but is included in the safety population.

Authorization approach in pediatric population
Extrapolate efficacy data of BAM+ETE from clinical studies in adults with COVID-19 to pediatric patients based on PK-exposure matching. Justification for full extrapolation was based on (1) common initial stage of COVID-19 in adults and pediatric patients; (2) similar course of SARS-CoV-2 infection in pediatric patients compared to adults; and (3) similar BAM+ETE mechanism of action, regardless of host.

Enrollment criteria for Blaze-1 (PYAB) pediatric addendum
Inclusion: are 0 (≥32 weeks gestational age AND ≥1.5kg) to 17 years of age AND satisfy at least one risk factor, have one or more COVID-19 symptoms[2], were not hospitalized for COVID-19, and had sample collection for the first positive SARS-CoV-2 viral infection determination ≤3 days prior to the start of the infusion.
Exclusion: have a diagnosis of Multisystem Inflammatory Syndrome in Children (MIS-C) or have a history of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study[3].

Study interventions, dose, and mode of administration
- WBD participants were infused with a total dose volume of 60 mL if ≥40kg, and 1.9-30 mL if <40kg, over at least 16 minutes.
- Non-WBD participants were infused with a total dose volume of 200 mL over at least 60 minutes.
- Participants assigned to PBO arm received 200 mL 0.9% Sodium Chloride Injection.

Duration of study intervention
Each participant received a single dose of study intervention. Participants were followed for 85 days post-treatment.

Statistical & PK Analysis Plan
Participant PK profiles were simulated following different WBD using the current PK model with established allometric relationships[4] for a typical monoclonal antibody to enable a Monte Carlo assessment to achieve adequate power of the trial to estimate population PK model in pediatrics across the weight range. BAM+ETE concentration data were analyzed using a population PK approach via nonlinear mixed-effects modeling with NONMEM software. Safety and efficacy data were summarized descriptively. For continuous measures, number of participants, mean, standard deviation, median, minimum, and maximum were included. For categorical measures, frequency counts and percentages were included.

Interim & final analysis:
- Safety & efficacy data cutoff September 8th, 2021 - *Analysis completed.*
- PK data cutoff September 27th, 2021 - *Analysis completed*.
- Final analysis data cutoff January 25, 2022 - *Analysis not completed*.

RESULTS

Table 1- Participant Demographics & Clinical Characteristics

Demographics & Clinical Characteristics	Pbo (N=14)	350/700 BAM+ETE* (N=6)	700/1400 BAM+ETE (N=10)	2800/2800 BAM+ETE (N=4)	WBD BAM+ETE (N=91)
Sex, n (%)					
Female	5 (35.7)	3 (50.0)	7 (70.0)	1 (25.0)	42 (46.2)
Male	9 (64.3)	3 (50.0)	3 (30.0)	3 (75.0)	49 (53.8)
Age, n (%)**					
0 to <2	0	0	0	0	5 (5.5)
2 to <6	0	0	0	0	10 (11.0)
6 to <12	0	0	0	0	36 (39.6)
12 to ≤17	14 (100.0)	6 (100.0)	10 (100.0)	4 (100.0)	40 (44.0)
Race, n (%)#					
Asian	2 (14.3)	0	1 (10.0)	0	0 (0)
Black or African American	2 (14.3)	2 (33.3)	2 (20.0)	0	64 (71.9)
White	10 (71.4)	4 (66.7)	7 (70.0)	4 (100.0)	22 (24.7)
Multiple	0	0	0	0	3 (3.4)
Ethnicity					
Hispanic or Latino	4 (28.6)	2 (33.3)	3 (30.0)	3 (75.0)	13 (14.4)
Duration of Symptoms, mean days	4	4.17	2.7	4	3.62
Baseline Viral Load, mean	5.81	6.58	7.0	3.61	6.48
Disease Severity, n (%)					
Mild	12 (85.7)	5 (83.3)	5 (50.0)	4 (100.0)	84 (92.3)
Moderate	2 (14.3)	1 (16.7)	5 (50.0)	0	7 (7.7)

