

#SO 29

PK, SNA, and Efficacy Against RSV MALRI From a Phase 1b/2a Study of the Monoclonal Antibody Clesrovimab (MK-1654) in Infants

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Background

- Respiratory syncytial virus (RSV) is a major cause of infant morbidity worldwide<sup>1–3</sup>
  - Primary cause of lower respiratory tract infection (LRTI) in infants and young children
  - Currently there are no licensed vaccines, and monoclonal antibody (mAb) prophylaxis is only available for high-risk infants
- A potent RSV-neutralizing mAb with extended half-life to enable a single dose per season has the potential to meet unmet medical needs for a broader infant population
  - The typical half-life of an antibody without any half-life extension in children is ~20 days<sup>4</sup>
- Clesrovimab (MK-1654), an RSV-neutralizing mAb, is currently in phase 3 trials for the prevention of RSV-associated disease in infants
  - Binds with high affinity to antigenic site IV of RSV fusion protein<sup>5</sup>
  - High potency in vitro against a range of RSV-A and RSV-B clinical isolates<sup>5</sup>
  - The fragment crystallizable (Fc) region is engineered with 3 mutations for half-life extension<sup>5</sup>

Objectives

- From the interim analysis of the Phase 1b/2a infant study (NCT03524118):
  - Characterize pharmacokinetics (PK) of clesrovimab in preterm and full-term infants
  - Determine RSV serum-neutralizing antibody (SNA) titers
  - Predict the efficacy of clesrovimab from day 1 to day 150 using a published model<sup>6</sup>
  - Summarize exploratory efficacy analysis for RSV medically attended lower respiratory tract infection (MALRI) from day 1 to day 150

Methods

- Study design:**
  - Phase 1b/2a:** Double-blind, randomized, placebo-controlled, single-ascending-dose
  - Population:** N=181 preterm (29–35 weeks gestational age) and full-term infants, 2 weeks to 8 months of age; were randomized 4:1 to clesrovimab or placebo respectively, in 5 panels:

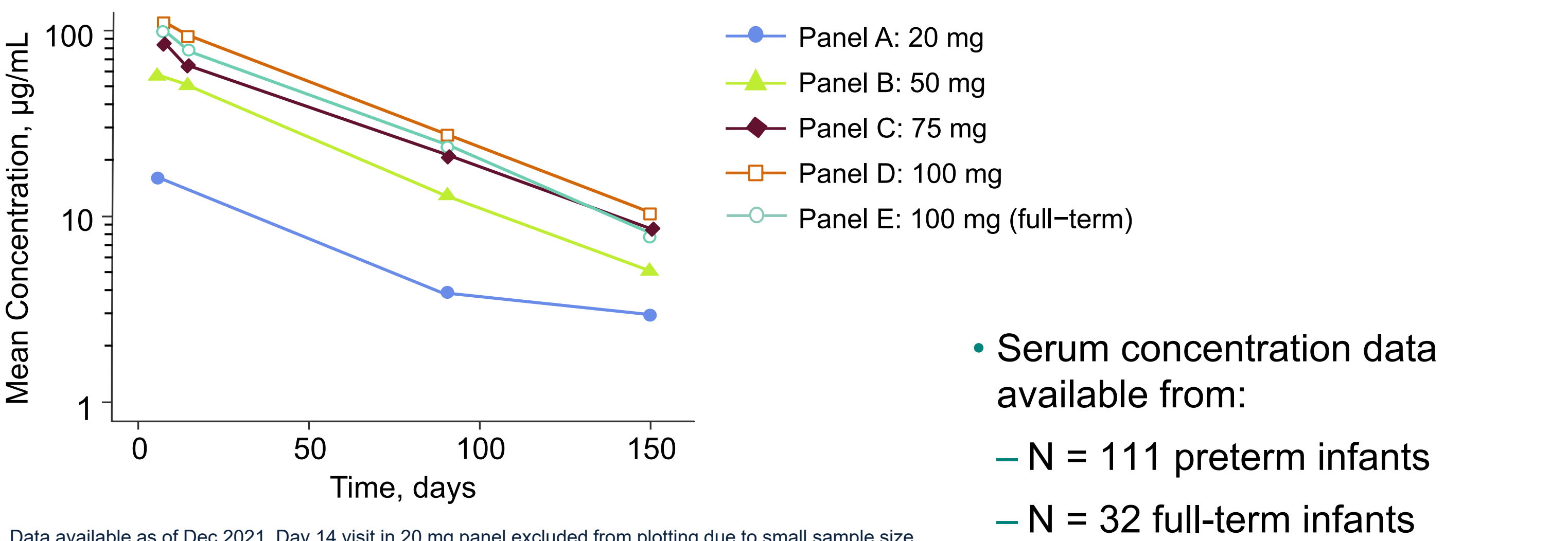
Dose escalation panels – preterm infants			
Panel A	Panel B	Panel C	Panel D
MK-1654 20 mg N=8	MK-1654 50 mg N=32	MK-1654 75 mg N=40	MK-1654 100 mg N=32
Placebo N=2	Placebo N=8	Placebo N=10	Placebo N=8
Full-term infants			
Panel E			
MK-1654 100 mg N=32			
Placebo N=8			

