

RESPONSE TO CBER COMMUNICATION REGARDING ADVERSE EVENTS
RECEIVED ON DECEMBER 05, 2020 (EUA 27073 IR#7)

The Sponsor acknowledges CBER's communication regarding Adverse events.

This document provides the Sponsor's responses to CBER's requests (in **Bold**).

Item 1:

Please provide Overall Summary Tables for Rates of Solicited AEs by Baseline Serostatus, and Grade within 7 days after each dose (for review purposes) in two separate tables based on age. [Source Tables 14.3.1.1.7 and 14.3.1.1.8 submitted as part of EUA data Extraction: 11Nov2020.]

- **Frequency Sol AEs (local and systemic) by baseline status and grade, -1st dose, - 2nd dose within 7 days after each dose in 18-64 years**
 - **Table 1: seronegative at baseline**
 - **Table 2: seropositive at baseline**
- **Frequency Sol AEs (local and systemic) by baseline status and grade, -1st dose, 2nd dose within 7 days after each dose in ≥ 65 years of age**
 - **Table 3: seronegative at baseline**
 - **Table 4: seropositive at baseline**

Sponsor Response:

The Sponsor acknowledges that the request is to provide overall summary tables for rates of solicited adverse reactions by baseline SARS-COV-2 status, grade, dose and age group. Given that only a very small proportion of participants have baseline positive SARS-COV-2 [overall: 675/30350 (2.2%); 18-64 years of age: 607/22830 (2.7%); and ≥ 65 years: 68/7520 (0.9%), in Safety Set, source Table 14.1.3.2.2], two sets of tables are provided below: [Table 1.1](#) by age group (18-64 years, ≥ 65 years), grade and dose [source Table 14.3.1.1.4 and Table 14.3.1.1.5]; and [Table 1.2](#) by baseline SARS-COV-2 status (Negative, Positive), grade and dose [source Table 14.3.1.1.7, Table 14.3.1.1.8].

Table 1.1 Frequency of Solicited Adverse Reactions (local and systemic) by Age Group (18-64 years, ≥65 years) and Grade, -1st dose, -2nd dose within 7 days after each dose, Solicited Safety Set*

Age Group: 18-64 years of age [Source Table 14.3.1.1.4, Table 14.3.1.1.5]

	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Solicited Adverse Reaction				
Any	10262/11405 (90.0)	5736/11406 (50.3)	9664/10358 (93.3)	4648/10321 (45.0)
Grade 3 or 4	709/11405 (6.2)	276/11406 (2.4)	2216/10358 (21.4)	249/10321 (2.4)
-Local	9960/11401 (87.4)	2432/11404 (21.3)	9371/10357 (90.5)	2134/10317 (20.7)
Grade 3 or 4	452/11401 (4.0)	39/11404 (0.3)	766/10357 (7.4)	41/10317 (0.4)
Pain^a	9908/11401 (86.9)	2179/11404 (19.1)	9335/10357 (90.1)	1942/10317 (18.8)
Grade 3 or 4	367/11401 (3.2)	23/11404 (0.2)	479/10357 (4.6)	21/10317 (0.2)
Erythema^b (Redness)	345/11401 (3.0)	46/11404 (0.4)	928/10357 (9.0)	42/10317 (0.4)
Grade 3 or 4	34/11401 (0.3)	11/11404 (<0.1)	206/10357 (2.0)	12/10317 (0.1)
Swelling^b (Hardness)	768/11401 (6.7)	33/11404 (0.3)	1309/10357 (12.6)	35/10317 (0.3)
Grade 3 or 4	62/11401 (0.5)	3/11404 (<0.1)	176/10357 (1.7)	4/10317 (<0.1)
Lymphadenopathy^c	1322/11401 (11.6)	567/11404 (5.0)	1654/10357 (16.0)	444/10317 (4.3)
Grade 3 or 4	36/11401 (0.3)	13/11404 (0.1)	45/10357 (0.4)	10/10317 (<0.1)
-Systemic	6503/11405 (57.0)	5063/11406 (44.4)	8484/10358 (81.9)	3967/10320 (38.4)
Grade 3 or 4	368/11405 (3.2)	252/11406 (2.2)	1811/10358 (17.5)	217/10320 (2.1)
Fever	105/11403 (0.9)	39/11404 (0.3)	1806/10352 (17.4)	38/10315 (0.4)
Grade 3 or 4	14/11403 (0.1)	5/11404 (<0.1)	178/10352 (1.7)	3/10315 (<0.1)
Headache	4031/11401 (35.4)	3303/11404 (29.0)	6500/10357 (62.8)	2617/10317 (25.4)
Grade 3 or 4	219/11401 (1.9)	162/11404 (1.4)	515/10357 (5.0)	124/10317 (1.2)
Fatigue	4384/11401 (38.5)	3282/11404 (28.8)	7002/10357 (67.6)	2530/10315 (24.5)
Grade 3 or 4	121/11401 (1.1)	83/11404 (0.7)	1099/10357 (10.6)	81/10315 (0.8)
Myalgia	2698/11401 (23.7)	1626/11404 (14.3)	6353/10357	1312/10316

