COMIRNATY™ COVID-19 mRNA Vaccine (BNT162b2)

1. NAME OF THE MEDICINAL PRODUCT

COMIRNATY™ COVID-19 mRNA Vaccine (BNT162b2) concentrate for dispersion for injection

(hereinafter referred to as “COMIRNATY”)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This is a multidose vial and must be diluted before use.
One vial (0.45 mL) contains 6 doses of 0.3mL after dilution, see sections 4.2 and 6.6.

1 dose (0.3 mL) contains 30 micrograms of COVID-19 mRNA Vaccine (embedded in lipid nanoparticles).

Single-stranded, 5’-capped messenger RNA (mRNA) produced using a cell-free in vitro transcription from the corresponding DNA templates, encoding the viral spike (S) protein of SARS-CoV-2.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for dispersion for injection (sterile concentrate).
The vaccine is a white to off-white frozen dispersion (pH: 6.9-7.9).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

COMIRNATY is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2 virus, in individuals 12 years of age and older.

The use of this vaccine should be in accordance with official recommendations.

4.2 Posology and method of administration

Posology

*Individuals 12 years of age and older*

COMIRNATY is administered intramuscularly after dilution as a primary course of 2 doses (0.3 mL each). It is recommended to administer the second dose 3 weeks after the first dose (see sections 4.4 and 5.1).

A third dose of COMIRNATY may be administered intramuscularly at least 6 months after the second dose in individuals 18 years of age and older. The decision when and for whom to implement a third dose of COMIRNATY should be made based on available vaccine effectiveness data, taking into account limited safety data (see sections 4.4 and 5.1).

The interchangeability of COMIRNATY with other COVID-19 vaccines from other manufacturers to complete the primary vaccination course or the third dose has not been established. Individuals who have received 1 dose of COMIRNATY should receive a second dose of COMIRNATY to complete the primary vaccination course and for any additional doses.
Severely immunocompromised aged 12 years and older
A third dose may be given at least 28 days after the second dose to individuals who are severely immunocompromised (see section 4.4).

Paediatric population
The safety and efficacy of COMIRNATY in paediatric participants aged less than 12 years have not yet been established. Limited data are available.

Elderly population
No dosage adjustment is required in elderly individuals ≥ 65 years of age. The safety and immunogenicity of a third dose of COMIRNATY in individuals 65 years of age and older is based on safety and immunogenicity data in adults 18 to 55 years of age.

Method of administration
COMIRNATY should be administered intramuscularly after dilution (see section 6.6).

After dilution, vials of COMIRNATY contain six doses of 0.3 mL of vaccine. In order to extract six doses from a single vial, low dead-volume syringes and/or needles should be used. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres. If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial. Irrespective of the type of syringe and needle:

- Each dose must contain 0.3 mL of vaccine.
- If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.
- Do not pool excess vaccine from multiple vials.

The preferred site is the deltoid muscle of the upper arm.

Do not inject the vaccine intravascularly, subcutaneously or intradermally.

The vaccine should not be mixed in the same syringe with any other vaccines or medicinal products.

For precautions to be taken before administering the vaccine, see section 4.4.

For instructions regarding thawing, handling and disposal of the vaccine, see section 6.6.

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

General recommendations

Hypersensitivity and anaphylaxis
Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always
be readily available in case of an anaphylactic reaction following the administration of the vaccine.

Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of COMIRNATY.

**Myocarditis and pericarditis**

There is an increased risk of myocarditis and pericarditis following vaccination with COMIRNATY. These conditions can develop within just a few days after vaccination, and have primarily occurred within 14 days. They have been observed more often after the second vaccination, and more often in younger males (see section 4.8). Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.

Healthcare professionals should be alert to the signs and symptoms of myocarditis and pericarditis. Vaccinees (including parents or caregivers) should be instructed to seek immediate medical attention if they develop symptoms indicative of myocarditis or pericarditis such as (acute and persisting) chest pain, shortness of breath, or palpitations following vaccination.

Healthcare professionals should consult guidance and/or specialists to diagnose and treat this condition.

The risk of myocarditis after a third dose of COMIRNATY has not yet been characterized.

**Anxiety-related reactions**

Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, paraesthesia, hypoaesthesia and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.

**Concurrent illness**

Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.

**Thrombocytopenia and coagulation disorders**

As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.

**Immunocompromised individuals**

The efficacy and safety of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of COMIRNATY may be lower in immunocompromised individuals.