- Evaluations:**
  - Clesrovimab serum concentration (PK)
  - RSV SNA
  - Anti-drug antibodies (ADAs)
  - Safety through at least day 365
  - Active RSV surveillance during the season, collecting respiratory symptoms and swabs for respiratory panel polymerase chain reaction (PCR)

Results

- Serum concentration data was available from: n=111 preterm infants and n=32 full-term infants
- Clesrovimab concentrations increased in a dose-proportional manner (**Figure 1**)
- Clesrovimab was shown to have an extended half-life in preterm and full-term infants (**Table 1**), with a mean half-life of approximately 42 days

Figure 1. Clesrovimab serum concentration over time



References

1. Shi T et al. *Lancet*. 2017;390(10098):946–958. 2. Mazur NI et al. *Clin Infect Dis*. 2021;73(suppl 3):S229–S237. 3. Leader S et al. *J Pediatr*. 2003;143(suppl 5):S127–132. 4. Synagis (palivizumab) injections, for intramuscular use. Full prescribing information. MedImmune LLC; 2014. 5. Tang A et al. *Nat Commun*. 2019;10(1):4153. 6. Maas BM et al. *EBioMedicine*. 2021;73:103651. 7. Kulkarni PS et al. *Viral Immunol*. 2018;31(2):195–203. 8. Chan ISF et al. *Communications in Statistics-Theory and Methods*. 1998;27(6):1305-1322.

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Table 1. Clesrovimab pharmacokinetic parameters in preterm and full-term infants

Population	Panel	IM dose	n <sup>a</sup>	T <sub>max</sub> <sup>b</sup> (day)	C <sub>max</sub> (µg/mL)	C <sub>150</sub> (µg/mL)	AUCinf (day·µg/mL)	t <sub>1/2</sub> (day)
Preterm	A	20 mg	6	5.00 [4.00–8.00]	23.2 (19.0)	2.28 (75.1)	1600 (43.5)	44.5 (32.0)
	B	50 mg	33	6.00 [4.00–16.00]	59.3 (36.5)	5.07 (38.0)	3810 (30.0)	41.3 (11.9)
	C	75 mg	40	6.00 [3.00–18.00]	88.3 (28.3)	8.36 (39.8)	5830 (26.9)	42.9 (14.6)
	D	100 mg	32	6.00 [4.00–19.00]	107 (35.3)	9.51 (47.0)	7080 (31.1)	41.6 (16.8)
Full-term	E	100 mg	32	5.00 [4.00–19.00]	90.8 (19.2)	8.18 (27.4)	5940 (17.8)	40.0 (9.7)

Parameter summary is based on individual post-hoc estimation from population PK analysis. Values reported as geometric mean (geometric CV%) unless otherwise stated. <sup>a</sup>n refers to the number of participants who received each dose of MK-1654. <sup>b</sup>T<sub>max</sub> reported as median [min, max].

