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Clesrovimab (MK-1654): Pediatric Clinical Program

Presentation to the Advisory Committee on Immunization Practices

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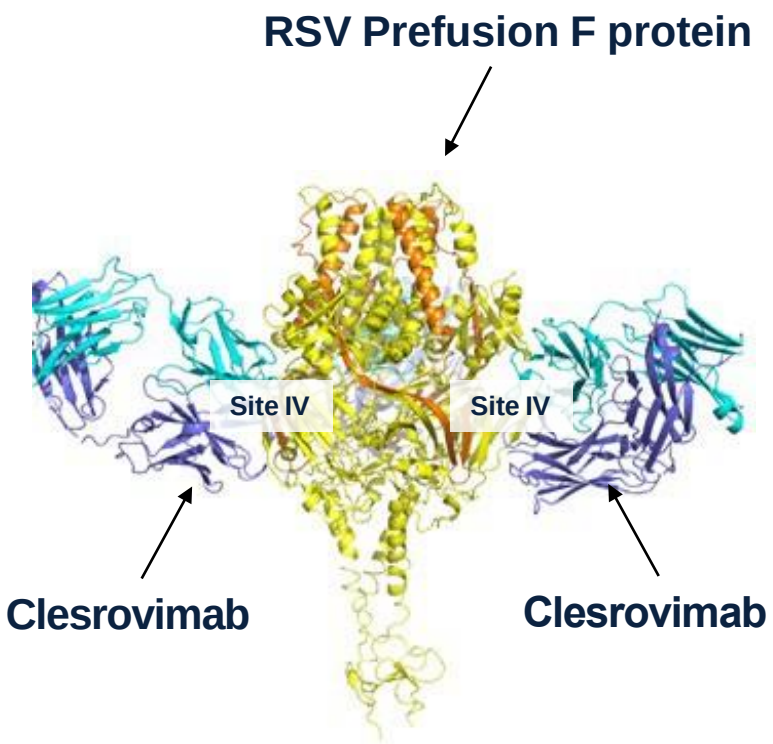
Clesrovimab is a human monoclonal antibody with four unique molecular characteristics that enable robust and durable protection from RSV



1. Binds with **high affinity** to **site IV** of RSV F protein, prevents fusion of virus to host cells and blocks entry to provide **direct protection**[1]
   - Binding epitope on site IV is **highly conserved**, with 99.8% identity among >15,000 reported RSV-A and RSV-B sequences[2]
2. **High potency** *in vitro* and **equipotent against RSV-A and RSV-B**[a]
3. YTE substitutions enable **extended half-life (~44 days)**
4. Achieves **high nasal tissue distribution** and concentrations at sites of RSV infection[3]

Notes: a. Clesrovimab is ~50-fold more potent in vitro than palivizumab; **Abbreviations**: F=Fusion; RSV=Respiratory Syncytial Virus; **Sources**: 1. Tang A et al. *Nat Commun*. 2019; 2. RSV GeneBank sequences as of April 1, 2024; 3. Phuah JY et al. *Biomed Pharmacother.* 2023.

Proposed Indication and Dosing

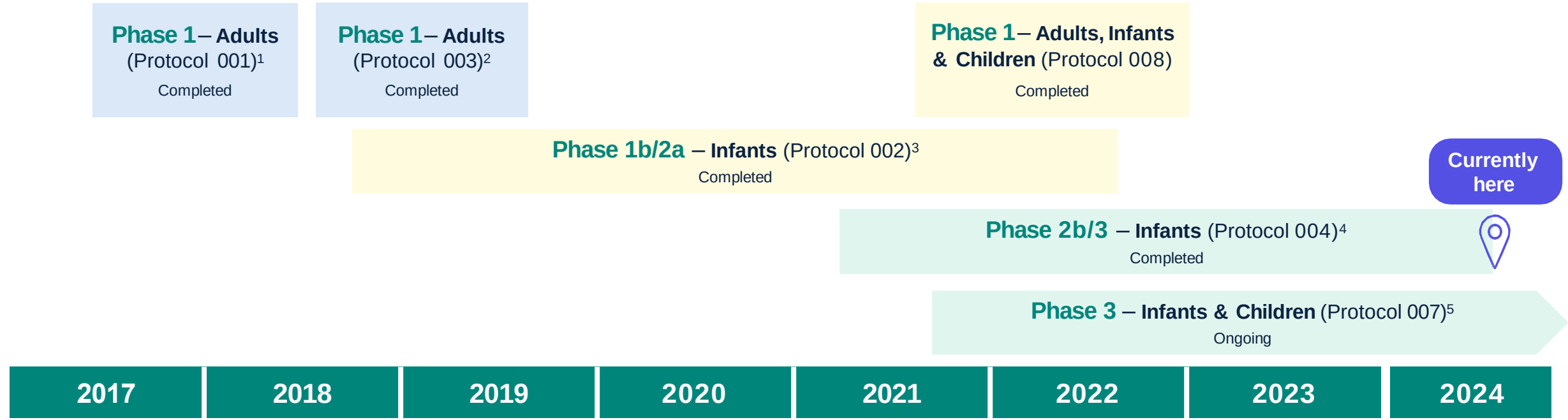
Proposed Indication

- Prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season

Proposed Dosing and Administration

- 105 mg/0.7 mL administered as a single intramuscular (IM) injection
- Clesrovimab **dosing is the same for all infants regardless of weight**

