30 January 2025
EMA/60558/2025
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

mRESVIA

Respiratory syncytial virus mRNA vaccine (nucleoside modified)

Procedure no: EMEA/H/C/006278/P46/004

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	02 Dec 2024	02 Dec 2024	☐
☐	CHMP Rapporteur Assessment Report	06 Jan 2025	17 Jan 2025	☐
☐	CHMP members comments	20 Jan 2025	20 Jan 2025	☐
☐	Updated CHMP Rapporteur Assessment Report	23 Jan 2025	23 Jan 2025	☐
☒	CHMP adoption of conclusions:	30 Jan 2025	30 Jan 2025	☐

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1. Introduction

On 06 Nov2024, the MAH submitted a completed paediatric study for mRESVIA, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

Reference eCTD Sequence: 011

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study mRNA-1345-P101 for the paediatric cohorts 5 and 6 is a stand alone submission.

2.2. Information on the pharmaceutical formulation used in the study

Dispersion for injection (30 µg or 15 µg or placebo

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study mRNA- 1345-P101 for the paediatric cohorts 5 and 6

2.3.2. Clinical study mRNA- 1345-P101

Description

Clinical study mRNA- 1345-P101 is a Phase 1, Randomized, Observer-Blind, Placebo- Controlled, Dose Escalation Study to Evaluate the Safety, Reactogenicity, and Immunogenicity of mRNA-1345, an mRNA Vaccine Targeting Respiratory Syncytial Virus (RSV), in Healthy Younger Adults Aged 18 to 49 Years, Women of Child-Bearing Potential Aged 18 to 40 Years, Healthy Older Adults Aged 65 to 79 Years, Japanese Older Adults Aged ≥ 60 Years, and RSV-Seropositive Children Aged 12 to 59 Months.

This current procedure covers paediatric cohorts 5 and 6 (final analysis with a database lock of 14-March-2024) with 18 July 2024 as the End of Study (EoS) date, LPLV 18Jul24, and database lock Dec24.

Study P101 enrolled 2 pediatric cohorts of RSV-seropositive children aged 12 to 59 months.

Participants were randomized in a 3:1 ratio via interactive response technology to receive either mRNA-1345 30 µg or placebo (Cohort 5) or mRNA-1345 15 µg or placebo (Cohort 6). All participants received a 3-dose injection series administered 56 days apart (Day 1, Day 57, and Day 113). Enrollment for Cohort 6 commenced after completion of Cohort 5. Cohort 5 was initiated on 23 Jun 2021 (first participant randomized) and Cohort 6 concluded on 28 Mar 2024 (LPLV).

Methods

Study participants

Study participants were RSV-seropositive children aged 12 to 59 months who had completed routine age-appropriate immunizations according to local guidelines. Participants were required to have height and weight above the third percentile for their age at enrollment

46 Participants were randomly assigned to receive 3 injections of 15 µg or 30 µg mRNA-1345 (15 participants and 16 participants, respectively) or placebo (15 participants)

(Reference: Study mRNA-1345-P101 Final CSR Addendum 1 [Pediatric Cohorts] Sections 3.3.1, 5.1 and 5.4)

Treatments

First injection: all (100%) participants in the mRNA-1345 15 µg and placebo groups, and 15/16 (93.8%) participants in the 30µg group

Second injection: 14/15 (93.3%) and 12/16 (75.0%) participants in the mRNA-1345 15 µg and 30 µg groups, and 11/15 (73.3%) participants in the placebo group

Third injection: 11/15 (73.3%) and 10/16 (62.5%) participants in the mRNA-1345 15 µg and 30 µg groups, and 10/15 (66.7%) participants in the placebo group

All (100%) participants in the mRNA-1345 (15 µg and 30 µg) and placebo groups completed ≥28 days of follow-up after the first injection received. 11/15 (73.3%) Participants in the mRNA-1345 15 µg group, 12/15 (80.0%) participants in the mRNA-1345 30 µg group, and 9/15 (60%) participants in the placebo group completed ≥12 months of follow-up after the first injection.