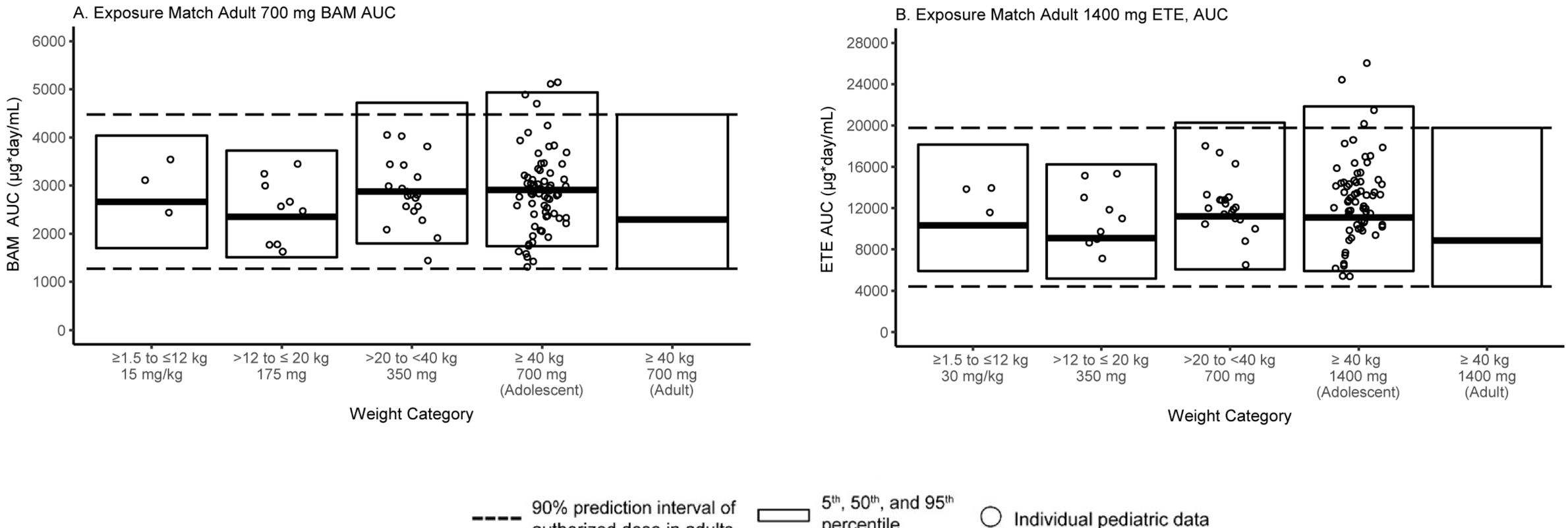
*Treatment group includes participants (N=5) that received 15-minute BAM+ETE infusions and a participant (N=1) that received a 3-minute BAM+ETE infusion. The participant that received a 3-minute infusion was included in the safety population but excluded from the efficacy population due to post-baseline swab measurement.

**Percentages may not total 100% due to rounding.

#n=2 missing from WBD BAM+ETE within Race demographics.

KEY RESULT

Figure 1- Pediatric PK is exposure-matched thus comparable to adult PK for BAM and ETE



RESULTS

Table 2- Treatment-Emergent Adverse Events (TEAEs)

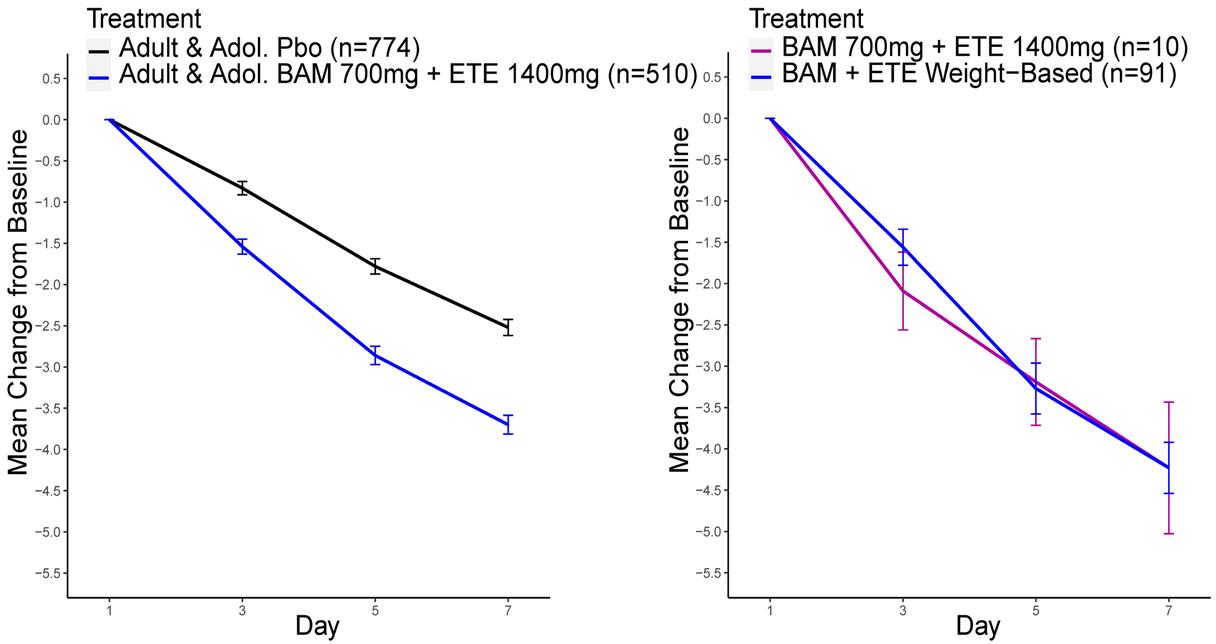
	Pbo (n=14)	350+700 BAM+ETE* (n=6)	700+1400 BAM+ETE (n=10)	2800+2800 BAM+ETE (n=4)	WBD BAM+ETE (n=91)
Overall TEAE	0	1	1	0	14
TEAE by severity					
Mild	0	0	0	0	9
Moderate	0	1	1	0	4
Severe	0	0	0	0	1
TEAE in ≥5% of participants					
Blood creatine phosphokinase increased	0	0	0	0	6
White blood cell count decrease	0	0	0	0	5
Infusion site extravasation	0	1	0	0	0
Rash	0	0	1	0	0