Figure 2. Serum-neutralizing antibody titers through to day 150

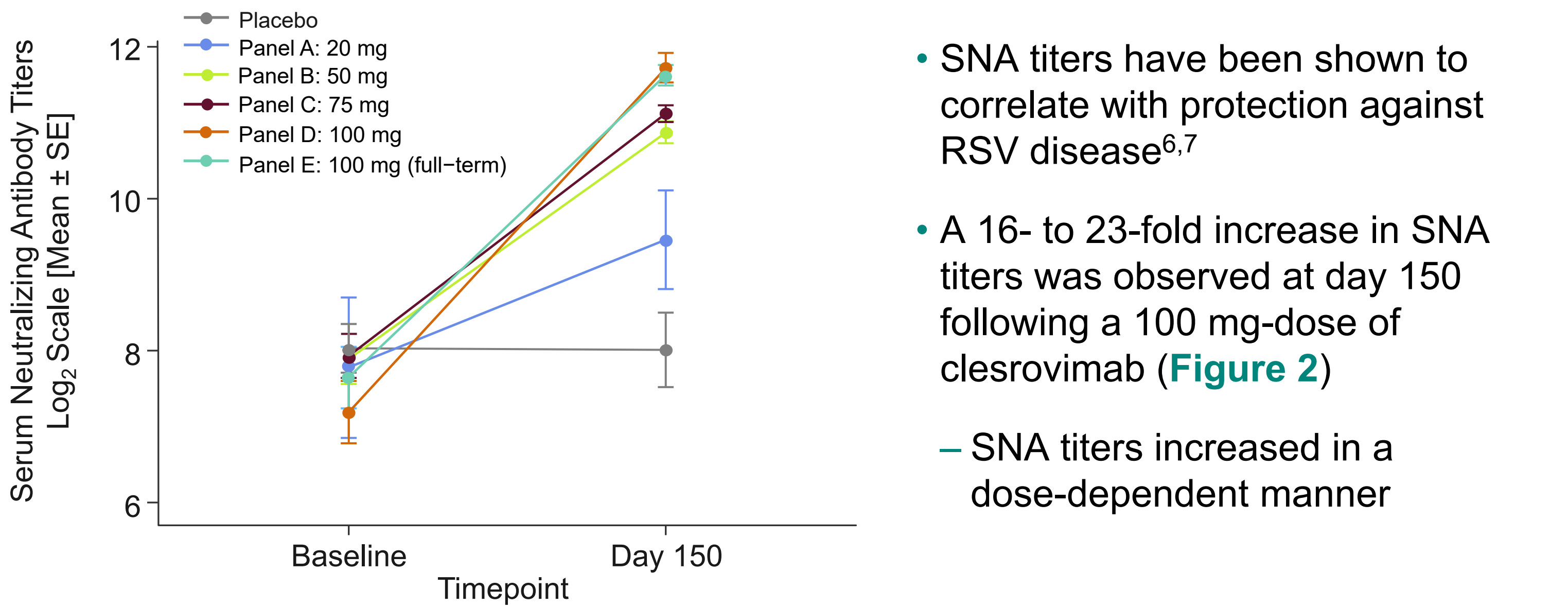


Figure 3. Predicted clesrovimab efficacy against RSV-associated MALRI, day 1 to day 150 post-dose by modeling

