Pharmacokinetics, Efficacy, and Safety of a SARS-CoV-2 Antibody Treatment in Pediatric Participants: an open-label addendum of a placebo-controlled, randomized phase 2/3 trial

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Supplementary Material

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BLAZE-1 Protocol Criteria for Arms 7-14, 20-21

Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Are ≥12 years of age at the time of screening.
2. Are currently not hospitalized.
3. Have one or more mild or moderate COVID-19 symptoms: (FDA May 2020, Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/covid-19-developing-drugs-and-biological-products-treatment-or-prevention)
   i. Fever
   ii. Cough
   iii. Sore throat
   iv. Malaise
   v. Headache
   vi. Muscle pain
   vii. Gastrointestinal symptoms, or viii. Shortness of breath with exertion
4. Must have sample collection for first positive SARS-CoV-2 viral infection determination ≤3 days prior to start of the infusion.
5. Are males or females, including pregnant females (pregnancy was not allowed in arms 7-9)
6. Understand and agree to comply with planned study procedures.
7. Agree to the collection of nasopharyngeal swabs and venous blood.
8. The participant or legally authorized representative give signed informed consent and/or assent.
9. Are ≥18 years of age and satisfy at least one of the following at the time of screening:
   - Are pregnant.
   - Are ≥ 65 years of age.
   - Have a BMI ≥ 35.
   - Have chronic kidney disease.
   - Have type 1 or type 2 diabetes.
   - Have immunosuppressive disease.
   - Are currently receiving immunosuppressive treatment, or
   - Are ≥ 55 years of age AND have
     - cardiovascular disease, OR
     - hypertension, OR
     - chronic obstructive pulmonary disease or other chronic respiratory disease
10. Are 12-17 years of age (inclusive) AND satisfy at least one of the following at the time of screening:
    - Are pregnant (except for arms 7-9).
    - Have a BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm
    - Have sickle cell disease.
    - Have congenital or acquired heart disease.
    - Have neurodevelopmental disorders, for example, cerebral palsy.
    - Have a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19).

- Have asthma or reactive airway or other chronic respiratory disease that requires daily medication for control.
- Have type 1 or type 2 diabetes.
- Have chronic kidney disease.
- Have immunosuppressive disease, or
- Are currently receiving immunosuppressive treatment.

Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Have SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300, respiratory rate ≥30 per minute, heart rate ≥125 per minute (FDA May 2020) CONFIDENTIAL Protocol number J2W-MC-PYAB(m) 55.
2. Require mechanical ventilation or anticipated impending need for mechanical ventilation.
3. Have known allergies to any of the components used in the formulation of the interventions.
4. Have hemodynamic instability requiring use of pressors within 24 hours of randomization.
5. Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention.
6. Have any co-morbidity requiring surgery within <7 days, or that is considered life threatening within 29 days.
7. Have any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study.
8. Have a history of a positive SARS-CoV-2 serology test.
9. Have a history of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study.
10. Have received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing.
11. Have received treatment with a SARS-CoV-2 specific monoclonal antibody.
12. Have received convalescent COVID-19 plasma treatment.
13. Have participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.
14. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
15. Are breast feeding.
16. Are investigator site personnel directly affiliated with this study, and
17. Have body weight <40 kg.
18. Have participated in a previous SARS-CoV-2 vaccine study (only for arms 7-9).

BLAZE-1 Pediatric Addendum Protocol Criteria for Arm 22

Inclusion Criteria

Participants are eligible to be included in this addendum only if all of the following criteria apply:

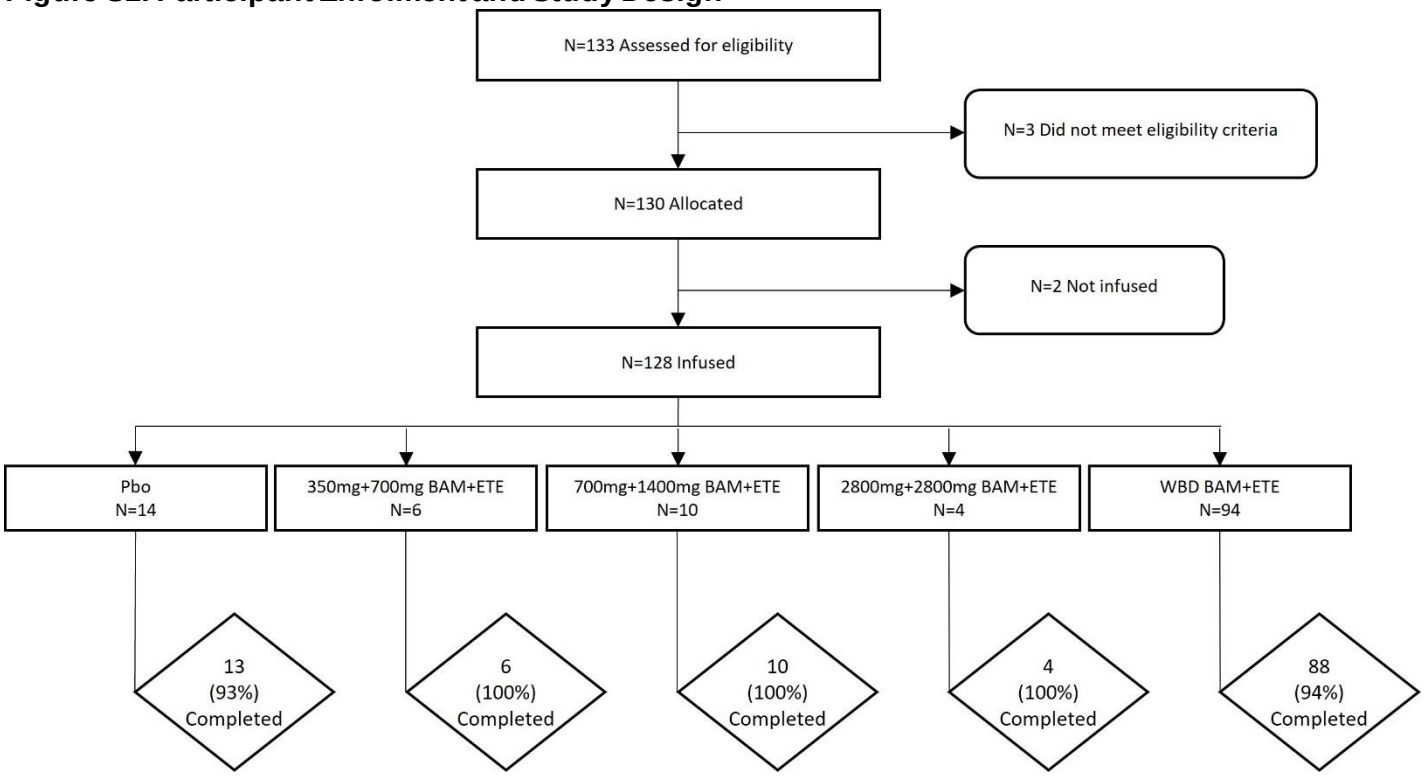
1. Must have sample collection for first positive SARS-CoV-2 viral infection determination ≤3 days prior to start of the infusion.
2. Are males or females, including pregnant females.
3. Understand and agree to comply with planned study procedures.
4. Agree to the collection of nasopharyngeal swabs and venous blood.
5. The participant or legally authorized representative give signed informed consent and/or assent.
6. Are 0 (≥ 32 weeks gestational age AND ≥ 1.5 kg) to 17 years of age (inclusive) AND satisfy at least one of the following risk factors at the time of screening:
   - Are pregnant.
   - Have a BMI ≥85th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm
   - Have sickle cell disease.
   - Have congenital or acquired heart disease.
   - Have neurodevelopmental disorders, for example, cerebral palsy, autism, or Down syndrome (FAIR Health 2020; Spreat et al. 2020).
   - Have a medical-related technological dependence, for example, tracheostomy, gastrostomy, or positive pressure ventilation (not related to COVID-19).
   - Have asthma, cystic fibrosis, reactive airways disease or other chronic respiratory disease that requires daily medication for control.
   - Have type 1 or type 2 diabetes.
   - Have chronic kidney disease.
   - Have immunosuppressive disease, or
   - Are currently receiving immunosuppressive treatment, or
   - Are <1 year of age.
7. Have one or more COVID-19 symptoms (CDC December 2020, FDA February 2021)
   - shortness of breath or difficulty breathing
   - nasal congestion or runny nose
   - fever
   - chills
   - sore throat
   - stomachache
   - nausea
   - vomiting
   - diarrhea
   - cough
   - tiredness
   - muscle or body aches and pain
   - headache
   - new loss of smell, or new loss of taste
   - poor appetite or poor feeding (in babies).

Exclusion Criteria

Participants are excluded from this addendum if any of the following criteria apply:

1. Have SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300, respiratory rate ≥30 per minute, heart rate ≥125 per minute due to COVID-19 (FDA February 2021).
2. Require mechanical ventilation or anticipated impending need for mechanical ventilation due to COVID-19.
3. Have known allergies to any of the components used in the formulation of the interventions.
4. Have hemodynamic instability requiring use of pressors within 24 hours of randomization.
5. Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention.
6. Have any co-morbidity requiring surgery within <7 days, or that is considered life threatening within 29 days.
7. Have any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study.
8. Have a history of a positive SARS-CoV-2 serology test.
9. Have a history of a positive SARS-CoV-2 test prior to the one serving as eligibility for this study.
10. Have received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing.
11. Have received treatment with a SARS-CoV-2 specific monoclonal antibody.
12. Have received convalescent COVID-19 plasma treatment.
13. Have participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.
14. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
15. Mothers who are breast feeding.
16. Are investigator site personnel directly affiliated with this study.
17. Have a diagnosis of MIS-C in the opinion of the investigator.
18. Are currently hospitalized for treatment of COVID-19. Other reasons for hospitalization are acceptable.

