Impact of antidrug antibodies on the pharmacokinetics, pharmacodynamics, and safety of clesrovimab in a phase 2b/3 trial (CLEVER)

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Background

- Clesrovimab is a human half-life–extended monoclonal antibody that targets the respiratory syncytial virus (RSV) fusion protein[1,2]
- Results of the pivotal phase 2b/3 study, CLEVER, demonstrated the efficacy of a single dose of clesrovimab (105 mg) given before or during the first RSV season in reducing the incidence of RSV-associated medically attended lower respiratory infection and RSV-associated hospitalization in healthy infants, compared with placebo[3]
- The CLEVER study showed that clesrovimab was well tolerated in healthy preterm and full-term infants born during or entering their first RSV season, with a safety profile generally comparable to that of placebo[3]

Objective

- To assess the impact of antidrug antibodies (ADA) on the pharmacokinetics (PK), pharmacodynamics (PD), and safety of clesrovimab through RSV seasons 1 and 2 (no study intervention)

Methods

Study design

- CLEVER (MK-1654-004; NCT04767373) was a double-blind, randomized, placebo-controlled, multicenter phase 2b/3 study conducted to evaluate the efficacy and safety of a single dose of clesrovimab in healthy preterm and full-term infants entering their first RSV season. Approximately 3300 participants were randomized 2:1 to receive either clesrovimab 105 mg or placebo
- The first 1650 participants were followed up through Day 515 post dose (RSV seasons 1 and 2), and the remaining participants were followed up through Day 365 (RSV season 1 only)

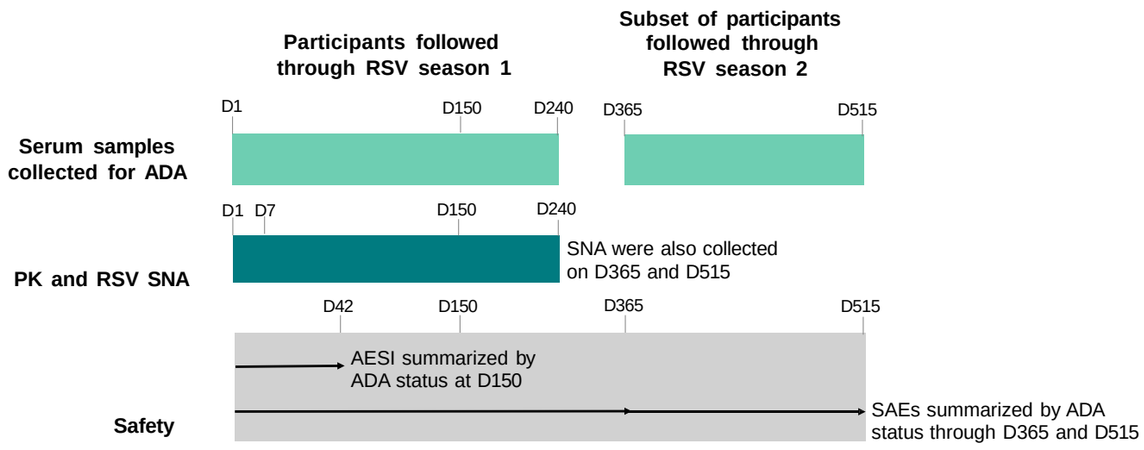
ADA assay

- Details of the ADA assay method were previously described[2]
  - Briefly, ADA positivity was determined using a screening assay cut point of 1.15 (based on the signal to noise ratio) targeting a 5% false-positive rate
  - A confirmatory assay was used to test samples that were determined to be ADA-positive (ADA+), with a sensitivity of 3.85 ng/mL, a drug tolerance of 451 µg/mL, and a cut point of 16.6 (based on percentage inhibition), allowing for a 1% false-positive rate
  - Samples confirmed to be positive were analyzed for titer (defined as the reciprocal of the highest dilution that produced a positive signal greater than the cut point), and participants with positive ADA responses were further classified as treatment-emergent positive (negative at baseline and positive post dose) or treatment-boosted positive (positive at baseline and post-dose titer ≥2-fold higher than baseline)
- The ADA+ population included treatment-emergent ADA+ participants (negative at baseline and positive post dose) and treatment-boosted ADA+ participants (positive at baseline and a post-dose titer ≥2-fold higher than baseline)