The recommendation to consider a third dose in severely immunocompromised individuals is based on limited serological evidence from a case-series in the literature from the clinical management of patients with iatrogenic immunocompromisation after solid organ transplantation (see section 4.2).

**Duration of protection**

The duration of protection afforded by the vaccine is unknown as it is still being determined by ongoing clinical trials.

**Limitations of vaccine effectiveness**

As with any vaccine, vaccination with COMIRNATY may not protect all vaccine recipients. Individuals may not be fully protected until 7 days after their second dose of vaccine.
Excipients:
This vaccine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially ‘potassium-free’.
This vaccine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction
No interaction studies have been performed.
Concomitant administration of COMIRNATY with other vaccines has not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited experience with use of COMIRNATY in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development (see section 5.3). Administration of COMIRNATY in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.

Breast-feeding
It is unknown whether COMIRNATY is excreted in human milk.

Fertility
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines
COMIRNATY has no or negligible influence on the ability to drive and use machines. However, some of the effects mentioned under section 4.8 may temporarily affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of safety profile
The safety of COMIRNATY was evaluated in participants 12 years of age and older in 2 clinical studies that included 23,205 participants (comprised of 22,074 participants 16 years of age and older and 1,131 adolescents 12 to 15 years of age) that have received at least one dose of COMIRNATY.

The overall safety profile of COMIRNATY in adolescents 12 to 15 years of age was similar to that seen in participants 16 years of age and older.

Additionally, 306 existing Phase 3 participants 18 to 55 years of age received a third dose of COMIRNATY approximately 6 months after the second dose. The overall safety profile for the third dose was similar to that seen after 2 doses.

Participants 16 years of age and older – after 2 doses
In Study 2, a total of 22,026 participants 16 years of age or older received at least 1 dose of COMIRNATY and a total of 22,021 participants 16 years of age or older received placebo (including 138 and 145 adolescents 16 and 17 years of age in the vaccine and placebo groups, respectively). A total of 20,519 participants 16 years of age or older received 2 doses of COMIRNATY.

At the time of the analysis of Study 2 with a data cut-off of 13 March 2021 for the placebo-controlled blinded follow-up period up to the participants’ unblinding dates, a total of 25,651 (58.2%) participants (13,031 COMIRNATY and 12,620 placebo) 16 years of age or older were followed up for ≥ 4 months after the second dose. This included a total of 15,111 (7,704 COMIRNATY and 7,407 placebo) participants 16 to 55 years of age and a total of 10,540 (5,327 COMIRNATY and 5,213 placebo) participants 56 years of age and older.

The most frequent adverse reactions in participants 16 years of age and older that received 2 doses were injection site pain (> 80%), fatigue (> 60%), headache (> 50%), myalgia (> 40%), chills (> 30%), arthralgia (> 20%), pyrexia and injection site swelling (> 10%) and were usually mild or moderate in intensity and resolved within a few days after vaccination. A slightly lower frequency of reactogenicity events was associated with greater age.

The safety profile in 545 participants 16 years of age and older receiving COMIRNATY, that were seropositive for SARS-CoV-2 at baseline, was similar to that seen in the general population.

Adolescents 12 to 15 years of age – after 2 doses
In an analysis of Study 2, based on data up to the cutoff date of 13 March 2021, 2,260 adolescents (1,131 COMIRNATY and 1,129 placebo) were 12 to 15 years of age. Of these, 1,308 adolescents (660 COMIRNATY and 648 placebo) have been followed for at least 2 months after the second dose of COMIRNATY. The safety evaluation in Study 2 is ongoing.

The most frequent adverse reactions in adolescents 12 to 15 years of age that received 2 doses were injection site pain (> 90%), fatigue and headache (> 70%), myalgia and chills (> 40%), arthralgia and pyrexia (> 20%).

Participants 18 years of age and older – after third dose
A subset from Study 2 Phase 2/3 participants of 306 adults 18 to 55 years of age who completed the original COMIRNATY 2-dose course, received a third dose of COMIRNATY approximately 6 months (range of 4.8 to 8.0 months) after receiving Dose 2.

The most frequent adverse reactions in participants 18 to 55 years of age were injection site pain (> 80%), fatigue (> 60%), headache (> 40%), myalgia (> 30%), chills and arthralgia (> 20%).

Tabulated list of adverse reactions from clinical studies and post-authorisation experience in individuals 12 years of age and older

Adverse reactions observed during clinical studies are listed below according to the following frequency categories:

- Very common (≥ 1/10),
- Common (≥ 1/100 to < 1/10),
- Uncommon (≥ 1/1,000 to < 1/100),
- Rare (≥ 1/10,000 to < 1/1,000),
- Very rare (< 1/10,000),
- Not known (cannot be estimated from the available data).