	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Solicited Adverse Reaction				
			(61.3)	(12.7)
Grade 3 or 4	73/11401 (0.6)	38/11404 (0.3)	1032/10357 (10.0)	39/10316 (0.4)
Arthralgia	1892/11401 (16.6)	1327/11404 (11.6)	4685/10357 (45.2)	1087/10315 (10.5)
Grade 3 or 4	48/11401 (0.4)	29/11404 (0.3)	603/10357 (5.8)	36/10315 (0.3)
Nausea/Vomiting	1069/11401 (9.4)	908/11404 (8.0)	2209/10357 (21.3)	754/10315 (7.3)
Grade 3 or 4	6/11401 (<0.1)	8/11404 (<0.1)	8/10357 (<0.1)	8/10315 (<0.1)
Chills	1051/11401 (9.2)	730/11404 (6.4)	5001/10357 (48.3)	611/10315 (5.9)
Grade 3 or 4	17/11401 (0.1)	8/11404 (<0.1)	151/10357 (1.5)	14/10315 (0.1)

Age Group: ≥65 years of age [Source Table 14.3.1.1.4, Table 14.3.1.1.5]

	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Solicited Adverse Reaction				
Any	3058/3762 (81.3)	1546/3748 (41.2)	3213/3589 (89.5)	1294/3549 (36.5)
Grade 3 or 4	144/3762 (3.8)	92/3748 (2.5)	522/3589 (14.5)	85/3549 (2.4)
-Local	2805/3762 (74.6)	566/3746 (15.1)	3010/3587 (83.9)	473/3549 (13.3)
Grade 3 or 4	77/3762 (2.0)	39/3746 (1.0)	212/3587 (5.9)	29/3549 (0.8)
Pain^a	2782/3762 (74.0)	481/3746 (12.8)	2990/3587 (83.4)	421/3549 (11.9)
Grade 3 or 4	50/3762 (1.3)	32/3746 (0.9)	96/3587 (2.7)	17/3549 (0.5)
Erythema^b (Redness)	86/3761 (2.3)	19/3746 (0.5)	265/3587 (7.4)	13/3549 (0.4)
Grade 3 or 4	8/3761 (0.2)	2/3746 (<0.1)	75/3587 (2.1)	3/3549 (<0.1)
Swelling^b (Hardness)	166/3761 (4.4)	19/3746 (0.5)	386/3587 (10.8)	13/3549 (0.4)
Grade 3 or 4	20/3761 (0.5)	3/3746 (<0.1)	69/3587 (1.9)	7/3549 (0.2)
Lymphadenopathy^c	231/3761 (6.1)	155/3746 (4.1)	302/3587 (8.4)	90/3549 (2.5)