The median duration of follow-up from the first injection across all treatment groups was 451.0 days (range: 34 to 561 days).

(Reference: Study mRNA-1345-P101 Final CSR Addendum 1 [Pediatric Cohorts] Section 5.1 and 5.6).

Objectives and Outcomes/endpoints

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary Safety	
To evaluate the tolerability and reactogenicity of 3 injections of 2 dose levels of mRNA-1345 given 56 days apart in RSV-seropositive children.	• Solicited local and systemic ARs through 7 days after each injection. • Unsolicited AEs through 28 days after each injection. • SAEs and MAAEs throughout the entire study period.
Secondary Immunogenicity	
To evaluate the Ab response to each vaccine dose level in RSV-seropositive children.	• GMT of serum RSV neutralizing and GMC of serum RSV-binding Abs across prespecified study timepoints. • GMFR of postbaseline/baseline Ab titers. • Proportion of participants with ≥2-fold and ≥4-fold increases in Ab titers from baseline.

Abbreviations: Ab = antibody; AEs = adverse events; ARs = adverse reactions; GMC = geometric mean concentration; GMFR = geometric mean fold-rise; GMT = geometric mean titer; MAAEs = medically attended adverse events; RSV = respiratory syncytial virus; SAEs = serious adverse events.

Ref: CSR Section 2

Sample size

A total of 46 pediatric participants were randomly assigned to receive the study intervention resulting in 16 participants in the mRNA-1345 30 µg group, 15 participants in the mRNA-1345 15 µg group, and 15 participants in the placebo group.

Randomisation and blinding (masking)

Two pediatric cohorts (Cohorts 5 and 6) were to be enrolled and randomized in a 3:1 ratio via IRT (Interactive Response Technology) to receive mRNA-1345 or placebo.

Statistical Methods

The planned analyses, statistical tests, and determination of sample size are described in the SAP (Version 6.0 dated 30 Oct 2023) for the mRNA-1345-P101 study (Appendix 16.1.9).

Results

Participant flow

RSV-seropositive children in Cohort 5 received 30 µg of mRNA-1345 or placebo. After this cohort was fully enrolled, Cohort 6 started enrolling children to receive 15 µg of mRNA-1345 or placebo. Note that the initial plan had been to dose escalate to 100 µg for Cohort 5, but emerging data from the Sponsor's pediatric COVID-19 vaccine trials suggested that the 100µg dose could result to an increased fever rate, as well as a Grade 4 fever that occurred in a participant in Cohort 5 led to the decision to instead test the lower dose of 15 µg (refer to Protocol Amendment 6).

Recruitment

A total of 46 pediatric participants were randomly assigned to receive the study intervention.

Of the 31 participants who received mRNA-1345, 9 (29.0%) participants discontinued the study vaccine. Reasons for study vaccine discontinuation included lost to follow-up, protocol violation, other (fear of needles and at Sponsor request due to low RSV nAb titers at start of study), solicited AE (fever of 105°F), and withdrawal of consent (Listing 16.2.1.1.4).

A total of 22/31 (71.0%) participants in the mRNA-1345 groups and 9/15 (60.0%) participants in the placebo group completed the study. The reasons for study discontinuation for placebo participants were lost to follow-up, protocol violation, withdrawal of consent, and other (Sponsor request due to low RSV nAb titers at start of study).

The reasons for study discontinuation in the mRNA-1345 30 µg group were lost to follow-up and other (1 participant moved 10 hours away and 1 participant missed first injection due to inadequate study supplies onsite). Lost to follow-up was the only reason for study discontinuation in the 15µg group.

No participants discontinued from the study due to an AE in the pediatric cohorts, according to the MAH (Listing 16.2.1.1.4).

Baseline data

Age in the pediatric cohorts ranged from 17 to 59 months. Mean age was 38.9 months in the mRNA-1345 15 µg group, 42.6 months in the mRNA-1345 30 µg group, and 38.4 months in the placebo group.