Table 1: Adverse reactions from COMIRNATY clinical trials and post-authorisation experience in
individually 12 years of age and older

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common (≥ 1/10)</th>
<th>Common (≥ 1/100 to &lt; 1/10)</th>
<th>Uncommon (≥ 1/1,000 to &lt; 1/100)</th>
<th>Rare (≥ 1/10,000 to &lt; 1/1,000)</th>
<th>Very rare (&lt; 1/10,000)</th>
<th>Not known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Lymphadenopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Hypersensitivity reactions (e.g. rash, pruritus, urticaria, angioedema)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Lethargy</td>
<td>Acute peripheral facial paralysis</td>
<td></td>
<td></td>
<td>Paraesthesia; Hypoaesthesia</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td></td>
<td></td>
<td>Myocarditis; Pericarditis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhoea</td>
<td>Nausea; Vomiting</td>
<td></td>
<td></td>
<td></td>
<td>Erythema multiforme</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td>Hyperhidrosis; Night sweats</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia; Myalgia</td>
<td></td>
<td>Pain in extremity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Injection site pain; Fatigue; Chills; Pyrexia; Injection site swelling</td>
<td>Injection site redness</td>
<td>Asthenia; Malaise; Injection site pruritus</td>
<td></td>
<td></td>
<td>Extensive swelling of vaccinated limb; Facial swelling</td>
</tr>
</tbody>
</table>

SmPC for Hong Kong (v18), clean (last revision 26 Jan 2022)
Ref: European SmPC (20 Jan 2022)
a. A higher frequency of lymphadenopathy (5.2% vs 0.4%) was observed in participants receiving a third
dose compared to participants receiving 2 doses.
b. The frequency category for urticaria and angioedema was Rare.
c. Through the clinical trial safety follow-up period to 14 November 2020, acute peripheral facial paralysis
(or palsy) was reported by four participants in the COVID-19 mRNA Vaccine group. Onset was Day 37
after Dose 1 (participant did not receive Dose 2) and Days 3, 9, and 48 after Dose 2. No cases of acute
peripheral facial paralysis (or palsy) were reported in the placebo group.
d. Adverse reaction determined post-authorisation.
e. Refers to vaccinated arm.
f. A higher frequency of pyrexia was observed after the second dose compare to the first dose.
g. Facial swelling in vaccine recipients with a history of injection of dermatological fillers has been
reported in the post-marketing phase.

Description of selected adverse reactions

Myocarditis
The increased risk of myocarditis after vaccination with Comirnaty is highest in younger males (see section
4.4).

Two large European pharmacoepidemiological studies have estimated the excess risk in younger males
following the second dose of Comirnaty. One study showed that in a period of 7 days after the second dose
there were about 0.265 (95% CI 0.255 - 0.275) extra cases of myocarditis in 12-29 year old males per
10,000 compared to unexposed persons. In another study, in a period of 28 days after the second dose there
were 0.57 [95% CI 0.39 – 0.75] extra cases of myocarditis in 16-24 year old males per 10,000 compared to
unexposed persons.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows
continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are
asked to report any suspected adverse reactions to local regulatory authorities per local requirements and
include Batch/Lot number, if available.

Alternatively, healthcare professionals can also contact respective company representatives of local
suppliers/distributors for assistance in such reporting.

4.9 Overdose

Overdose data is available from 52 study participants included in the clinical trial that due to an error in
dilution received 58 micrograms of COMIRNATY. The vaccine recipients did not report an increase in
reactogenicity or adverse reactions.

In the event of overdose, monitoring of vital functions and possible symptomatic treatment is
recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: vaccines, other viral vaccines, ATC code: J07BX03

Mechanism of action
The nucleoside-modified messenger RNA in COMIRNATY is formulated in lipid nanoparticles, which
enable delivery of the non replicating RNA into host cells to direct transient expression of the SARS-
CoV-2 S antigen. The mRNA codes for membrane-anchored, full-length S with two point mutations within the central helix. Mutation of these two amino acids to proline locks S in an antigenically preferred prefusion conformation. The vaccine elicits both neutralizing antibody and cellular immune responses to the spike (S) antigen, which may contribute to protection against COVID-19.