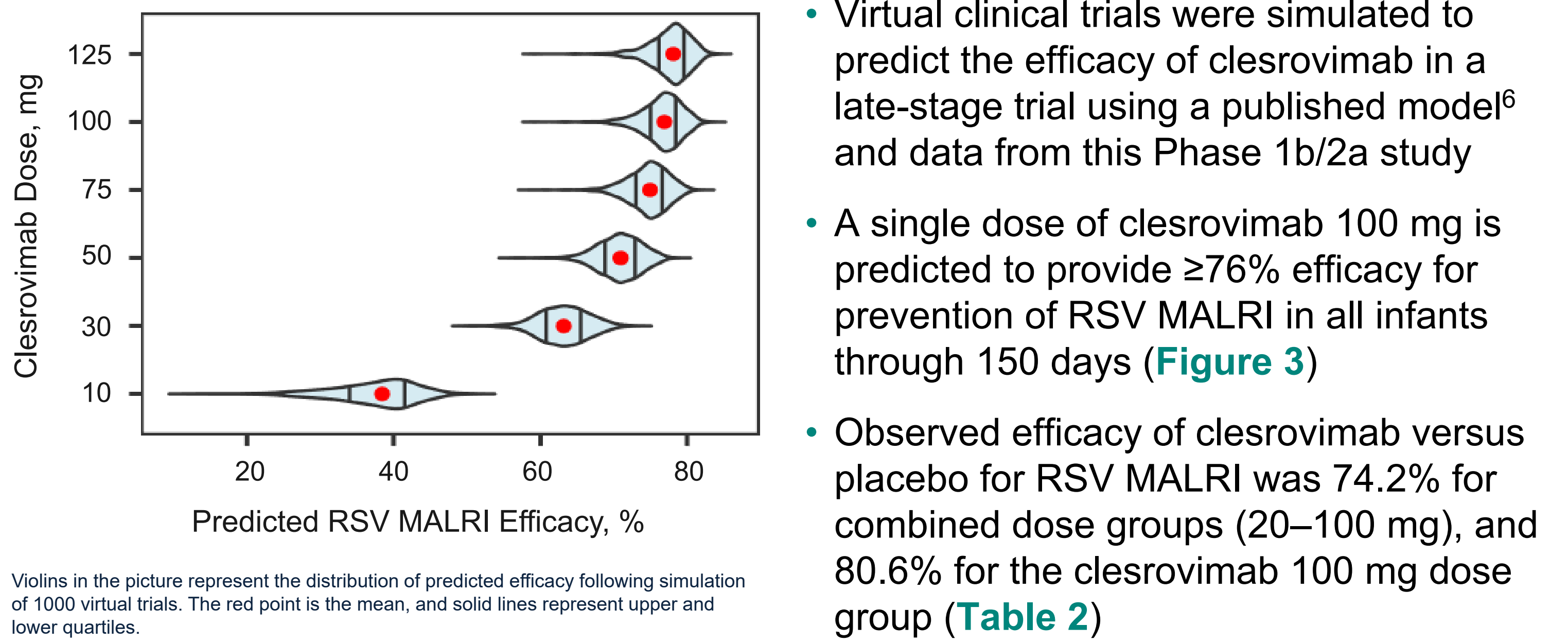


Table 2. Observed clesrovimab efficacy against RSV-associated MALRI Days 1 to 150 post-dose in the Phase 1b/2a study

	Clesrovimab		Placebo		Observed efficacy % (95% CI)
	Participants in full analysis set	RSV-associated MALRI cases	Participants in full analysis set	RSV-associated MALRI cases	
Combined clesrovimab dose groups vs. placebo	143	3	38	3	74.2 (–92.9, 96.5)
Clesrovimab 100 mg vs. placebo	64	1	38	3	80.6 (–141.2, 99.6)

95% CI estimated based on exact binomial method proposed by Chan and Bohidar.<sup>8</sup>

Conclusions

- The site IV-specific RSV-neutralizing mAb clesrovimab, demonstrated an extended half-life of approximately 42 days in infants
- Administration of clesrovimab was associated with dose-dependent increases in RSV SNA titers through day 150
- In this phase 1b/2a study, the observed efficacy of clesrovimab in the prevention of RSV MALRI aligns with previously published model-based efficacy predictions
- Although subject to limitations (small sample size and resulting wide range of CIs), these data support continued evaluation of clesrovimab in phase 3 studies for the prevention of RSV-associated disease in infants (NCT04767373 and NCT04938830)