	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Solicited Adverse Reaction				
Grade 3 or 4	12/3761 (0.3)	14/3746 (0.4)	21/3587 (0.6)	8/3549 (0.2)
-Systemic	1818/3761 (48.3)	1335/3748 (35.6)	2580/3589 (71.9)	1102/3549 (31.1)
Grade 3 or 4	84/3761 (2.2)	63/3748 (1.7)	389/3589 (10.8)	59/3549 (1.7)
Fever	10/3760 (0.3)	7/3748 (0.2)	366/3587 (10.2)	5/3549 (0.1)
Grade 3 or 4	1/3760 (<0.1)	3/3748 (<0.1)	19/3587 (0.5)	1/3549 (<0.1)
Headache	921/3761 (24.5)	724/3745 (19.3)	1665/3587 (46.4)	635/3549 (17.9)
Grade 3 or 4	52/3761 (1.4)	34/3745 (0.9)	107/3587 (3.0)	32/3549 (0.9)
Fatigue	1251/3761 (33.3)	851/3745 (22.7)	2094/3587 (58.4)	695/3549 (19.6)
Grade 3 or 4	30/3761 (0.8)	23/3745 (0.6)	248/3587 (6.9)	20/3549 (0.6)
Myalgia	743/3761 (19.8)	443/3745 (11.8)	1683/3587 (46.9)	385/3549 (10.8)
Grade 3 or 4	17/3761 (0.5)	9/3745 (0.2)	201/3587 (5.6)	10/3549 (0.3)
Arthralgia	618/3761 (16.4)	456/3745 (12.2)	1252/3587 (34.9)	381/3549 (10.7)
Grade 3 or 4	13/3761 (0.3)	8/3745 (0.2)	122/3587 (3.4)	7/3549 (0.2)
Nausea/Vomiting	194/3761 (5.2)	166/3745 (4.4)	425/3587 (11.8)	129/3549 (3.6)
Grade 3 or 4	4/3761 (0.1)	4/3745 (0.1)	11/3587 (0.3)	3/3549 (<0.1)
Chills	202/3761 (5.4)	148/3745 (4.0)	1099/3587 (30.6)	144/3549 (4.1)
Grade 3 or 4	7/3761 (0.2)	6/3745 (0.2)	27/3587 (0.8)	2/3549 (<0.1)

*Solicited Safety Set: all randomized participants who received ≥ 1 vaccine or control dose and contributed to any solicited adverse reaction data

Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicited adverse reactions.

n= # of participants with specified reaction.

N= number of exposed subjects who submitted any data for the event, percentages are based on n/N.

^a Pain- Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization.

^b Erythema and Swelling/Induration- Grade 3: $>100\text{mm}/>10\text{cm}$; Grade 4: necrosis/exfoliative dermatitis.

^c Lymphadenopathy defined as localized axillary swelling or tenderness ipsilateral to the vaccination arm - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization.

Table 1.2 Frequency of Solicited Adverse Reactions (local and systemic) by Baseline SARS-COV-2 status (Negative, Positive) and Grade, -1st dose, -2nd dose within 7 days after each dose, Solicited Safety Set*

Baseline SARS-COV-2 Status: Negative [Source Table 14.3.1.1.7, Table 14.3.1.1.8]

	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Solicited Adverse Reaction				
Any	12591/14301 (88.0)	6888/14356 (48.0)	12291/13286 (92.5)	5674/13252 (42.8)
Grade 3 or 4	786/14301 (5.5)	343/14356 (2.4)	2626/13286 (19.8)	319/13252 (2.4)
-Local	12080/14297 (84.5)	2830/14353 (19.7)	11821/13283 (89.0)	2473/13249 (18.7)
Grade 3 or 4	497/14297 (3.5)	71/14353 (0.5)	927/13283 (7.0)	65/13249 (0.5)
Pain^a	12013/14297 (84.0)	2507/14353 (17.5)	11770/13283 (88.6)	2242/13249 (16.9)
Grade 3 or 4	392/14297 (2.7)	50/14353 (0.3)	545/13283 (4.1)	34/13249 (0.3)
Erythema^b (Redness)	406/14296 (2.8)	60/14353 (0.4)	1152/13283 (8.7)	51/13249 (0.4)
Grade 3 or 4	40/14296 (0.3)	11/14353 (<0.1)	261/13283 (2.0)	14/13249 (0.1)
Swelling^b (Hardness)	884/14296 (6.2)	49/14353 (0.3)	1639/13283 (12.3)	47/13249 (0.4)
Grade 3 or 4	78/14296 (0.5)	6/14353 (<0.1)	232/13283 (1.7)	11/13249 (<0.1)
Lymphadenopathy^c	1445/14296 (10.1)	677/14353 (4.7)	1869/13283 (14.1)	502/13249 (3.8)
Grade 3 or 4	43/14296 (0.3)	24/14353 (0.2)	64/13283 (0.5)	18/13249 (0.1)
-Systemic	7814/14300 (54.6)	6053/14356 (42.2)	10568/13286 (79.5)	4833/13251 (36.5)
Grade 3 or 4	405/14300 (2.8)	294/14356 (2.0)	2119/13286 (15.9)	264/13251 (2.0)
Fever	78/14298 (0.5)	38/14355 (0.3)	2093/13279 (15.8)	42/13247 (0.3)
Grade 3 or 4	12/14298 (<0.1)	7/14355 (<0.1)	192/13279 (1.4)	4/13247 (<0.1)
Headache	4634/14296 (32.4)	3795/14352 (26.4)	7834/13283 (59.0)	3103/13249 (23.4)
Grade 3 or 4	242/14296 (1.7)	184/14352 (1.3)	592/13283 (4.5)	151/13249 (1.1)
Fatigue	5303/14296 (37.1)	3903/14352 (27.2)	8719/13283 (65.6)	3062/13247 (23.1)
Grade 3 or 4	136/14296 (1.0)	95/14352 (0.7)	1301/13283 (9.8)	94/13247 (0.7)