**Efficacy**

Study 2 is a multicentre, multinational, Phase 1/2/3 randomised, placebo-controlled, observer-blind dose-finding, vaccine candidate selection and efficacy study in participants 12 years of age and older. Randomisation was stratified by age: 12 to 15 years of age, 16 to 55 years of age, or 56 years of age and older, with a minimum of 40% of participants in the ≥ 56-year stratum. The study excluded participants who were immunocompromised and those who had previous clinical or microbiological diagnosis of COVID-19. Participants with pre-existing stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrolment, were included as were participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV).

*Efficacy in participants 16 years of age and older – after 2 doses*

In the Phase 2/3 portion of Study 2, based on data accrued through 14 November 2020, approximately 44,000 participants were randomised equally and were to receive 2 doses of COVID-19 mRNA Vaccine or placebo. The efficacy analyses included participants that received their second vaccination within 19 to 42 days after their first vaccination. The majority (93.1%) of vaccine recipients received the second dose 19 days to 23 days after Dose 1. Participants are planned to be followed for up to 24 months after Dose 2, for assessments of safety and efficacy against COVID-19. In the clinical study, participants were required to observe a minimum interval of 14 days before and after administration of an influenza vaccine in order to receive either placebo or COVID-19 mRNA Vaccine. In the clinical study, participants were required to observe a minimum interval of 60 days before or after receipt of blood/plasma products or immunoglobulins within through conclusion of the study in order to receive either placebo or COVID-19 mRNA Vaccine.

The population for the analysis of the primary efficacy endpoint included, 36,621 participants 12 years of age and older (18,242 in the COVID-19 mRNA Vaccine group and 18,379 in the placebo group) who did not have evidence of prior infection with SARS-CoV-2 through 7 days after the second dose. In addition, 134 participants were between the ages of 16 to 17 years of age (66 in the COVID-19 mRNA Vaccine group and 68 in the placebo group) and 1,616 participants 75 years of age and older (804 in the COVID-19 mRNA Vaccine group and 812 in the placebo group).

At the time of the primary efficacy analysis, participants had been followed for symptomatic COVID-19 for in total 2,214 person-years for the COVID-19 mRNA Vaccine and in total 2,222 person-years in the placebo group.

There were no meaningful clinical differences in overall vaccine efficacy in participants who were at risk of severe COVID-19 including those with 1 or more comorbidities that increase the risk of severe COVID-19 (e.g. asthma, body mass index (BMI) $\geq 30$ kg/m$^2$, chronic pulmonary disease, diabetes mellitus, hypertension).

The vaccine efficacy information is presented in Table 2.
Table 2: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of infection prior to 7 days after Dose 2 – evaluable efficacy (7 days) population

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>COVID-19 mRNA Vaccine N(^a) = 18,198 Cases n(^b)</th>
<th>Placebo N(^a) = 18,325 Cases n(^b)</th>
<th>Vaccine efficacy %(95% CI(^c))</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants</td>
<td>8</td>
<td>162</td>
<td>95.0 (90.0, 97.9)</td>
</tr>
<tr>
<td>16 to 64 years</td>
<td>7</td>
<td>143</td>
<td>95.1 (89.6, 98.1)</td>
</tr>
<tr>
<td>65 years and older</td>
<td>1</td>
<td>19</td>
<td>94.7 (66.7, 99.9)</td>
</tr>
<tr>
<td>65 to 74 years</td>
<td>1</td>
<td>14</td>
<td>92.9 (53.1, 99.8)</td>
</tr>
<tr>
<td>75 years and older</td>
<td>0</td>
<td>5</td>
<td>100.0 (-13.1, 100.0)</td>
</tr>
</tbody>
</table>

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 [*Case definition: (at least 1 of) fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea or vomiting.]

* Participants who had no serological or virological evidence (prior to 7 days after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by nucleic acid amplification tests (NAAT) [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = number of participants in the specified group.
b. n\(^b\) = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n\(^2\) = Number of participants at risk for the endpoint.
e. Two-sided Confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time. CI not adjusted for multiplicity.

Efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 94.6\% (95\% confidence interval of 89.6\% to 97.6\%) in participants 16 years of age and older with or without evidence of prior infection with SARS-CoV-2.

Additionally, subgroup analyses of the primary efficacy endpoint showed similar efficacy point estimates across genders, ethnic groups, and participants with medical comorbidities associated with high risk of severe COVID-19.

Updated efficacy analyses were performed with additional confirmed COVID-19 cases accrued during blinded placebo-controlled follow-up, representing up to 6 months after Dose 2 in the efficacy population.