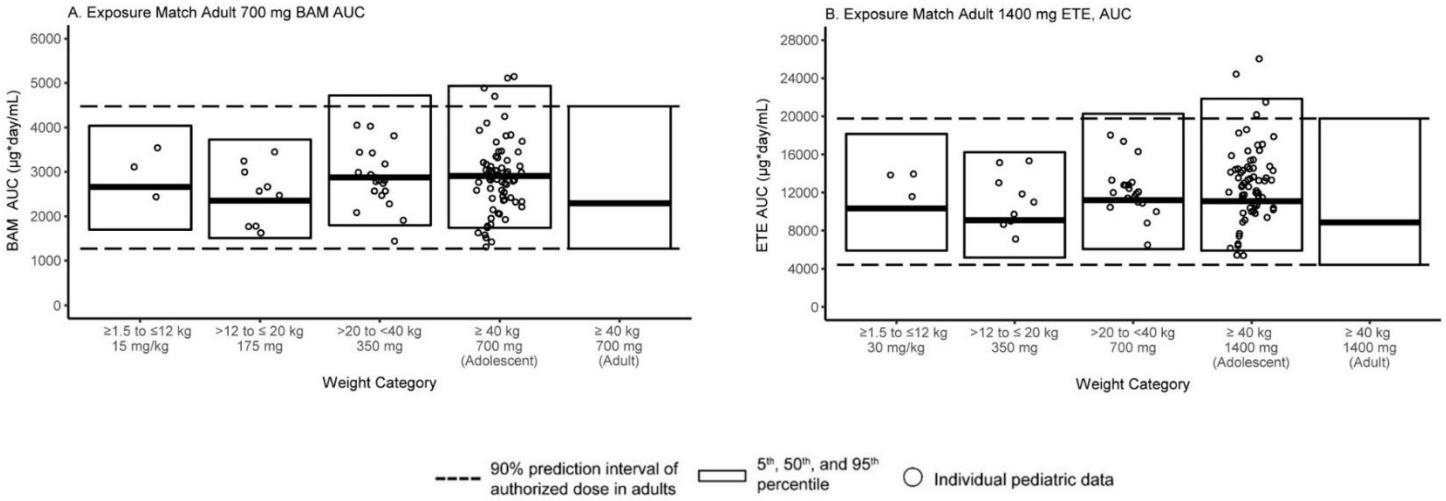
Figure S1. Participant Enrolment and Study Design



BLAZE-1 study design with pediatric participant eligibility, treatment allocation, infusion, and completion for open label, WBD arms (n=94), and fixed dosing arms (n=34).

BAM+ETE=Bamlanivimab and etesevimab; Pbo=Placebo; WBD=Weight-Based Dosing

Figure S2: Pediatric AUC for BAM and ETE and exposure-matched adults.



Area under the concentration versus time curve from zero to infinity (AUC) for each WBD category in the BLAZE-1 pediatric PK population are overlaid with 90% prediction intervals for adults receiving the authorized dose of 700/1400 mg BAM+ETE. Pediatric serum AUC by weight category for BAM- (left) and ETE- (right) matched adults AUC (5th and 95th percentile) administered BAM 700 mg + ETE 1400 mg dose.

AUC=Area Under the Curve; BAM=Bamlanivimab; ETE=Etesevimab; WBD=Weight-Based Dosing