	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Solicited Adverse Reaction				
Myalgia	3194/14296 (22.3)	1937/14352 (13.5)	7673/13283 (57.8)	1589/13248 (12.0)
Grade 3 or 4	80/14296 (0.6)	41/14352 (0.3)	1189/13283 (9.0)	45/13248 (0.3)
Arthralgia	2337/14296 (16.3)	1671/14352 (11.6)	5680/13283 (42.8)	1382/13247 (10.4)
Grade 3 or 4	53/14296 (0.4)	34/14352 (0.2)	699/13283 (5.3)	40/13247 (0.3)
Nausea/Vomiting	1170/14296 (8.2)	1012/14352 (7.1)	2518/13283 (19.0)	841/13247 (6.3)
Grade 3 or 4	8/14296 (<0.1)	12/14352 (<0.1)	18/13283 (0.1)	10/13247 (<0.1)
Chills	1124/14296 (7.9)	822/14352 (5.7)	5850/13283 (44.0)	712/13247 (5.4)
Grade 3 or 4	20/14296 (0.1)	13/14352 (<0.1)	174/13283 (1.3)	15/13247 (0.1)

Baseline SARS-COV-2 Status: Positive [Source Table 14.3.1.1.7, Table 14.3.1.1.8]

	Vaccine Group Dose 1 n/N (%)	Placebo Group Dose 1 n/N (%)	Vaccine Group Dose 2 n/N (%)	Placebo Group Dose 2 n/N (%)
Solicited Adverse Reaction				
Any	259/340 (76.2)	134/334 (40.1)	164/203 (80.8)	74/213 (34.7)
Grade 3 or 4	28/340 (8.2)	14/334 (4.2)	27/203 (13.3)	3/213 (1.4)
-Local	244/340 (71.8)	58/334 (17.4)	151/203 (74.4)	37/212 (17.5)
Grade 3 or 4	13/340 (3.8)	3/334 (0.9)	12/203 (5.9)	2/212 (0.9)
Pain^a	242/340 (71.2)	54/334 (16.2)	148/203 (72.9)	31/212 (14.6)
Grade 3 or 4	10/340 (2.9)	1/334 (0.3)	8/203 (3.9)	1/212 (0.5)
Erythema^b (Redness)	9/340 (2.6)	3/334 (0.9)	8/203 (3.9)	1/212 (0.5)
Grade 3 or 4	2/340 (0.6)	2/334 (0.6)	3/203 (1.5)	1/212 (0.5)
Swelling^b (Hardness)	20/340 (5.9)	2/334 (0.6)	10/203 (4.9)	1/212 (0.5)
Grade 3 or 4	1/340 (0.3)	0/334	2/203 (1.0)	0/212
Lymphadenopathy^c	52/340 (15.3)	16/334 (4.8)	27/203 (13.3)	10/212 (4.7)

Grade 3 or 4	4/340 (1.2)	1/334 (0.3)	2/203 (1.0)	0/212
-Systemic	208/340 (61.2)	118/334 (35.3)	135/203 (66.5)	66/213 (31.0)
Grade 3 or 4	22/340 (6.5)	12/334 (3.6)	19/203 (9.4)	1/213 (0.5)
Fever	31/340 (9.1)	6/333 (1.8)	27/203 (13.3)	1/212 (0.5)
Grade 3 or 4	3/340 (0.9)	1/333 (0.3)	2/203 (1.0)	0/212
Headache	129/340 (37.9)	79/334 (23.7)	88/203 (43.3)	40/212 (18.9)
Grade 3 or 4	11/340 (3.2)	7/334 (2.1)	5/203 (2.5)	0/212
Fatigue	132/340 (38.8)	70/334 (21.0)	92/203 (45.3)	49/212 (23.1)
Grade 3 or 4	9/340 (2.6)	4/334 (1.2)	11/203 (5.4)	1/212 (0.5)
Myalgia	122/340 (35.9)	46/334 (13.8)	101/203 (49.8)	29/212 (13.7)
Grade 3 or 4	6/340 (1.8)	2/334 (0.6)	10/203 (4.9)	0/212
Arthralgia	85/340 (25.0)	38/334 (11.4)	66/203 (32.5)	21/212 (9.9)
Grade 3 or 4	5/340 (1.5)	2/334 (0.6)	3/203 (1.5)	0/212
Nausea/Vomiting	40/340 (11.8)	25/334 (7.5)	32/203 (15.8)	11/212 (5.2)
Grade 3 or 4	0/340	0/334	0/203	0/212
Chills	80/340 (23.5)	26/334 (7.8)	69/203 (34.0)	14/212 (6.6)
Grade 3 or 4	3/340 (0.9)	1/334 (0.3)	0/203	0/212