The updated vaccine efficacy information is presented in Table 3.

SmPC for Hong Kong (v18)_clean (last revision26Jan2022)
Ref: European SmPC (20Jan2022)
Table 3: Vaccine efficacy – First COVID-19 occurrence from 7 days after Dose 2, by age subgroup – participants without evidence of prior SARS-CoV-2 infection* prior to 7 days after Dose 2 – evaluable efficacy (7 days) population during the placebo-controlled follow-up period

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>COVID-19 mRNA Vaccine</th>
<th>Placebo</th>
<th>Vaccine efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=20,998 Cases n1b</td>
<td>N=21,096 Cases n1b</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Surveillance timec (n2d)</td>
<td>Surveillance timec (n2d)</td>
<td></td>
</tr>
<tr>
<td>All participantsf</td>
<td>77</td>
<td>850</td>
<td>91.3 (89.0, 93.2)</td>
</tr>
<tr>
<td></td>
<td>6.247 (20,712)</td>
<td>6.003 (20,713)</td>
<td></td>
</tr>
<tr>
<td>16 to 64 years</td>
<td>70</td>
<td>710</td>
<td>90.6 (87.9, 92.7)</td>
</tr>
<tr>
<td></td>
<td>4.859 (15,519)</td>
<td>4.654 (15,515)</td>
<td></td>
</tr>
<tr>
<td>65 years and older</td>
<td>7</td>
<td>124</td>
<td>94.5 (88.3, 97.8)</td>
</tr>
<tr>
<td></td>
<td>1.233 (4192)</td>
<td>1.202 (4226)</td>
<td></td>
</tr>
<tr>
<td>65 to 74 years</td>
<td>6</td>
<td>98</td>
<td>94.1 (86.6, 97.9)</td>
</tr>
<tr>
<td></td>
<td>0.994 (3350)</td>
<td>0.966 (3379)</td>
<td></td>
</tr>
<tr>
<td>75 years and older</td>
<td>1</td>
<td>26</td>
<td>96.2 (76.9, 99.9)</td>
</tr>
<tr>
<td></td>
<td>0.239 (842)</td>
<td>0.237 (847)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Participants who had no evidence of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at Visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at Visits 1 and 2), and had negative NAAT (nasal swab) at any unscheduled visit prior to 7 days after Dose 2 were included in the analysis.

a. N = Number of participants in the specified group.
b. n1 = Number of participants meeting the endpoint definition.
c. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.
d. n2 = Number of participants at risk for the endpoint.
e. Two-sided 95% confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
f. Included confirmed cases in participants 12 to 15 years of age: 0 in the COVID-19 mRNA Vaccine group; 16 in the placebo group.

In the updated efficacy analysis, efficacy of COVID-19 mRNA Vaccine in preventing first COVID-19 occurrence from 7 days after Dose 2 compared to placebo was 91.1% (95% CI of 88.8% to 93.0%) in participants in the evaluable efficacy population with or without evidence of prior infection with SARS-CoV-2.

Additionally, the updated efficacy analyses by subgroup showed similar efficacy point estimates across sexes, ethnic groups, geography and participants with medical comorbidities and obesity associated with high risk of severe COVID-19.

Efficacy against severe COVID-19

Updated efficacy analyses of secondary efficacy endpoints supported benefit of the COVID-19 mRNA Vaccine in preventing severe COVID-19.

As of 13 March 2021, vaccine efficacy against severe COVID-19 is presented only for participants with or without prior SARS-CoV-2 infection (Table 4) as the COVID-19 case counts in participants without prior SARS-CoV-2 infection were the same as those in participants with or without prior SARS-CoV-2 infection in both the COVID-19 mRNA Vaccine and placebo groups.
Table 4: Vaccine efficacy – First severe COVID-19 occurrence in participants with or without prior SARS-CoV-2 infection based on the Food and Drug Administration (FDA)* after Dose 1 or from 7 days after Dose 2 in the placebo-controlled follow-up

<table>
<thead>
<tr>
<th></th>
<th>COVID-19 mRNA Vaccine Cases n1a</th>
<th>Placebo Cases n1a</th>
<th>Vaccine efficacy % (95% CI)c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surveillance time (n2b)</td>
<td>Surveillance time (n2b)</td>
<td></td>
</tr>
<tr>
<td>After Dose 1d</td>
<td>1</td>
<td>30</td>
<td>96.7 (80.3, 99.9)</td>
</tr>
<tr>
<td></td>
<td>8.439b (22,505)</td>
<td>8.288b (22,435)</td>
<td></td>
</tr>
<tr>
<td>7 days after Dose 2f</td>
<td>1</td>
<td>21</td>
<td>95.3 (70.9, 99.9)</td>
</tr>
<tr>
<td></td>
<td>6.522b (21,649)</td>
<td>6.404b (21,730)</td>
<td></td>
</tr>
</tbody>
</table>