PK and PD analyses

- Serum samples for identification of ADA against clesrovimab were collected on Day 1 (pre-dose) and Days 150 and 240 post dose (RSV season 1) and from a subset of participants continuing in RSV season 2 on Days 365 and 515 (**Figure 1**)
- Clesrovimab serum concentration and RSV serum-neutralizing antibodies (SNA) were measured on Day 1 (pre-dose) and Days 7, 150, and 240 post dose, and summarized by ADA status on Day 150 (**Figure 1**)
- Serious adverse events (SAEs) through Days 365 and 515 post dose were summarized by ADA status through Days 365 and 515, respectively, and AEs of special interest (AESIs) through Day 42 post dose were summarized by ADA status on Day 150

Figure 1. Serum sample collection and ADA analysis



ADA, antidrug antibody; AESI, adverse events of special interest; D, day; PK, pharmacokinetic; RSV, respiratory syncytial virus; SAE, serious adverse event; SNA, serum-neutralizing antibody.
Not all participants had samples collected at each time point. Safety was assessed on days 1 through 5 post dose (solicited injection site AEs, solicited systemic AEs, body temperature), days 1 through 42 post dose (non-SAEs, AESI) and through Day 365 post dose (SAEs). Active surveillance for RSV infection was collected days 1 to 180 post dose in RSV season 1 and days 365 to 515 post dose in RSV season 2.

Results

- The proportion of participants who were ADA+ to clesrovimab was low on Day 150 (120/2112 [5.7%]) and increased through Day 240 (124/1033 [12.0%]), Day 365 (214/564 [37.9%]), and Day 515 (345/589 [58.6%]) (**Table 1**)
- The proportion of evaluable participants who were ADA+ at any time point in the study was 22.8% (515/2254 participants)
- ADA titers were low for all ADA+ participants from days 1 through 180 (data not shown)

Table 1. Development of ADA to clesrovimab

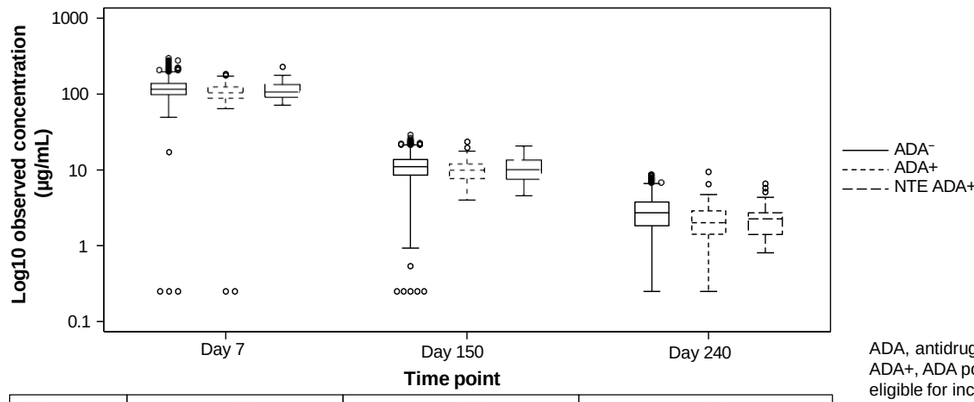
	Day 150	Day 240	Day 365	Day 515
Evaluable participants, n	2112	1033	564	589
Positive ADA response to clesrovimab, n (%)	120 (5.7)	124 (12.0)	214 (37.9)	345 (58.6)
Treatment-emergent positive, n (%)	115 (5.4)	119 (11.5)	210 (37.2)	334 (56.7)
Treatment-boosted positive, n (%)	5 (0.2)	5 (0.5)	4 (0.7)	11 (1.9)

ADA, antidrug antibody.