Clesrovimab Clinical Development Program



Phase 1:
Safety and PK – adults

Phase 1b/2a:
Safety and PK – infants

Phase 2b/3:
Efficacy, safety and PK – infants & children

Abbreviations: PK=Pharmacokinetics; RSV=Respiratory Syncytial Virus; **Sources:** 1. Aliprantis AO et al. Clin Pharmacol Drug Dev. 2021;10(5):556-566; 2. Orito Y et al. Clin Transl Sci. 2022;15(7):1753-1763; 3. Madhi SA, Simoes EAF, Acevedo A, et al. A phase 1b/2a single-ascending-dose study to evaluate the safety, tolerability, and pharmacokinetics of an RSV-neutralizing antibody, clesrovimab, in preterm and full-term infants. Oral and Poster presentation. 8th ReSViNET Conference February 13-16, 2024 Mumbai, India; 4. clinicaltrials.gov (NCT04767373); 5. clinicaltrials.gov (NCT04938830).

Protocol 004:

A Phase 2b/3 Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Clesrovimab in Healthy Preterm and Full-Term Infants

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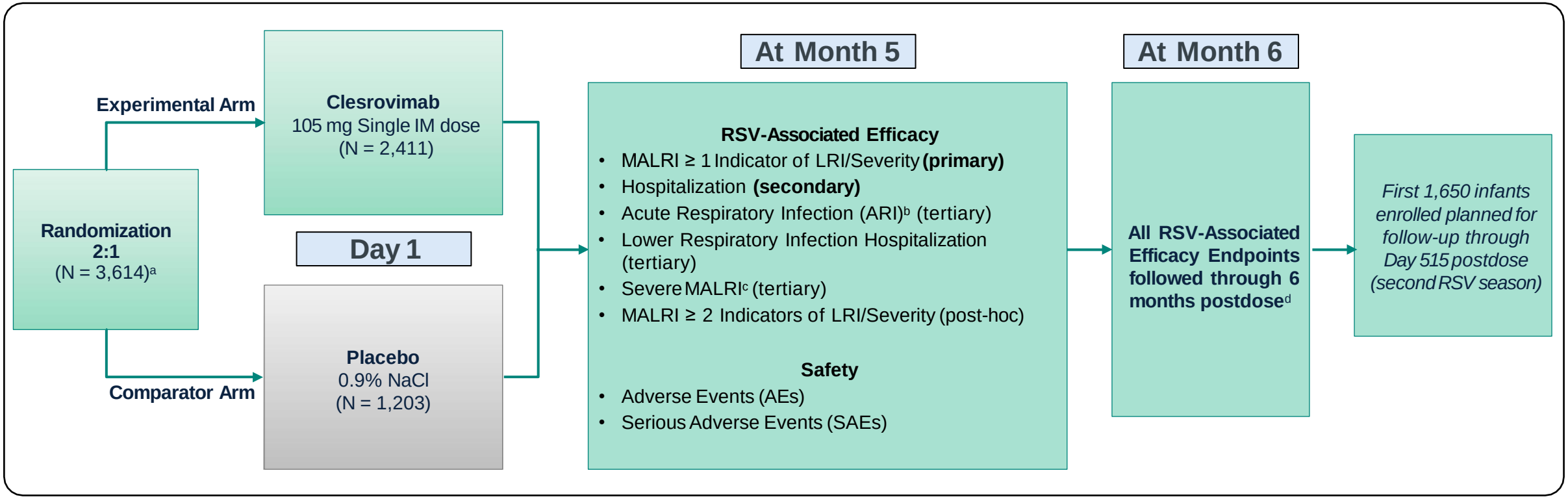
Protocol 004: Study Design

Phase 2b/3 randomized, double-blinded, placebo-controlled with active RSV surveillance through 6 months

Objective: Efficacy and safety of clesrovimab in healthy preterm and full-term infants entering their first RSV season

- **Phase 2b cohort**: First 300 infants enrolled
- **Phase 3 cohort**: Seamless enrollment following Phase 2b cohort