Note: Confirmed cases were determined by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and at least 1 symptom consistent with COVID-19 (symptoms included: fever; new or increased cough; new or increased shortness of breath; chills; new or increased muscle pain; new loss of taste or smell; sore throat; diarrhoea; vomiting).

* Severe illness from COVID-19 as defined by FDA is confirmed COVID-19 and presence of at least 1 of the following:
  - Clinical signs at rest indicative of severe systemic illness (respiratory rate ≥ 30 breaths per minute, heart rate ≥ 125 beats per minute, saturation of oxygen ≤ 93% on room air at sea level, or ratio of arterial oxygen partial pressure to fractional inspired oxygen < 300 mm Hg);
  - Respiratory failure [defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)];
  - Evidence of shock (systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, or requiring vasopressors);
  - Significant acute renal, hepatic, or neurologic dysfunction;
  - Admission to an Intensive Care Unit;
  - Death.

a. n1 = Number of participants meeting the endpoint definition.
b. n2 = Number of participants at risk for the endpoint.
c. Two-side confidence interval (CI) for vaccine efficacy is derived based on the Clopper and Pearson method adjusted to the surveillance time.
d. Efficacy assessed based on the Dose 1 all available efficacy (modified intention-to-treat) population that included all randomised participants who received at least 1 dose of study intervention.
e. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from Dose 1 to the end of the surveillance period.
f. Efficacy assessed based on the evaluable efficacy (7 Days) population that included all eligible randomised participants who receive all dose(s) of study intervention as randomised within the predefined window, have no other important protocol deviations as determined by the clinician.
g. Total surveillance time in 1,000 person-years for the given endpoint across all participants within each group at risk for the endpoint. Time period for COVID-19 case accrual is from 7 days after Dose 2 to the end of the surveillance period.

**Efficacy and immunogenicity in adolescents 12 to 15 years of age – after 2 doses**

In an analysis of Study 2 in adolescents 12 to 15 years of age without evidence of prior infection, there were no cases in 1005 participants who received the vaccine and 16 cases out of 978 who received placebo. The point estimate for efficacy is 100% (95% confidence interval 75.3, 100.0). In participants with or without evidence of prior infection there were 0 cases in the 1119 who received vaccine and 18 cases in 1110 participants who received placebo. This also indicates the point estimate for efficacy is 100% (95% confidence interval 78.1, 100.0).

In Study 2, an analysis of SARS-CoV-2 neutralising titres 1 month after Dose 2 was conducted in a randomly selected subset of participants who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after Dose 2, comparing the response in adolescents 12 to 15 years of age (n = 190) to participants 16 to 25 years of age (n = 170).
The ratio of the geometric mean titres (GMT) in the 12 to 15 years of age group to the 16 to 25 years of age group was 1.76, with a 2-sided 95% CI of 1.47 to 2.10. Therefore, the 1.5-fold non-inferiority criterion was met as the lower bound of the 2-sided 95% CI for the geometric mean ratio [GMR] was > 0.67.

**Immunogenicity in participants 18 years of age and older – after third dose**

Effectiveness of a dose of COMIRNATY was based on an assessment of 50% neutralizing antibody titers (NT50) against SARS-CoV-2 (USA_WA1/2020). In Study 2, analyses of NT50 1 month after the third dose compared to 1 month after the primary series in individuals 18 through 55 years of age who had no serological or virological evidence of past SARS-CoV-2 infection up to 1 month after the third dose vaccination demonstrated noninferiority for both geometric mean ratio (GMR) and difference in seroresponse rates. Seroresponse for a participant was defined as achieving a ≥ 4-fold rise in NT50 from baseline (before primary series). These analyses are summarized in Table 5.