Table S1: Viral Load Change from Baseline to Day 3, 5, and 7

Treatment	Baseline viral load, mean (SD)	Change from baseline in normalized viral load, mean (SD)			Persistent high viral load at Day 7, n (%)
		Day 3	Day 5	Day 7	
Total (N=127)	6.3 (2.5)	-1.5 (1.8)	-2.0 (2.5)	-4.0 (2.8)	13 (10.2)
All BAM+ETE (n=113)	6.4 (2.5)	-1.5 (1.9)	-3.1 (2.6)	-4.2 (2.7)	10 (8.8)
Pbo (n=14)	5.8 (2.6)	-1.1 (2.1)	-2.2 (1.3)	-2.2 (2.9)	3 (21.4)
350/700 (n=5)	6.6 (1.7)	-0.7 (1.0)	-2.6 (1.3)	-4.1 (2.3)	0
700/1400 (n=10)	6.7 (1.8)	-2.4 (1.4)	-2.8 (1.7)	-4.2 (2.3)	0
2800/2800 (n=4)	3.6 (4.2)	-1.3 (2.0)	-0.6 (2.1)	-1.4 (1.6)	0
WBD (n=94)	6.5 (2.4)	-1.5 (1.9)	-3.3 (2.7)	-4.4 (2.7)	10 (10.6)
0 to <2 years (n=8)	5.9 (3.3)	-0.5 (1.1)	-3.1 (2.4)	-3.9 (2.8)	1 (12.5)
2 to <6 years (n=10)	6.5 (2.0)	-1.7 (1.6)	-3.4 (2.0)	-4.1 (1.9)	0
6 to <12 years (n=36)	6.6 (2.2)	-1.4 (2.0)	-3.7 (3.1)	-4.3 (2.7)	5 (13.9)
12 to ≤17 years (n=40)	6.5 (2.6)	-1.7 (1.9)	-2.9 (2.7)	-4.6 (3.0)	4 (10.0)

BAM+ETE=Bamlanivimab and etesevimab; SD=Standard Deviation; WBD=Weight-Based Dosing.

Table S2: Symptom Resolution in Pediatric Population

Symptom Outcome	WBD	Fixed Dosing				All	
	BAM+ETE (n=94)	Pbo (n=14)	350/700 BAM+ETE (n=5)	700/1400 BAM+ETE (n=10)	2800/2800 BAM+ETE (n=4)	Pooled BAM+ETE (n=113)	Total (N=127)
Baseline Symptoms*							
Body aches and pains, n (%)	32 (34.0)	7 (50.0)	2 (40.0)	4 (40.0)	1 (25.0)	39 (34.5)	46 (36.2)
Chills, n (%)	24 (25.5)	3 (21.4)	0	3 (30.0)	1 (25.0)	28 (24.8)	31 (24.4)
Cough, n (%)	77 (81.9)	8 (57.1)	3 (60.0)	10 (100.0)	2 (50.0)	92 (81.4)	100 (78.7)
Diarrhea, (n (%)	14 (14.9)	0	0	0	0	14 (12.4)	14 (15.9)
Fatigue, n (%)	52 (55.3)	8 (57.1)	3 (60.0)	7 (70.0)	2 (50.0)	64 (56.6)	72 (56.7)
Fever, n (%)	42 (44.7)	8 (57.1)	1 (20.0)	1 (10.0)	0	44 (38.9)	52 (40.9)
Headache, n (%)	52 (55.3)	8 (57.1)	2 (40.0)	4 (40.0)	3 (75.0)	61 (54.0)	69 (54.3)
Nasal congestion, n (%)	69 (73.4)	0	0	0	0	69 (61.1)	69 (73.4)
Nausea, n (%)	15 (16.0)	0	0	0	0	15 (13.3)	15 (16.0)
Shortness of breath, n (%)	15 (16.0)	3 (21.4)	3 (60.0)	4 (40.0)	1 (25.0)	23 (20.4)	26 (20.5)
Stomachache, n (%)	26 (27.7)	0	0	0	0	26 (23.0)	26 (27.7)
Sore throat, n (%)	30 (31.9)	6 (42.9)	2 (40.0)	6 (60.0)	2 (50.0)	40 (35.4)	46 (36.2)
Vomiting, n (%)	6 (6.4)	0	0	0	0	6 (5.3)	6 (4.7)
Proportion of participants with complete symptom resolution†, n (%)							
Day 3	17 (18.1)	1 (7.1)	1 (20.0)	1 (10.0)	0	19 (16.8)	20 (15.7)
Day 5	39 (41.5)	2 (14.3)	2 (40.0)	2 (20.0)	1 (25.0)	44 (38.9)	46 (36.2)
Day 7	53 (55.3)	4 (28.6)	2 (40.0)	3 (30.0)	3 (75.0)	60 (53.1)	64 (50.4)

Day 11	72 (76.6)	11 (78.6)	2 (40.0)	7 (70.0)	4 (100.0)	85 (75.2)	96 (75.6)
Proportion of participants with sustained complete symptom resolution‡, n (%)	81 (86.2)	13 (92.9)	5 (100.0)	8 (80.0)	4 (100.0)	98 (86.7)	111 (87.4)

*Percentage of response is calculated by n/(number of participants with non-missing values)*100.
†Complete symptom resolution defined as all symptoms on the symptom questionnaire scored as 0.
‡Sustained complete symptom resolution defined as 2 consecutive assessments with all symptoms on the symptom questionnaire scored as 0.
BAM+ETE=Bamlanivimab and etesevimab; Pbo=Placebo; WBD=Weight-Based Dosing.