Gender was balanced in the 15µg group (53.3% male and 46.7% female), while variability was observed in the 30µg group (31.3% male and 68.8% female). The placebo group included 60.0% male and 40.0% female participants.

Of the 46 randomized participants, 29 (63.0%) were White, 10 (21.7%) were Black or African American, 3 (6.5%) identified as other, 3 (6.5%) identified as multiple races, and 1 (2.2%) identified as Asian.

(Refer to CSR Section 5.4)

Numbers analysed

Table 2 Number of Participants in Each Analysis Set by Treatment Arm – Paediatric Cohorts

	3-dose				
	Placebo n (%)	mRNA-1345 15 µg n (%)	mRNA-1345 30 µg n (%)	mRNA-1345 Total n (%)	Overall n (%)
Randomized Set[b]	15 (100)	15 (100)	16 (100)	31 (100)	46 (100)
Safety Set[a]	15 (100)	15 (100)	15 (100)	30 (100)	45 (100)
Solicited Safety Set[a]	15 (100)	15 (100)	15 (100)	30 (100)	45 (100)
Full Analysis Set[b]	12 (80.0)	15 (100)	14 (87.5)	29 (93.5)	41 (89.1)
Per-Protocol Set[b]	11 (73.3)	13 (86.7)	14 (87.5)	27 (87.1)	38 (82.6)

Notes: n = Number of randomized participants in category with nonmissing data.
% = n/N × 100

a. Numbers were based on actual vaccination group and percentages are based on the number of participants in Safety Set.

b. Numbers were based on planned vaccination group and percentages are based on the number of participants in Randomization Set.

Source: Table 14.1.2.4.

Ref Table 5, CSR

Immunogenicity results

Immunogenicity was assessed by measuring serum nAbs against RSV-A and RSV-B, and bAb titers against the RSV-F protein (both preF and postF conformations). Analyses were conducted at Baseline (Screening), Month 1 (Day 29, 1 month after the first injection), Month 3 (Day 85, 1 month after the second injection), and Month 5 (Day 141, 1 month after the third injection).

Immunogenicity analyses were performed primarily using the PP Set and analyzed by participant cohorts. Key details of statistical analyses that were carried out for immunogenicity are presented in Study mRNA-1345-P101 Final CSR Addendum 1 (Pediatric Cohorts) Section 4.1.4.2.

Immunogenicity was assessed as a secondary objective in the study. The study was not designed to evaluate efficacy.

The immunogenicity objective was to evaluate the antibody response to each injection dose level (15 µg or 30 µg) of mRNA-1345 in baseline RSV-seropositive children (Cohort 5 and Cohort 6). Study endpoints included: GMT (IU/mL) of serum RSV nAbs and GMC (AU/mL) of serum RSV bAbs across Baseline, Month 1, Month 3, and Month 5; GMFR of postbaseline/baseline antibody titers; and the proportion of participants with ≥2-fold and ≥4-fold increases in antibody titers from Baseline.

- RSV-A and RSV-B nAbs and preF and postF bAbs were confirmed to be present at Baseline in the mRNA-1345 and placebo groups, suggestive of prior exposure to RSV.
- A single injection of mRNA-1345 15 µg and 30 µg increased nAb titers against RSV-A and RSV-B, as well as bAb concentrations against preF and postF. There was no apparent dose response in the Month 1 GMTs/GMCs. Although the Month 1 GMFRs were numerically higher for the mRNA-1345 30 µg group, this was due to lower baseline values compared with the mRNA-1345 15 µg group. The nAb response to mRNA-1345 measured by GMFR was lowest in those participants with the highest baseline antibody titer.
- The Month 1 RSV nAb GMTs in IU/mL for the mRNA-1345 15 µg group, mRNA-1345 30 µg group, and placebo group were 11,440.4, 8376.1, and 642.6, respectively, for RSV-A; and

5940.3, 4931.9, and 490.2, respectively, for RSV-B. The Month 1 nAb GMFRs for the mRNA-1345 15 µg, mRNA-1345 30 µg, and placebo groups were 18.94, 34.88, and 1.44, respectively, for RSV-A; and 7.21, 14.26, and 1.24, respectively, for RSV-B.