Notes: a. N=Number of randomized participants, dosed with clesrovimab or placebo; b. ARI: Includes both upper and lower respiratory tract infection; c. Severe MALRI: Severe hypoxemia (SpO2 <90% on room air at sea level; <87% on room air at altitude ≥1800 m) or the need for high flow nasal cannula, oxygen mask, or mechanical ventilatory support; d. 6 month endpoints have the same designation as 5 month endpoints aside from Hospitalization through 6 months, which is a tertiary endpoint, and MALRI ≥ 1indicator of LRI/Severity, which is a secondary endpoint; **Abbreviations**: ARI=Acute Respiratory Infection; IM=Intramuscular; LRI=Lower Respiratory Tract Infection; MALRI=Medically-Attended Lower Respiratory Tract Infection; NaCl=Sodium Chloride; RSV=Respiratory Syncytial Virus.

Protocol 004: Baseline Characteristics

	Clesrovimab N = 2,411		Placebo N = 1,203	
Participants	**n**	**(%)**	**n**	**(%)**
Age at Randomization (Months)				
<6	1,923	(79.8)	964	(80.1)
≥6 to <9	383	(15.9)	192	(16.0)
≥9	105	(4.4)	47	(3.9)
Mean (SD)	3.7 (2.6)		3.7 (2.6)	
Median (Range)	3.0 (0 to 12)		3.1 (0 to 12)	
Body Weight at Randomization (kg)				
Mean (SD)	5.8 (2.0)		5.9 (2.0)	
Median (Range)	5.8 (1.6 to 11.9)		5.8 (1.6 to 11.6)	
Gestational Age				
Early and Moderate Preterm Infant (≥29 to <35 weeks)	422	(17.5)	209	(17.4)
Late Preterm and Full-term Infant (≥35 weeks)	1,989	(82.5)	994	(82.6)
Race				
American Indian Or Alaska Native	50	(2.1)	18	(1.5)
Asian	641	(26.6)	320	(26.6)
Black Or African American	326	(13.5)	171	(14.2)
Multiple	302	(12.5)	138	(11.5)
Native Hawaiian Or Other Pacific Islander	1	(0.0)	1	(0.1)
White	1,082	(44.9)	550	(45.7)
Missing[a]	9	(0.4)	5	(0.4)
Ethnicity				
Hispanic Or Latino	682	(28.3)	335	(27.8)
Not Hispanic Or Latino	1,660	(68.9)	834	(69.3)
Not Reported, Unknown, or Missing	69	(2.9)	34	(2.8)
Sex				
Male	1,228	(50.9)	617	(51.3)
Female	1,183	(49.1)	586	(48.7)

- Baseline characteristics of infants were similar in both clesrovimab and placebo arms
- A total of 3,614 healthy infants were dosed
- 2,411 infants received clesrovimab and 1,203 infants received placebo
- Enrolled a diverse population across race and ethnicity from 22 countries, across 5 continents
- 631 participants were preterm infants (≥29 to <35 weeks)
- 2,983 were full-term infants (≥35 weeks)

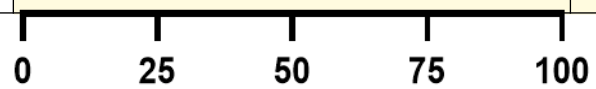
Note: a. Includes 8 participants from South Africa who have race reported as "Colored" which is not a standard category on the form; **Abbreviation:** SD=Standard Deviation.

Protocol 004: Efficacy

Single dose of clesrovimab protects healthy preterm and full-term infants against mild, moderate, and severe RSV disease through 5 months

Increasing Disease Severity

RSV-Associated Endpoint[a] *(Through 5 months)*	Endpoint Designation	Efficacy through 5 months		
		Clesrovimab (n = 2,398)	Placebo (n = 1,201)	Observed Efficacy %, (95% CI)
		# of Cases	# of Cases	
Severe MALRI	Tertiary	**2**	**12**	**91.7 (62.9, 98.1)**
LRI Hospitalization	Tertiary	**5**	**27**	**90.9 (76.2, 96.5)**
Hospitalization	Secondary	**9**	**28**	**84.2[d] (66.6, 92.6)**
MALRI requiring ≥ 2 Indicators of LRI/Severity[b]	Post-Hoc	**10**	**41**	**88.0 (76.1, 94.0)**
MALRI requiring ≥ 1 Indicator of LRI/Severity	Primary	**60**	**74**	**60.4[c] (44.1, 71.9)**
Acute Respiratory Infection (ARI)	Tertiary	**148**	**148**	**52.0 (39.5, 61.9)**



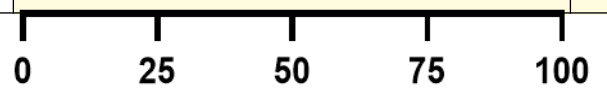
Notes: a. ARI and MALRI include both inpatient and outpatient cases; b. MALRI requiring ≥ 2 indicators of LRI/severity endpoint is most comparable to nirsevimab's primary endpoint in the MELODY trial; c. Primary endpoint, p<0.001 (criterion=lower bound of the 95% CI >25%); d. Secondary endpoint, p<0.001 (criterion=lower bound of the 95% CI >0%); **Abbreviations:** ARI=Acute Respiratory Infection; LRI=Lower Respiratory Tract Infection; MALRI=Medically-Attended Lower Respiratory Tract Infection.