PK and PD

- Serum concentrations of clesrovimab and RSV SNA titers were comparable across the subgroups based on ADA status at Day 150 (**Figure 2, Figure 3**)
- On Day 150, the geometric mean (95% confidence interval [CI]) clesrovimab serum concentration was 10.3 (10.1–10.5) versus 9.4 (8.8–10.0) for ADA-negative (ADA^-) versus ADA+ subgroups, respectively (**Figure 2**)
- The geometric mean (95% CI) RSV A SNA titer was 2474.0 (2340.2–2615.5) versus 2384.1 (1927.6–2948.7) for ADA^- versus ADA+ subgroups, respectively, on Day 150 (**Figure 3**)

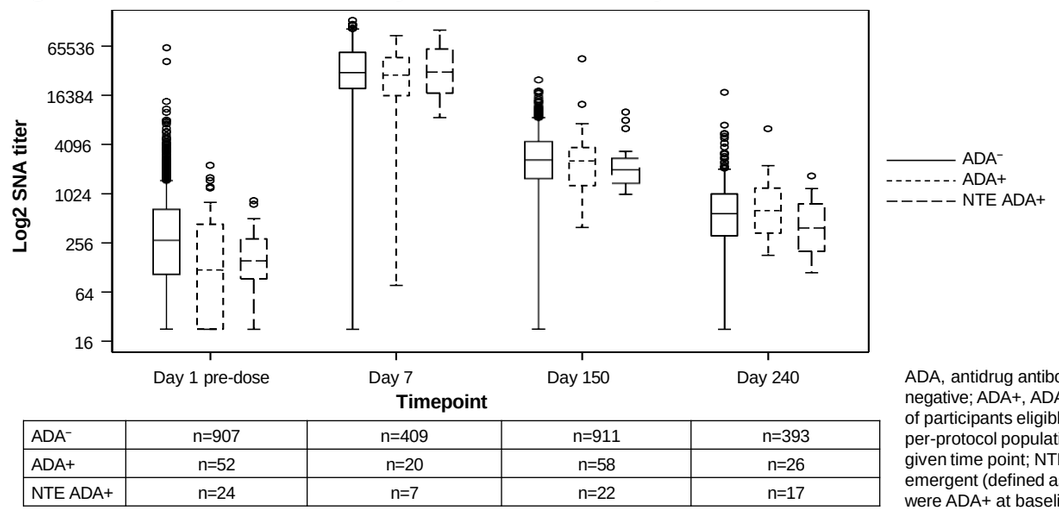
Figure 2. Observed serum concentrations by ADA status at Day 150



ADA^-	n=866	n=1903	n=841
ADA+	n=56	n=119	n=54
NTE ADA+	n=22	n=50	n=27

ADA, antidrug antibody; ADA^-, ADA negative; ADA+, ADA positive; n, number of participants eligible for inclusion in the per-protocol population with a result at the given timepoint; NTE, non-treatment emergent (defined as participants who were ADA+ at baseline and post dose).

Figure 3. RSV A SNA titers by ADA status at Day 150



ADA^-	n=907	n=409	n=911	n=393
ADA+	n=52	n=20	n=58	n=26
NTE ADA+	n=24	n=7	n=22	n=17

ADA, antidrug antibody; ADA^-, ADA negative; ADA+, ADA positive; n, number of participants eligible for inclusion in the per-protocol population with a result at the given time point; NTE, nontreatment-emergent (defined as participants who were ADA+ at baseline and post dose).