*N=6 consists of 5 participants that received a 15-minute BAM+ETE infusion and 1 participants that received a 3-minute BAM+ETE infusion. Participant with 3-minute infusion was included in the safety population but excluded from the efficacy analysis due to no post-baseline swab measurement.

- **No discontinuation from study due to adverse events, serious adverse events, hospitalization or deaths.**
- There was 1 moderate infusion site extravasation related to study treatment in an adolescent patient who received 350mg+700mg BAM+ETE over a 3-minute rapid IV infusion.
- There was 1 non-immediate hypersensitivity event (rash) that occurred more than 24 hours after infusion and no clinical outcome was associated with this increase.
- The severe TEAE was an increase in blood creatine phosphokinase on Day 1. The increase was reduced by 50% on Day 3 and had normalized by Day 29.

RESULTS

Figure 2- Viral load change from baseline to day 3, 5, and 7



Left Panel: Adult & Adolescent (Adol., ≥12-18 years of age) data at authorized dose of BAM+ETE

Right Panel: Pediatric (<18 years of age) data at authorized dose and WBD of BAM+ETE

Table 3- Viral load change decreased from day 3 to day 7

Treatment*	Baseline Viral Load	Change from Baseline in Normalized Viral Load, Mean		
		Day 3	Day 5	Day 7
Pbo (N=14)	5.81	-1.20	-2.15	-2.17
All BAM+ETE (N=110)	6.41	-1.54	-3.12	-4.10
350+700 (N=5)	6.58	-0.67	-2.56	-4.08
700+1400 (N=10)	7.0	-2.09	-3.19	-4.23
2800+2800 (N=4)	3.61	-1.32	-0.57	-1.35
WBD (N=91)	6.48	-1.56	-3.27	-4.23
0 to <2 years (N=5)	5.25	-0.51	-1.69	-3.0
2 to <6 years (N=10)	6.49	-1.65	-3.35	-4.07
6 to <12 years (N=36)	6.61	-1.57	-3.74	-4.19
12 to ≤17 years (N=40)	6.52	-1.65	-2.97	-4.38

*Excluding WBD, treatment group ages were 12 to ≤17 years of age.

CONCLUSIONS

- The PK analysis confirms that the weight-based doses selected for pediatric patients (0 to <12 years) provide comparable exposures to those observed in adults (≥18 years) and pediatric patients ages 12 to <18 years, weighing at least 40 kg. Thereby, the PK analysis results supported extrapolation of efficacy from adults based on exposure-matching for authorization.