**Table 5:** SARS-CoV-2 neutralization assay - NT50 (titer)† (SARS-CoV-2 USA_WA1/2020) – GMT and seroresponse rate comparison of 1 month after third dose to 1 month after primary series – participants 18 through 55 years of age without evidence of infection up to 1 month after third dose* – third dose evaluable immunogenicity population±

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>1 month after third dose (95% CI)</th>
<th>1 month after primary series (95% CI)</th>
<th>1 month after third dose/- 1 month after primary series (97.5% CI)</th>
<th>Met noninferiority objective (Y/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Geometric mean 50% neutralizing titer (GMTb)</strong></td>
<td>212a</td>
<td>2466.0b (2202.6, 2760.8)</td>
<td>750.6b (656.2, 858.6)</td>
<td>3.29c (2.77, 3.90)</td>
<td>Yd</td>
</tr>
<tr>
<td><strong>Seroresponse rate (%) for 50% neutralizing titer</strong></td>
<td>200c</td>
<td>99.5% (97.2%, 100.0%)</td>
<td>98.0% (95.0%, 99.5%)</td>
<td>1.5%g (-0.7%, 3.7%)</td>
<td>Yi</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; GMR = geometric mean ratio; GMT = geometric mean titer; LLOQ = lower limit of quantitation; N-binding = SARS-CoV-2 nucleoprotein-binding; NAAT = nucleic acid amplification test; NT50 = 50% neutralizing titer; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; Y/N = yes/no.

† SARS-CoV-2 NT50 were determined using the SARS-CoV-2 mNeonGreen Virus Microneutralization Assay. The assay uses a fluorescent reporter virus derived from the USA_WA1/2020 strain and virus neutralization is read on Vero cell monolayers. The sample NT50 is defined as the reciprocal serum dilution at which 50% of the virus is neutralized.

* Participants who had no serological or virological evidence (up to 1 month after receipt of a third dose of COMIRNATY) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative and SARS-CoV-2 not detected by NAAT [nasal swab]) and had a negative NAAT (nasal swab) at any unscheduled visit up to 1 month after the third dose were included in the analysis.

± All eligible participants who had received 2 doses of COMIRNATY as initially randomized, with Dose 2 received within the predefined window (within 19 to 42 days after Dose 1), received a third dose of COMIRNATY, had at least 1 valid and determinate immunogenicity result after third dose from a blood collection within an appropriate window (within 28 to 42 days after the third dose), and had no other important protocol deviations as determined by the clinician.

a. n = Number of participants with valid and determinate assay results at both sampling time points within specified window.
b. GMTs and 2-sided 95% CIs were calculated by exponentiating the mean logarithm of the titers and the corresponding CIs (based on the Student t distribution). Assay results below the LLOQ were set to 0.5 × LLOQ.
c. GMRs and 2-sided 97.5% CIs were calculated by exponentiating the mean differences in the logarithms of the assay and the corresponding CIs (based on the Student t distribution).

d. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is ≥ 0.80.

e. n = Number of participants with valid and determinate assay results for the specified assay at baseline, 1 month after Dose 2 and 1 month after the third dose within specified window. These values are the denominators for the percentage calculations.

f. Number of participants with seroresponse for the given assay at the given dose/sampling time point. Exact 2-sided CI based on the Clopper and Pearson method.

g. Difference in proportions, expressed as a percentage (1 month after third dose – 1 month after Dose 2).

h. Adjusted Wald 2-sided CI for the difference in proportions, expressed as a percentage.

i. Noninferiority is declared if the lower bound of the 2-sided 97.5% CI for the percentage difference is > -10%.

Paediatric population
Further evidence is awaited for less than 12 years of age.

5.2 Pharmacokinetic properties
Not applicable.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeat dose toxicity and reproductive and developmental toxicity.

General toxicity
Rats intramuscularly administered COMIRNATY (receiving 3 full human doses once weekly, generating relatively higher levels in rats due to body weight differences) demonstrated some injection site oedema and erythema and increases in white blood cells (including basophils and eosinophils) consistent with an inflammatory response as well as vacuolation of portal hepatocytes without evidence of liver injury. All effects were reversible.

Genotoxicity/Carcinogenicity
Neither genotoxicity nor carcinogenicity studies were performed. The components of the vaccine (lipids and mRNA) are not expected to have genotoxic potential.

Reproductive toxicity
Reproductive and developmental toxicity were investigated in rats in a combined fertility and developmental toxicity study where female rats were intramuscularly administered COMIRNATY prior to mating and during gestation (receiving 4 full human doses that generate relatively higher levels in rat due to body weight differences, spanning between pre-mating day 21 and gestational day 20). SARS-CoV-2 neutralizing antibody responses were present in maternal animals from prior to mating to the end of the study on postnatal day 21 as well as in foetuses and offspring. There were no vaccine-related effects on female fertility, pregnancy, or embryo-foetal or offspring development. No COMIRNATY data are available on vaccine placental transfer or excretion in milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315)
2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide (ALC-0159)
1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
Cholesterol
Potassium chloride
Potassium dihydrogen phosphate
Sodium chloride
Disodium phosphate dihydrate
Sucrose
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial:
Frozen vial
9 months at -90 °C to -60 °C.