Protocol 004: Efficacy

Durable across all endpoints through 6 months

Increasing Disease Severity

RSV-Associated Endpoint[a] (Through 6 months)	Endpoint Designation	Efficacy through 6 months		
		Clesrovimab (n = 2,398)	Placebo (n = 1,201)	Observed Efficacy %, (95% CI)
		# of Cases	# of Cases	
Severe MALRI	Tertiary	2	12	91.7 (62.9, 98.1)
LRI Hospitalization	Tertiary	5	28	91.2 (77.2, 96.6)
Hospitalization	Tertiary	11	29	81.3 (62.5, 90.7)
MALRI requiring ≥ 2 Indicators of LRI/Severity[b]	Post-Hoc	11	42	87.2 (75.1, 93.4)
MALRI requiring ≥ 1 Indicator of LRI/Severity	Secondary	64	77	59.5 (43.3, 71.1)
Acute Respiratory Infection (ARI)	Tertiary	161	154	50.0 (37.4, 60.1)



Notes: a. ARI and MALRI include both inpatient and outpatient cases; b. MALRI requiring ≥ 2 indicators of LRI/severity endpoint is most comparable to nirsevimab's primary endpoint in the MELODY trial;
Abbreviations: ARI=Acute Respiratory Infection; LRI=Lower Respiratory Tract Infection; MALRI=Medically-Attended Lower Respiratory Tract Infection.

Protocol 004: All-Cause Endpoints

All-cause Endpoint *(Through 5 months Postdose)*	Clesrovimab (N = 2,411)				Placebo (N = 1,203)				Observed Efficacy (%) Estimate (95% CI)[c]
	n	Number of Events	Total Follow-Up Time (months)[a]	Incidence Rate Over 5 months[b], %	n	Number of Events	Total Follow-Up Time (months)[a]	Incidence Rate over 5 months[b], %	
Outpatient and Inpatient MALRI due to any cause	2,398	526	10,349.2	25.4	1,201	296	5,063.8	29.2	13.1 (-0.6; 24.8)
LRI Hospitalization due to any cause	2,398	60	11,711.8	2.6	1,201	58	5,774.0	5.0	49.0 (26.7, 64.5)

Notes: a. One month is defined as 30 days for the total follow-up time calculation; b. Five months is defined as 150 days; c. Estimate and 95% CI of efficacy were estimated from the modified Poisson regression with robust variance method; Every participant is counted a single time for each applicable endpoint category; A participant may appear in more than one endpoint category; For each participant, only the first occurrence of the case for each endpoint category is counted for the analysis; N=Number of participants randomized and dosed with clesrovimab or placebo; n=Number of participants eligible for inclusion in the full analysis set population; **Abbreviations:** CI=Confidence Interval; LRI=Lower Respiratory Tract Infection; MALRI=Medically-Attended Lower Respiratory Tract Infection.

Protocol 004: Safety

Well-tolerated in healthy preterm and full-term infants with a safety profile that is generally comparable to placebo

Participants with AEs	Clesrovimab Na = 2,409	Placebo Na = 1,202
	n (%)	n (%)
Overall Solicited and Unsolicited AEs *(Days 1-365 postdose)*		
≥ 1 AE	1,816 (75.4)	918 (76.4)
Drug-related AE	587 (24.4)	296 (24.6)
Any SAE	278 (11.5)	149 (12.4)
Drug-related SAE[b]	1 (0.0)	1 (0.1)
Death[c]	7 (0.3)	3 (0.2)
Solicited AEs *(Days 1-5 postdose)*		
Injection site pain	122 (5.1)	77 (6.4)
Injection site erythema	90 (3.7)	40 (3.3)
Injection site swelling	65 (2.7)	31 (2.6)
Irritability	450 (18.7)	237 (19.7)
Somnolence	303 (12.6)	171 (14.2)
Decreased appetite	106 (4.4)	61 (5.1)
Solicited Temperature *(Days 1-5 postdose)*		
Temp < 100.4 °F	2,319 (96.3)	1,154 (96.0)
Temp ≥ 100.4 °F	89 (3.7)	48 (4.0)
AESI *(Days 1-42 postdose)*		
Rash[d]	11 (0.5)	4 (0.3)
Anaphylaxis/hypersensitivity	1 (0.0)[e]	0 (0.0)