- RSV preF and postF bAbs followed similar trends as the RSV nAbs. At each timepoint after mRNA-1345 vaccination, preF GMFRs were greater than postF GMFRs, suggesting that mRNA-1345 preferentially boosts antibodies to the preF conformation.
- The second and third injections of mRNA-1345 15 µg or 30 µg did not substantially impact neutralizing or binding antibody titers in these initially RSV-seropositive participants.
- Immunogenicity results for the FAS were similar to results for the PP Set.

Safety results

Solicited Adverse Reactions (ADRs)

Solicited local ADRs

Table 3 ***Summary of Solicited Adverse Reactions Through 7***

Table 7: Summary of Solicited Adverse Reactions Through 7 Days by Toxicity Grade for Each Injection – Pediatric Cohorts (Solicited Safety Set)

Solicited Adverse Reactions Category Grade	Placebo			mRNA-1345 15 µg			mRNA-1345 30 µg		
	First Injection	Second Injection	Third Injection	First Injection	Second Injection	Third Injection	First Injection	Second Injection	Third Injection
	(N=15) n (%)	(N=11) n (%)	(N=10) n (%)	(N=15) n (%)	(N=14) n (%)	(N=11) n (%)	(N=15) n (%)	(N=12) n (%)	(N=10) n (%)
Solicited adverse reactions - N1	15	11	9	14	14	11	15	8	9
Any solicited adverse reactions	7 (46.7)	7 (63.6)	5 (55.6)	7 (50.0)	9 (64.3)	5 (45.5)	8 (53.3)	5 (62.5)	6 (66.7)
95% CI	(21.3, 73.4)	(30.8, 89.1)	(21.2, 86.3)	(23.0, 77.0)	(35.1, 87.2)	(16.7, 76.6)	(26.6, 78.7)	(24.5, 91.5)	(29.9, 92.5)
Grade 1	3 (20.0)	7 (63.6)	3 (33.3)	5 (35.7)	7 (50.0)	5 (45.5)	1 (6.7)	3 (37.5)	1 (11.1)
Grade 2	3 (20.0)	0	2 (22.2)	1 (7.1)	1 (7.1)	0	5 (33.3)	1 (12.5)	3 (33.3)
Grade 3	1 (6.7)	0	0	1 (7.1)	1 (7.1)	0	1 (6.7)	1 (12.5)	2 (22.2)
Grade 4	0	0	0	0	0	0	1 (6.7)	0	0

Abbreviation: CI = confidence interval.
Notes: N = Number of participants in Solicited Safety Set.
N1 = Number of participants in the Solicited Safety Set who submitted any data for the event.
n = Number of participants in N1 reporting the event.
% = n/N1 × 100.
95% confidence intervals for the percentages are computed using the Clopper-Pearson method.
Participants are counted once based on the highest grade reported for each solicited symptom.
Source: Table 14.3.1.1.4.

Ref Table 7, CSR

The most common solicited local AR was "tenderness at injection site". Further, "groin or underarm gland swelling or tenderness", "swelling", and "erythema" were observed with a tendency to more severe reports for the 30µg-dose.