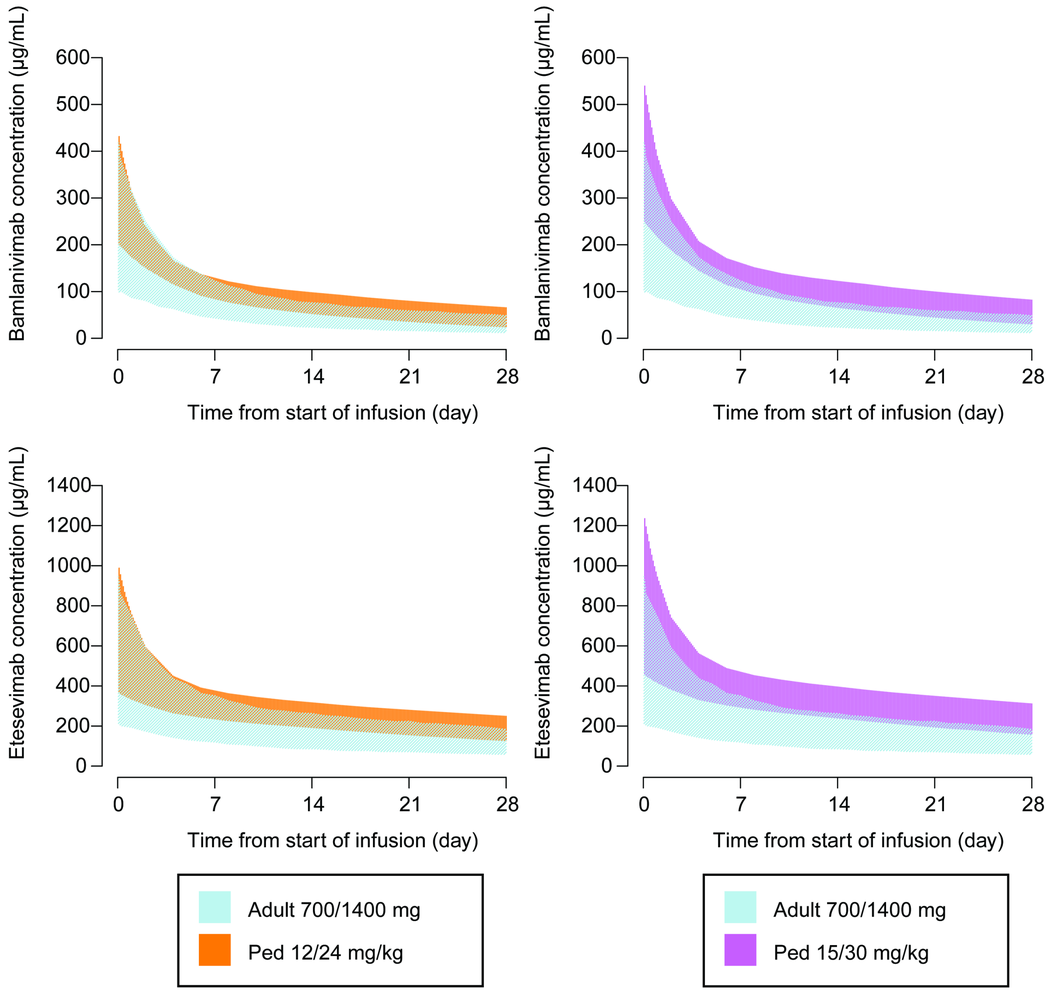
- Pre-specified parameters support efficacy extrapolation from adults to pediatric patients.

- The safety profile of BAM + ETE in pediatric patients ages 0 to <12 years old identified no new safety risks compared to the established safety profile.

- In contrast to adults, no COVID-19 hospitalizations or deaths were reported in pediatric populations.

Additional Key Information

Figure 3- Dosing adjusted in BAM+ETE fact sheet in pediatric patients weighing ≤12 kg



*Dosing adjusted to account for maturation function[5]

Additional Key Information

Disclosures

HU, JC, MB, LM, DP, MH, and MW are employees of Eli Lilly and Company. HU, JC, DP, MH, and MW are stock/shareholders of Eli Lilly and Company. This study was sponsored by Eli Lilly and Company. Medical writing services were provided by Carmen Deveau and Eli Lilly and Company, and was funded by Eli Lilly and Company.

Author Correspondence:

Mark Williams, MD
drmark@lilly.com

Acknowledgements:

Supported by Eli Lilly and Company
AbCellera Biologics
National Institute of Allergy and Infectious Diseases Vaccine Research Center
Junshi Biosciences
Institute of Microbiology of the Chinese Academy of Sciences
Clinical Trial Sites (BLAZE-1, NCT04427501)

Michael Dougan - Massachusetts General Hospital, Boston, MA; Jason Morris - Care Access, Lake Charles, LA; Robert Finberg - University of Massachusetts Memorial Medical Center, Worcester, MA; Masoud Azizad - Valley Clinical Trials Northridge, Northridge, CA; Carl Dukes - Sun Research Institute, San Antonio, TX; Awawu Igbinadolor - Monroe Biomedical Research, Monroe, NC; Timothy Quinn - Sky Clinical Research Network Group, Ridgeland, MS; Michelle Evans - Paramount Research Solutions, College Park, GA; Jeffrey A. Potts - Great Lakes Research Group, Bay City, MI; James B. Hall - Sky Clinical Prime and Health Wellness Clinic, Fayette, MS; Dwight Blake - Rophe Adult and Pediatric Medicine, Union City, GA; Bhaktasharan Patel - Future Innovative Treatments, Colorado Springs, CO; Luis Abrishamian - South Bay Clinical Research Institute, Torrance, CA; Jocelyn Ang - Children's Hospital of Michigan, Detroit, MI.

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