- Proportion of participants with AEs, including solicited AEs, drug-related AEs, and SAEs, were generally comparable between intervention groups; majority of AEs were Grade 1 or 2 toxicity
- Most (≥ 96%) participants in either intervention group had a maximum temperature <100.4 °F
- There were no serious AESI of rash, anaphylaxis or hypersensitivity observed in either intervention group
  - Proportion of participants with AESI in the category of rash (all non-serious) was low in either intervention group
  - One participant[e] experienced a non-serious AESI in the category of anaphylaxis/hypersensitivity, which was a Grade 2 event of bronchospasm on Day 3 postdose in clesrovimab group, not considered related to study intervention by investigator
- No deaths were considered related to study intervention by investigator; no pattern identified with respect to cause of death or timing; largely attributable to underlying co-morbidities

Notes: a. N = number of participants randomized and dosed and included in the safety population; b. One infant had an SAE of body temperature increased in the clesrovimab group (with rectal temperature 38°C on Day 4 and with adenovirus detected in stool on Day 8) and one infant had an SAE of B-cell lymphoma in the placebo group; c. One death occurred in the clesrovimab group on Day 487 after study discontinuation (discontinued study based on physician's recommendation); d. All AESI of rash were non-serious; All events were Grade 1 or 2 toxicity except for one Grade 3 event of urticaria on Day 9 postdose in clesrovimab group, not considered related to study intervention by investigator. **Abbreviations**: AE=Adverse Event; AESI=Adverse Events of Special Interest; SAE=Serious Adverse Event.

Protocol 004: Conclusions

Efficacy

- Clesrovimab, administered as a single dose for infants of all weights, provides robust **protection against mild, moderate, and severe RSV disease** for all healthy infants, including term and preterm
- Clinical data demonstrate **over 90% efficacy in preventing RSV LRI hospitalizations** through 6 months
- Clesrovimab efficacy is durable across all efficacy endpoints **through 6 months**
- There was **no shifting** of RSV disease burden seen in the second RSV season

Safety

- **Clesrovimab is well tolerated in healthy preterm and full-term infants** born during or entering their first RSV season, with a safety profile that is generally comparable to placebo

Abbreviations: LRI=Lower Respiratory Tract Infection; MALRI=Medically-Attended Lower Respiratory Tract Infection; RSV=Respiratory Syncytial Virus.

Protocol 007:

A Phase 3, Multicenter, Randomized, Partially Blinded, Palivizumab- Controlled Study to Evaluate the Safety, Efficacy, and Pharmacokinetics of Clesrovimab in Infants and Children at Increased Risk for Severe RSV Disease

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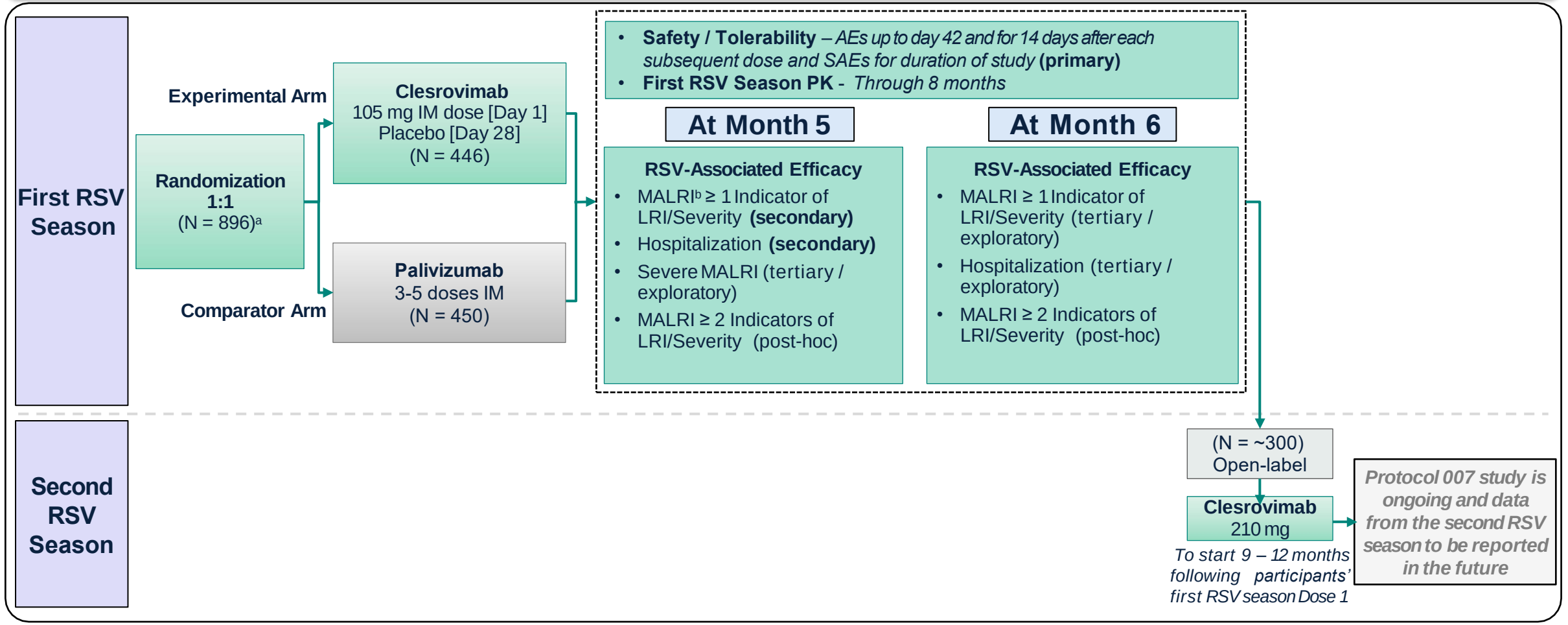
Protocol 007: Study Design