Solicited systemic ADRs

Table 4 ***Summary of Solicited Systemic Adverse Reactions Through 7***

Solicited Adverse Reactions Category Grade	Placebo			mRNA-1345 15 µg			mRNA-1345 30 µg		
	First Injection	Second Injection	Third Injection	First Injection	Second Injection	Third Injection	First Injection	Second Injection	Third Injection
	(N=15) n (%)	(N=11) n (%)	(N=10) n (%)	(N=15) n (%)	(N=14) n (%)	(N=11) n (%)	(N=15) n (%)	(N=12) n (%)	(N=10) n (%)
Solicited systemic adverse reactions - N1	15	11	9	14	14	11	15	8	9
Any solicited systemic adverse reactions	5 (33.3)	6 (54.5)	3 (33.3)	7 (50.0)	7 (50.0)	4 (36.4)	8 (53.3)	1 (12.5)	4 (44.4)
95% CI	(11.8, 61.6)	(23.4, 83.3)	(7.5, 70.1)	(23.0, 77.0)	(23.0, 77.0)	(10.9, 69.2)	(26.6, 78.7)	(0.3, 52.7)	(13.7, 78.8)
Grade 1	3 (20.0)	6 (54.5)	1 (11.1)	5 (35.7)	7 (50.0)	4 (36.4)	3 (20.0)	0	2 (22.2)
Grade 2	2 (13.3)	0	2 (22.2)	1 (7.1)	0	0	4 (26.7)	1 (12.5)	1 (11.1)
Grade 3	0	0	0	1 (7.1)	0	0	0	0	1 (11.1)
Grade 4	0	0	0	0	0	0	1 (6.7)	0	0
Fever - N1	15	11	9	14	14	11	15	8	9
Any	1 (6.7)	0	1 (11.1)	3 (21.4)	2 (14.3)	0	4 (26.7)	0	2 (22.2)
Grade 1	0	0	0	1 (7.1)	2 (14.3)	0	1 (6.7)	0	1 (11.1)
Grade 2	1 (6.7)	0	1 (11.1)	2 (14.3)	0	0	2 (13.3)	0	1 (11.1)
Grade 3	0	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	1 (6.7)	0	0
Irritability/Crying - N1	15	11	9	14	14	11	15	7	9
Any	4 (26.7)	5 (45.5)	2 (22.2)	6 (42.9)	4 (28.6)	4 (36.4)	6 (40.0)	1 (14.3)	2 (22.2)
Grade 1	2 (13.3)	5 (45.5)	1 (11.1)	4 (28.6)	4 (28.6)	4 (36.4)	3 (20.0)	0	1 (11.1)
Grade 2	2 (13.3)	0	1 (11.1)	1 (7.1)	0	0	3 (20.0)	1 (14.3)	0
Grade 3	0	0	0	1 (7.1)	0	0	0	0	1 (11.1)
Loss of appetite - N1	15	11	9	14	14	11	15	7	9
Any	3 (20.0)	0	1 (11.1)	1 (7.1)	3 (21.4)	0	5 (33.3)	1 (14.3)	2 (22.2)
Grade 1	3 (20.0)	0	0	1 (7.1)	3 (21.4)	0	4 (26.7)	1 (14.3)	2 (22.2)
Grade 3	0	0	1 (11.1)	0	0	0	1 (6.7)	0	0
Grade 4	0	0	0	0	0	0	0	0	0
Sleepiness - N1	15	11	9	14	14	11	15	7	9
Any	1 (6.7)	3 (27.3)	0	2 (14.3)	1 (7.1)	1 (9.1)	5 (33.3)	1 (14.3)	1 (11.1)
Grade 1	1 (6.7)	3 (27.3)	0	1 (7.1)	1 (7.1)	1 (9.1)	5 (33.3)	1 (14.3)	1 (11.1)
Grade 3	0	0	0	1 (7.1)	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0	0

Notes: N = Number of participants in Solicited Safety Set.
N1 = Number of participants in the Solicited Safety Set who submitted any data for the event.
n = Number of participants in N1 reporting the event.
% = n/N1 × 100.
95% confidence intervals for the percentages are computed using the Clopper-Pearson method.
Participants are counted once based on the highest grade reported for each solicited symptom.
Source: Table 14.3.1.1.4.

Ref Table 10, CSR

Solicited systemic ARs up to 7 days after injection were reported: for 7/14 (50.0%), 7/14 (50.0%), and 4/11 (36.4%) participants in the 15 µg group after the first, second, and third injections, respectively; for 8/15 (53.3%), 1/8 (12.5%), and 4/9 (44.4%) participants in the 30 µg group after the first, second, and third injections, respectively; and for 5/15 (33.3%), 6/11 (54.5%), and 3/9 (3.3%) participants in the placebo group after the first, second, and third injections, respectively

One Grade 3 AR was irritability/crying, reported for 1/14 participant in the 15 µg group after the first injection and 1/9 in the 30 µg group after the third injection.