*Solicited Safety Set: all randomized participants who received ≥ 1 vaccine or control dose and contributed to any solicited adverse reaction data

Note: Adverse reaction data were collected on the electronic diary (e-Diary) by participants and those collected on the eCRF indicated as solicited adverse reactions.

n= # of participants with specified reaction.

N= number of exposed subjects who submitted any data for the event, percentages are based on n/N.

^a Pain- Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization.

^b Erythema and Swelling/Induration- Grade 3: $>100\text{mm}/>10\text{cm}$; Grade 4: necrosis/exfoliative dermatitis.

^c Lymphadenopathy defined as localized axillary swelling or tenderness ipsilateral to the vaccination arm - Grade 3: any use of Rx pain reliever/prevents daily activity; Grade 4: requires E.R. visit or hospitalization.

Item 2:

Please also provide an overall table providing the duration of solicited AEs based on source Tables 14.3.1.4.4 –and 14.3.1.4.5

Sponsor Response:

As requested, the overall summary table for the duration (median in days) of solicited adverse reactions by age group and dose is provided in [Table 2.1](#) below based on source Table 14.3.1.4.4 and Table 14.3.1.4.5.

Table 2.1 Duration of Solicited Adverse Reactions - Median # Days, by Age Group (18-64 years, ≥65 years), -1st dose, -2nd dose within 7 days after each dose, Solicited Safety Set*

Age Group: 18-64 years of age [Source Table 14.3.1.4.4, Table 14.3.1.4.5]

Solicited Adverse Reaction	Vaccine Group Dose 1 Median # Days	Placebo Group Dose 1 Median # Days	Vaccine Group Dose 2 Median # Days	Placebo Group Dose 2 Median # Days
Any	3	2	3	2
-Local	2	1	3	1
Pain	2	1	3	1
Erythema (Redness)	2	1	2	1
Swelling (Hardness)	2	1	2	1
Lymphadenopathy[1]	1	1	2	1
-Systemic	2	2	2	2
Fever	1	1	1	1
Headache	1	1	2	1
Fatigue	2	2	2	2
Myalgia	1	1	2	2
Arthralgia	1	2	1	2
Nausea/Vomiting	1	1	1	1
Chills	1	1	1	1

Age Group: ≥65 years of age [Source Table 14.3.1.4.4, Table 14.3.1.4.5]

Solicited Adverse Reaction	Vaccine Group Dose 1 Median # Days	Placebo Group Dose 1 Median # Days	Vaccine Group Dose 2 Median # Days	Placebo Group Dose 2 Median # Days
Any	2	2	3	2
-Local	2	1	3	1
Pain	2	1	3	1
Erythema (Redness)	2	1	2	1
Swelling (Hardness)	1	2	2	1
Lymphadenopathy[1]	1	1	1	1
-Systemic	2	2	2	2
Fever	1	1	1	2
Headache	1	1	1	1
Fatigue	2	2	2	2
Myalgia	1	1	1	2
Arthralgia	1	2	1	2
Nausea/Vomiting	1	1	1	1
Chills	1	1	1	1

*Solicited Safety Set: all randomized participants who received ≥1 vaccine or control dose and contributed to any solicited adverse reaction data

[1] Lymphadenopathy: Localized axillary swelling or tenderness ipsilateral to the vaccination arm.

n = Number of exposed subjects who reported the event on any day within 7 days of the first injection. Number of days is calculated as the days of the solicited adverse reaction reported within the 7 days of injection including the day of injection. If the solicited AR continues beyond 7 days, the consecutive days a solicited adverse reaction is reported after 7 days are included.