Phase 3, multicenter, randomized, partially blinded, palivizumab-controlled trial conducted with active surveillance over 2 RSV seasons

Objective: Safety, pharmacokinetics and RSV-associated endpoint incidence rates of clesrovimab in infants & children at increased risk for severe RSV disease



Notes: a. N=Number of randomized infants, dosed with clesrovimab or palivizumab; b. MALRI is defined as the presence of the following in a clinical setting: 1) cough or difficulty breathing; AND 2) 1 or more of wheezing, chest wall in-drawing/retraction, rales/crackles, hypoxemia, tachypnea, or dehydration; AND 3) RSV-positive reverse transcriptase polymerase chain reaction (RT-PCR) nasopharyngeal sample;
Abbreviations: AE=Adverse Event; IM=Intramuscular; MALRI=Medically-Attended Lower Respiratory Tract Infection; PK=Pharmacokinetics; RSV=Respiratory Syncytial Virus; SAE=Serious Adverse Event.

Protocol 007: Baseline Characteristics

Participant Characteristics *(All Dosed Participants – First RSV Season)*	Clesrovimab N = 446		Palivizumab N = 450	
Participants in Population	**n**	**(%)**	**n**	**(%)**
Participants with Condition				
CLD	124	(27.8)	126	(28.0)
CHD	52	(11.7)	49	(10.9)
Neither CLD nor CHD less than 29 weeks gestational age[a]	26	(5.8)	24	(5.3)
Neither CLD nor CHD greater than or equal to 29 weeks gestational age[a]	244	(54.7)	251	(55.8)
Age at Randomization (Months)				
<6	409	(91.7)	390	(86.2)
≥6 to <9	33	(7.4)	51	(11.3)
≥9	4	(0.9)	9	(2.0)
Mean (SD)	3.0 (1.9)		3.0 (2.3)	
Body Weight at Randomization (kg)				
Mean (SD)	3.8 (1.5)		3.6 (1.5)	
Median (Range)	3.5 (1.1 to 9.6)		3.2 (1.5 to 9.1)	
Race				
American Indian Or Alaska Native	5	(1.1)	7	(1.6)
Asian	82	(18.4)	80	(17.8)
Black Or African American	67	(15.0)	71	(15.8)
Multiple	56	(12.6)	53	(11.8)
Native Hawaiian Or Other Pacific Islander	5	(1.1)	2	(0.4)
White	231	(51.8)	237	(52.7)
Ethnicity				
Hispanic Or Latino	138	(30.9)	146	(32.4)
Not Hispanic Or Latino	296	(66.4)	296	(65.8)
Not Reported or Unknown	12	(2.7)	8	(1.8)
Sex				
Male	225	(50.4)	221	(49.1)
Female	221	(49.6)	229	(50.9)

- Baseline characteristics were similar in both clesrovimab and palivizumab arms
- Enrolled diverse population of different races and ethnicities from 27 countries, across 6 continents
- In total, 401 of 896 (44.8%) participants met the American Academy of Pediatrics (AAP) palivizumab eligibility criteria (101 CHD; 250 CLD; 50 <29 weeks GA)[1]

Notes: a. Range of gestational age was 23 to 41 weeks; **Abbreviations**: AAP=American Academy of Pediatrics; CHD=Congenital Heart Disease; CLD=Chronic Lung Disease; GA=Gestational Age; RSV=Respiratory Syncytial Virus; SD=Standard Deviation; **Source:** 1. Pediatrics. 2014 Aug 1;134(2):e620-38.