One Grade 4 event of fever was reported by 1/15 participant in the mRNA-1345 30 µg group, leading to discontinuation (see below).

The most common solicited systemic ARs was irritability/crying, others were loss of appetite, sleepiness, and fever.

The most relevant report is a Grade 4 event of fever reported for 1 participant in the 30 µg group after the first injection, as described below:

- 1 participant with past medical history of recent bilateral otitis media and pneumonia (Day -24 to Day -15 that was treated with amoxicillin) and intermittent rhinorrhea (ongoing at Day 1), received the study investigational product IM on 21 Sep 2021 (Day 1) at 12:00 PM. About 7 hours later, the participant had a body temperature of 100.3°F and received paracetamol (5 mL). The following day, on 22 Sep 2021 (Day 2), around 4:15AM, her body temperature was 105.7°F, which was re-checked a few minutes later, and reported to be 104.7°F. She received paracetamol (5 mL), and 30 minutes later, her body temperature was reported at 102.5°F. A temperature check done 2 hours later showed her to be afebrile. The participant continued receiving paracetamol every 4 hours that same day (22 Sep 2021 [Day 2]). Medical attention was not sought by the parents. The participant remained afebrile on Days 3 to 7 (temperature: 98.5°F to 98.8°F) postinjection. The parents reported this clinical information in the clinical trial eDiary, and the site contacted the parents after receiving a standard alert for high fever above 102.1°F (≥Grade 3 fever). Further IP dosing was discontinued after the event, but the participant remained in the study until completion (Day 457)

This solicited systemic Grade 4 AR, considered causally related to study injection, led to a study pause and was assessed by the DSMB. The DSMB conducted an unblinded safety review and following the safety review, no safety concerns were identified, and the study reopened to enrollment.

Unsolicited Adverse Reactions (ADRs) throughout the study

Throughout the study (from first injection through EOS), the overall incidence of TEAEs was 11/15 (73.3%) participants with 48 TEAEs in the mRNA-1345 15 µg group, 7/15 (46.7%) participants with 23 TEAEs in the 30 µg group, and 9/15 (60.0%) participants with 52 TEAEs in the placebo group (for details, refer to Table 15).

Table 5 ***Summary of Unsolicited Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Throughout the Study***

Overall	3-dose			
System Organ Class Preferred Term	Placebo (N=15) n (%)	mRNA-1345 15 µg (N=15) n (%)	mRNA-1345 30 µg (N=15) n (%)	mRNA-1345 Total (N=30) n (%)
Number of unsolicited adverse events	52	48	23	71
Number of participants reporting unsolicited TEAEs	9 (60.0)	11 (73.3)	7 (46.7)	18 (60.0)

Ref Table 15 (detail), CSR

Table 6 ***Overall Summary of Unsolicited Treatment-Emergent Adverse Events Throughout the Study by Treatment Arm***

Overall	Placebo (N=15) n (%)	mRNA-1345 15 ug (N=15) n (%)	mRNA-1345 30 ug (N=15) n (%)	mRNA-1345 Total (N=30) n (%)
Unsolicited TEAEs throughout the study, regardless of relationship to study vaccination				
All	9 (60.0)	11 (73.3)	7 (46.7)	18 (60.0)
Serious	0	0	0	0
Fatal	0	0	0	0
Medically attended	8 (53.3)	11 (73.3)	5 (33.3)	16 (53.3)
Leading to vaccination discontinuation	0	0	0	0
Leading to study discontinuation	0	0	0	0
Severe (≥Grade 3)	0	0	0	0
Nonserious[a]	9 (60.0)	11 (73.3)	7 (46.7)	18 (60.0)
Severe (≥Grade 3)[a]	0	0	0	0
At least 1 nonserious event[b]	9 (60.0)	11 (73.3)	7 (46.7)	18 (60.0)
Severe (≥Grade 3)[b]	0	0	0	0
AE of special interest	0	0	0	0