Safety

- The proportion of participants with SAEs from days 1–365 was comparable across the ADA^-, ADA+, and placebo groups based on ADA status through Day 365 in season 1 (11.9%, 11.7%, and 12.4%, respectively) and the proportion of participants with SAEs from days 365–515 was comparable across the ADA−, ADA+, and placebo groups based on ADA status through Day 515 in season 2 (3.4%, 2.9%, and 4.0%) (**Table 2**)

Table 2. SAEs by ADA status through Day 365 and through Day 515 post dose (incidence >0% in ≥1 treatment group, by system organ class)

	Days 1 to 365 post dose (all participants)			Days 365 to 515 post dose (participants with ADA results at Day 515)		
	Clesrovimab 105 mg		Placebo (n=1202)	Clesrovimab 105 mg		Placebo (n=501)
n (%)	ADA^- (n=1793)	ADA+[a] (n=358)		ADA^- (n=232)	ADA+[a] (n=345)	
Participants with ≥1 SAE	214 (11.9)	42 (11.7)	149 (12.4)	8 (3.4)	10 (2.9)	20 (4.0)
Blood and lymphatic system disorders	2 (0.1)	1 (0.3)	3 (0.2)	-	-	-
Cardiac disorders	1 (0.1)	0	2 (0.2)	-	-	-
Congenital, familial, and genetic disorders	3 (0.2)	1 (0.3)	0	0	1	0
Eye disorders	1 (0.1)	0	0	-	-	-
Gastrointestinal disorders	11 (0.6)	2 (0.6)	13 (1.1)	1 (0.4)	0	0
General disorders and administration site conditions	2 (0.1)	0	3 (0.2)	0	0	1 (0.2)
Hepatobiliary disorders	5 (0.3)	0	1 (0.1)	-	-	-
Immune system disorders	0	0	1 (0.1)	-	-	-
Infections and infestations	171 (9.5)	33 (9.2)	122 (10.1)	4 (1.7)	7 (2.0)	16 (3.2)
Injury, poisoning, and procedural complications	7 (0.4)	2 (0.6)	3 (0.2)	0	0	2 (0.4)
Investigations	1 (0.1)	0	4 (0.3)	-	-	-
Metabolism and nutrition disorders	2 (0.1)	2 (0.6)	5 (0.4)	1 (0.4)	0	0
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	0	0	1 (0.1)	-	-	-
Nervous system disorders	20 (1.1)	3 (0.8)	4 (0.3)	1 (0.4)	1 (0.3)	1 (0.2)
Renal and urinary disorders	1 (0.1)	0	1 (0.1)			
Psychiatric disorders	-	-	-	1 (0.4)	0	0
Respiratory, thoracic, and mediastinal disorders	8 (0.4)	4 (1.1)	11 (0.9)	1 (0.4)	1 (0.3)	1 (0.2)
Skin and subcutaneous tissue disorders	0	0	1 (0.1)	-	-	-
Vascular disorders	2 (0.1)	0	0	-	-	-

ADA, antidrug antibody; ADA−, ADA negative; ADA+, ADA positive; AE, adverse event; NTE, nontreatment emergent (defined as participants who were ADA+ at baseline and after dosing); SAE, serious adverse event.
ADA status for participants in the clesrovimab group is defined based on all available ADA results on Days 150, 240, and 365.
[a]The ADA+ population includes treatment-emergent ADA+ participants and treatment-boosted ADA+ participants.

- In RSV season 2, the proportion of participants with ADA+ status increased over time through Day 515. Although approximately half of participants developed ADA to clesrovimab at Day 515, the proportion of participants who experienced SAEs in RSV season 2 (days 365 through 515) was comparable across the ADA−, ADA+, and placebo groups based on ADA status through Day 515, suggesting that the development of ADA had no impact on the safety profile of clesrovimab, consistent with what was observed in RSV season 1
- No AESIs of anaphylaxis and hypersensitivity or rash were reported in the ADA+ subgroup based on ADA status on Day 150

Conclusions

- In the CLEVER study in healthy preterm and full-term infants, ADA had no effect on clesrovimab serum concentration or the ability of clesrovimab to neutralize RSV
- Additionally, the safety of clesrovimab, as assessed by SAEs, anaphylaxis and hypersensitivity AESI, and rash AESIs, was not impacted by ADA in both RSV seasons 1 and 2

References

1. Terstappen J, et al. *Lancet Infect Dis*. 2024;24:e747-e761.
2. Madhi SA, et al. *J Infect Dis*. 2024. https://doi.org:10.1093/infdis/jiae581.
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