Protocol 007: Safety

Well-tolerated in infants at increased risk of severe RSV disease with a safety profile that is generally comparable to palivizumab

Participants with AEs	Clesrovimab Nᵃ = 445 n (%)	Palivizumab Nᵃ = 450 n (%)
Overall Solicited and Unsolicited AEs *(following any dose, first RSV season)*		
≥ 1AE	323 (72.6)	344 (76.4)
Drug-related AE	120 (27.0)	127 (28.2)
Any SAE	99 (22.2)	110 (24.4)
Drug-related SAE	0 (0.0)	2 (0.4)
Death	8 (1.8)	4 (0.9)
Solicited AEs *(days 1-5 postdose, first RSV season)*		
Injection site pain	26 (5.8)	32 (7.1)
Injection site erythema	29 (6.5)	20 (4.4)
Injection site swelling	26 (5.8)	12 (2.7)
Irritability	116 (26.1)	125 (27.8)
Somnolence	74 (16.6)	72 (16.0)
Decreased appetite	52 (11.7)	49 (10.9)
Solicited Temperature *(days 1-5 postdose 1, first RSV season)*		
Temp < 100.4 °F	436 (98.0)	441 (98.0)
Temp ≥ 100.4 °F	9 (2.0)	9 (2.0)
AESI *(days 1-42 postdose 1, first RSV season)*		
Rash	3 (0.7)	1(0.2)
Anaphylaxis/hypersensitivity	0 (0.0)	0 (0.0)

- Proportion of participants with AEs, including solicited AEs, drug-related AEs, and SAEs, were generally comparable between intervention groups; majority of AEs were Grade 1or 2 toxicity
- Most (≥ 98%) participants in either intervention group had a maximum temperature postdose 1<100.4 °F
- No AESI of anaphylaxis/hypersensitivity were reported, and the proportion of participants with AESI of rash was low in either intervention group; all events were non-serious and Grade 1toxicity
- No deaths were considered related to study intervention by investigator; no pattern identified with respect to cause of death or timing; largely attributable to underlying co-morbidities

Notes: a. N = Number of participants randomized and dosed and included in the safety population; **Abbreviations:** AE=Adverse Event; AESI=Adverse Event of Special Interest; SAE=Serious Adverse Event.

Protocol 007: Incidence Rates

Comparable RSV disease incidence between clesrovimab and palivizumab groups

RSV-Associated Endpoint[a] *(Through 5 months Postdose)*	Clesrovimab (N = 446)			Palivizumab (N = 450)		
	n	Number of Events	Incidence Rate, % (95% CI)[d]	n	Number of Events	Incidence Rate, % (95% CI)[d]
MALRI Requiring ≥ 1 Indicator of LRI/Severity[b]	443	14	3.6 (2.0, 6.0)	437	12	3.0 (1.6, 5.3)
Hospitalization[c]	443	5	1.3 (0.4, 3.0)	437	6	1.5 (0.6, 3.3)

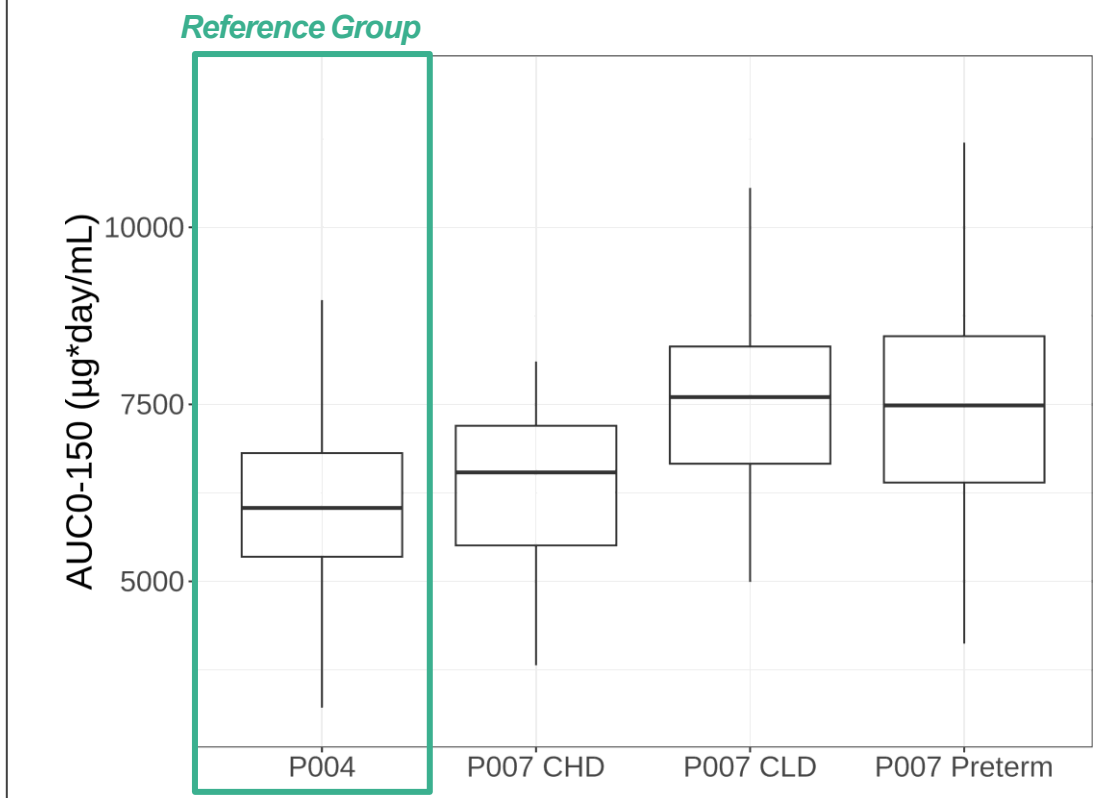
Note: Incidence rates in Protocol 007 are similar through 6 months postdose