Ref Table 11 (detail), CSR

Most of the unsolicited TEAEs throughout the study were in the SOC of infections and infestations, and most of the events by PT were reported for 1 participant, only. Most events by PT were Grade 1 and none were reported as ≥Grade 3 events.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths, no serious ADRs, no AEs of Special Interest

Medically Attended Adverse Events

Table 7 ***Summary of Unsolicited Medically-Attended Treatment-Emergent Adverse Events by Preferred Term of Any Vaccination Injection Throughout the Study***

Summaries of MAAEs are provided in Table 14.3.2.2.4.2 of the CSR regarding relation to respective vaccinations.

Overall

	3-dose			
Preferred Term	Placebo (N=15) n (%)	mRNA-1345 15 ug (N=15) n (%)	mRNA-1345 30 ug (N=15) n (%)	mRNA-1345 Total (N=30) n (%)
Number of unsolicited medically-attended adverse events	48	40	11	51
Number of participants reporting unsolicited medically-attended treatment-emergent adverse events	8 (53.3)	11 (73.3)	5 (33.3)	16 (53.3)

After 1st Injection

Preferred Term	3-dose Placebo (N=15) n (%)	3-dose mRNA-1345 15 ug (N=15) n (%)	3-dose mRNA-1345 30 ug (N=15) n (%)	3-dose mRNA-1345 Total (N=30) n (%)
Number of unsolicited medically-attended adverse events	19	24	2	26
Number of participants reporting unsolicited medically-attended treatment-emergent adverse events	6 (40.0)	6 (40.0)	2 (13.3)	8 (26.7)

After 2nd Injection

Preferred Term	3-dose Placebo (N=11) n (%)	3-dose mRNA-1345 15 ug (N=14) n (%)	3-dose mRNA-1345 30 ug (N=12) n (%)	3-dose mRNA-1345 Total (N=26) n (%)
Number of unsolicited medically-attended adverse events	5	5	3	8
Number of participants reporting unsolicited medically-attended treatment-emergent adverse events	2 (18.2)	3 (21.4)	3 (25.0)	6 (23.1)

After 3rd Injection

Preferred Term	3-dose Placebo (N=10) n (%)	3-dose mRNA-1345 15 ug (N=11) n (%)	3-dose mRNA-1345 30 ug (N=10) n (%)	3-dose mRNA-1345 Total (N=21) n (%)
Number of unsolicited medically-attended adverse events	24	11	6	17
Number of participants reporting unsolicited medically-attended treatment-emergent adverse events	6 (60.0)	6 (54.5)	2 (20.0)	8 (38.1)

Ref Table 14.3.2.2.4.2 (detail), CSR

Except for the MAAE of vomiting reported after the first injection in the 15µg group, all other MAAEs were reported as unrelated to treatment.

Medically Attended RSV Infections in Placebo Group

3 MAAEs of RSV infection were reported in 3 separate participants, all in the placebo group.

Diagnoses of the 3 RSV infections in the placebo group were by mid-turbinate swab only and not CLIA certified or validated study testing.

Case 1: 1 participant, Cohort 5 Placebo Group

Event: The participant reported a moderate RSV infection on Study Day 3.

Course: Treatments included prednisone and salbutamol. The condition was medically attended and classified as nonserious. The participant recovered on Study Day 13.

Additional Information: The participant tested positive for parainfluenza virus AB during a clinic visit several months later

Status: The participant completed the study on Study Day 470 (17 Nov 2022).

Case 2: 1 participant, Cohort 5 Placebo Group

Event: The participant reported a moderate RSV infection on Study Day 48 (Day 12 relative to most recent dose). Site was verbally informed via phone call that RSV was diagnosed by his medical doctor at an external clinic.

Course: No treatment was reported. The condition was nonserious and the participant recovered on Study Day 55.

Status: The participant was discontinued from the study by the Sponsor on Study Day 113 (16 Nov 2021) due to "RSV titers identified [low] at the start of the study."