Within the 9-month shelf-life unopened vials may be stored and transported at -25 °C to -15 °C for a single period of up to 2 weeks.

When stored frozen at -90 °C to -60 °C, 195-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 3 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes.

Thawed vial
1 month (31 days) at 2 °C to 8 °C
Within the 1-month shelf-life at 2 °C to 8 °C, up to 12 hours may be used for transportation.
Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C.

Once thawed, the vaccine should not be re-frozen.

Closed-lid vial trays containing 195 vials removed from frozen storage (< -60 °C) may be at room temperature (< 25 °C) for up to 5 minutes for transfer between ultra-low-temperature environments. After vial trays are returned to frozen storage following room temperature exposure, they must remain in frozen storage for at least 2 hours before they can be removed again.

Diluted medicinal product
Chemical and physical in-use stability, including during transportation, has been demonstrated for 6 hours at 2 °C to 30 °C after dilution in sodium chloride 9 mg/mL (0.9%) solution for injection. From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store at -90°C to -60°C.

Store in the original package in order to protect from light.

During storage, minimise exposure to room light, and avoid exposure to direct sunlight and ultraviolet light.
Thawed vials can be handled in room light conditions.

When you are ready to thaw or use the vaccine
• Open-lid vial trays, or vial trays containing less than 195 vials removed from frozen storage (< -60 °C) may be at room temperature (< 25 °C) for up to 3 minutes to remove vials or for transfer between ultra-low-temperature environments.
• Once a vial is removed from the vial tray, it should be thawed for use.
• After vial trays are returned to frozen storage following room temperature exposure, they must remain in frozen storage for at least 2 hours before they can be removed again.

For storage conditions after thawing and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2 mL clear multidose vial (type I glass) with a stopper (synthetic bromobutyl rubber) and a flip-off plastic cap with aluminium seal. Each vial contains 6 doses, see section 6.6.

Pack sizes: 1, 5 or 195 vials per box.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Handling instructions

COMIRNATY should be prepared by a healthcare professional using aseptic technique to ensure the sterility of the prepared dispersion.
**DILUTION**

| ![Image](Image) | • The thawed vaccine must be diluted in its original vial with 1.8 mL sodium chloride 9 mg/mL (0.9%) solution for injection, using a 21 gauge or narrower needle and aseptic techniques. |
| ![Image](Image) | • Equalise vial pressure before removing the needle from the vial stopper by withdrawing 1.8 mL air into the empty diluent syringe. |

1.8 mL of 0.9% sodium chloride injection

Pull back plunger to 1.8 mL to remove air from vial.
• Gently invert the diluted dispersion 10 times. Do not shake.
• The diluted vaccine should present as an off-white dispersion with no particulates visible. Do not use the diluted vaccine if particulates or discolouration are present.

• The diluted vials should be marked with the appropriate date and time.
• After dilution, store at 2 ºC to 30 ºC and use within 6 hours, including any transportation time.
• Do not freeze or shake the diluted dispersion. If refrigerated, allow the diluted dispersion to come to room temperature prior to use.

**PREPARATION OF INDIVIDUAL 0.3 mL DOSES OF COMIRNATY**

• After dilution, the vial contains 2.25 mL from which 6 doses of 0.3 mL can be extracted.
• Using aseptic technique, cleanse the vial stopper with a single-use antiseptic swab.
• Withdraw 0.3 mL of COMIRNATY.

    Low dead-volume syringes and/or needles should be used in order to extract 6 doses from a single vial. The low dead-volume syringe and needle combination should have a dead volume of no more than 35 microlitres.

    If standard syringes and needles are used, there may not be sufficient volume to extract a sixth dose from a single vial.

• Each dose must contain 0.3 mL of vaccine.
| | • If the amount of vaccine remaining in the vial cannot provide a full dose of 0.3 mL, discard the vial and any excess volume.  
| | • Discard any unused vaccine within 6 hours after dilution. |

**Disposal**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

### 7. DATE OF REVISION OF THE TEXT

26 Jan 2022

For any product enquiries, please call +852-800938618, or email to: infohk@fosunpharma.com.