Notes: a. MALRI includes both inpatient and outpatient cases; b. Defined as: RSV PCR positive and cough or difficulty breathing and at least 1 of the following: wheezing, chest wall indrawing/retractions, rales/crackles, hypoxemia, tachypnea, or dehydration due to respiratory symptoms; c. Respiratory Infection Hospitalization defined as: RSV PCR positive and hospital admission for respiratory illness; d. Confidence intervals were estimated by exact Poisson confidence limits; N=number of participants randomized and dosed with clesrovimab or palivizumab; n=number of participants eligible for inclusion in the full analysis set population; **Abbreviations**: CI=Confidence Interval; LRI=Lower Respiratory Tract Infection; MALRI=Medically-Attended Lower Respiratory Tract Infection.

Protocol 007: PK Bridging

Supports extrapolation of efficacy to infants with increased risk of severe RSV with no dose-adjustment necessary

PK exposures in infants at increased risk of severe RSV are similar to those in healthy infants



- **Non-inferiority trial in infants with increased risk of severe RSV would be infeasible** due to prohibitively large sample size in already small population
- In agreement with regulators, **PK bridging along with evaluation of estimation of efficacy in Protocol 007 was deemed acceptable** for assessment of efficacy in this population
- PK exposures in infants with increased risk for severe RSV **are similar** to those found in **healthy infants**, supporting extrapolation of efficacy to population of **preterm birth, CLD and/or CHD infants**, **without requiring dose adjustments**

Abbreviations: AUC=Area Under the Curve; CHD=Congenital Heart Disease; CLD=Chronic Lung Disease; PK=Pharmacokinetics; RSV=Respiratory Syncytial Virus.

Protocol 007: Conclusions

Safety

- The safety profile of clesrovimab in infants at increased risk of severe RSV disease is generally **comparable to palivizumab** and consistent with the safety profile in healthy infants

Efficacy

- **Efficacy in Protocol 007 population was inferred by efficacy established from Protocol 004,** based on comparable clesrovimab pharmacokinetic data
- **In infants at increased risk for severe RSV disease, a single dose of clesrovimab protects against RSV disease**, including RSV hospitalization, through 6 months

Abbreviations: RSV=Respiratory Syncytial Virus.

Summary

Clesrovimab Phase 2b/3 Study Conclusions

Efficacy

Clesrovimab, administered as **a single dose** for infants of any weight, provides robust protection against **mild, moderate, and severe** RSV disease for all infants, including term, preterm, and those with risk factors

- ✓ **In healthy infants,** clesrovimab is highly efficacious against a broad spectrum of RSV disease endpoints, with **no shifting** of RSV disease burden in second RSV season (Protocol 004)
- ✓ **Over 90% efficacy in preventing RSV LRI hospitalizations through 6 months**
- ✓ Clesrovimab **also protects infants at increased risk for severe RSV disease**, comparable to palivizumab (Protocol 007)
- ✓ The **dose is same** for infants of all weights
- ✓ **Efficacy is sustained through 6 months,** providing durable efficacy for an entire typical RSV season

Safety

Clesrovimab is well-tolerated in infants, with a safety profile that is generally comparable to controls and consistent across infant populations.

- Clesrovimab is well tolerated **in healthy preterm and full-term infants** born during or entering their first RSV season, with a safety profile that is generally comparable to placebo
- The safety profile of clesrovimab in infants at **increased risk for severe RSV disease** is generally comparable to palivizumab and consistent with the safety profile in healthy infants

Abbreviations: LRI=Lower Respiratory Tract Infection; MALRI=Medically-Attended Lower Respiratory Tract Infection; RSV=Respiratory Syncytial Virus.

Thank you

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