Case 3: 1 participant, Cohort 6 Placebo Group

Event: This participant reported a mild RSV infection beginning on Study Day 117 (Day 57 relative to most recent dose.

Course: No specific treatment was reported. The infection was classified as nonserious and medically attended. The participant recovered on Day 134.

Status: The participant completed the study on Study Day 561 (27 Feb 2024). The participant had a history of asthma, tympanostomy, adenoidectomy, perennial allergic rhinitis, otitis, media. Multiple additional respiratory AEs were reported throughout the study.

2.3.3. Discussion on clinical aspects

This current P46-procedure covers two paediatric cohorts of Clinical study mRNA- 1345-P101. Overall 46 participants were RSV-seropositive children aged 17 to 59 months, and received 30µg (Cohort 5), 15µg (Cohort 6), or placebo. All participants received a 3-dose injection series administered 56 days apart.

Immunogenicity was assessed by measuring serum nAbs against RSV-A and RSV-B, and bAb titers against the RSV-F protein (both preF and postF conformations). Immunogenicity Results are considered to meet the expectations as presented. With regard to the context of a P46 procedures, no open issues have been identified.

Safety addressed Solicited local and systemic ARs through 7 days after each injection, Unsolicited AEs through 28 days, and SAEs and MAAEs throughout the entire study period.

Frequency and severity of solicited local reactions are within the scope of similar vaccines in this age-group. Reactogenicity of 30µg is higher than the 15-µg-dose. Reactogenicity of 1st versus 2nd versus 3rd injection increases for the 30µg dose. The profile of local ARs was as expected.

Solicited systemic ARs show increased reactogenicity (frequency and severity) for the 30µg-dose compared with 15µg and placebo. This observation regards overall frequencies, but also severity for the observed reports.

The most relevant report is a Grade 4 fever after 1st vaccination "which led to study vaccination discontinuation", a study pause, and the decision to decrease the dosage to 15µg for the next cohort instead of increasing it (up to 100µg). The participant was discontinued from vaccination but remained in the study until completion. As the participant remained in the study without further dosing, this report is not reflected in the "study discontinuations due to a safety issue". This is correct for formal reasons, but hides potentially significant information on reactogenicity for the respective age-group and the respective dosage. The MAH is asked to rephrase this case in future reports of this study as "discontinued from vaccinations" to avoid misunderstandings.

Frequency and profile of unsolicited TAEs does not show a signal regarding PT, SOC, or dosage.

Overall, participant numbers are too low for allowing any generalized conclusion.

No deaths, no serious ADRs, no AEs of Special Interest have been reported.

Regarding MAAEs no signs of special interest have been described.

RSV-Infections have been documented throughout the study. However, all infections were reported in the Placebo-group. Of note, a clinical hold regarding potential enhancement of RSV infections especially in 4-8mo old infants is ongoing. Concerned is Clinical Study mRNA-1365-P101 Pediatric RSV/hMPV. However, for the herein discussed P46 procedure no implications for the SmPC are to be considered, currently.

3. CHMP's overall conclusion and recommendation

This current P46-procedure covers two paediatric cohorts of Clinical Study mRNA- 1345-P101. Overall 46 participants were RSV-seropositive children aged 17 to 59 months, and received 30µg (Cohort 5), 15µg (Cohort 6), or placebo. All participants received a 3-dose injection series administered 56 days apart.

Immunogenicity was assessed by measuring serum nAbs against RSV-A and RSV-B, and bAb titers against the RSV-F protein (both preF and postF conformations). Safety addressed Solicited local and systemic ARs through 7 days after each injection, Unsolicited AEs through 28 days, and SAEs and MAAEs throughout the entire study period.

RSV-Infections have been documented throughout the study. All documented infections were reported in the placebo-group.
Of note, a clinical hold regarding potential enhancement of RSV infections especially in 4-8mo old infants is ongoing. Concerned is Clinical Study mRNA-1365-P101 Pediatric RSV/hMPV.

Overall, based upon the submitted data, no amendment of the SmPC is considered to be necessary.

☒ Fulfilled:

No regulatory action required.