# RECOMMENDATION FOR AN EMERGENCY USE LISTING OF AZD1222 SUBMITTED BY AstraZeneca AB and manufactured by SK Bioscience Co Ltd.


## Abstract

*The active ingredient of COVID-19 Vaccine AstraZeneca, previously known as ChAdOx1 nCov-19, is a recombinant, replication-deficient simian adenovirus that encodes the SARS-CoV-2 (nCoV-19) spike protein with a tissue plasminogen activator (tPA) leader sequence. The applicant, AstraZeneca AB (Sweden), has submitted a CTD format application to WHO to support an EUL for COVID-19 Vaccine AstraZeneca manufactured by SK Bioscience Co Limited (Republic of Korea).*

*COVID-19 Vaccine AstraZeneca is indicated for active immunisation to prevent COVID-19 caused by SARS-CoV-2, in individuals 18 years of age and older.*

*The use of COVID-19 Vaccine AstraZeneca under an emergency situation is endorsed by the European Medicines Agency (EMA), the United Kingdom's Medicines and Healthcare products Regulatory Agency, as well as other regulatory authorities. The Ministry of Food and Drug Safety (MFDS) of the Republic of Korea granted a conditional Marketing Authorization.*

*This report was prepared by the product evaluation group (PEG) to be discussed by the technical advisory group for emergency use listing (TAG-EUL).*


## 1 Introduction

### 1.1 Background

The current COVID-19 pandemic is unprecedented in the 21st century and the global response draws on the lessons learned from other disease outbreaks over the past several decades.

On 30 January 2020, following the recommendations of the Emergency Committee, the WHO Director-General declared that the outbreak constitutes a Public Health Emergency of International Concern (PHEIC).

Scientists around the world on COVID-19 met at the World Health Organization's Geneva headquarters on 11–12 February 2020[1] to assess what is known about the new severe acute respiratory coronavirus - 2 (SARS-CoV-2) virus, agree on critical research questions that needed to be answered urgently, and find ways to collaborate to accelerate and fund priority research to curtail the pandemic.

[1] https://www.who.int/news/item/12-02-2020-world-experts-and-funders-set-priorities-for-covid-19-research

The discussion led to an agreement on two main goals. The first was to accelerate innovative research to help contain the spread of the epidemic and facilitate care for those affected. The second was to support research priorities that contribute to global research platforms for the current pandemic response in order to be better prepared for the next epidemic.

The WHO Research & Development (R&D) Blueprint[2] aims to improve coordination between scientists and global health professionals, accelerate the research and development process, and develop new norms and standards to learn from and improve the global response. Building on the response to recent outbreaks of Ebola virus disease, SARS-CoV and MERS-CoV, the R&D Blueprint has facilitated a coordinated and accelerated response to research into diagnostics, vaccines and therapeutics for the novel disease. This led to the establishment of an unprecedented program to develop a vaccine and strengthened channels for information sharing between countries.

## 1.2 COVID-19 vaccines

The current global COVID-19 public health emergency underscores the need to accelerate the development of COVID-19 candidate vaccines. The vaccine prioritization agenda has a public health and a vaccine component. The strategy includes the prioritization of vaccine platform approaches and/or candidates to be considered not only for development but also for evaluation in the context of the global COVID-19 outbreak. The COVID-19 vaccine pipeline of candidate vaccines for COVID-19 is reviewed and updated continuously. The vaccine development is carefully reviewed and discussed in order to assess their value in protecting against COVID-19 and a potential recommendation of use based on a careful benefit - risk approach.

The information available on COVID-19 candidate vaccines[3] and the new coronavirus (nCoV) epidemiology is closely monitored. The various platform technologies that are developed based on nucleic acids (both mRNA and DNA), viral vectored vaccine (e.g. MVA, VSV, Ad/ChAd), subunit proteins and the traditional platform of inactivated virus are reviewed. Some of the platforms may be easier and faster to manufacture at scale while other platforms may elicit a more rapid and robust protection. Technology platforms for which clinical experience, safety data and demonstrated usability already exist, could allow a more rapid advancement into final phases of clinical trials. The current epidemiological scenario is becoming increasingly complicated with the surge of virus variants due to mutations associated with increased viral transmission and the spread of COVID-19. These variants make effective changes in the virus's 'Spike' protein, which the virus uses to enter human cells and some of these variants are posing real challenges for vaccine's efficacy.

Vaccines that could exert protective immunity after a single dose are preferred, however most of the current candidate vaccines for COVID-19 require two doses.

### 1.2.1 The AstraZeneca Covid-19 vaccine

AZD1222, previously known as ChAdOx1 nCoV-19, is a novel recombinant replication-deficient chimpanzee adenovirus carrying a gene encoding the S protein antigen of SARS-CoV-2.

[2] https://apps.who.int/blueprint-brochure/
[3] https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

The genetic material in the vaccine, once injected into a person, enables the synthesis of Spike protein that triggers the immune response that protects against COVID-19. When a vaccinated person comes in contact with SARS-CoV-2, the immune system will recognize the virus and prevent it from infecting the body's cells.

### 1.3 Emergency Use Listing

The Emergency Use Listing (EUL) is a time limited risk-benefit assessment for emergency use of vaccines, medicines and in vitro diagnostics during a PHEIC when limited data are available and the products are not yet ready for licensure and WHO prequalification. As the EUL is time-limited in nature, the applicant is still expected to complete the development of the product and submit application for licensure and prequalification.

The issuance of an EUL for a product reflects WHO's recommendation for emergency use following a robust scientific risk benefit assessment. However, each WHO Member States has the sole prerogative to allow the emergency use of a product under an EUL within their country.

## 2 Assessment process

AstraZeneca's (AZ) Covid-19 vaccine manufactured in the Republic of Korea by SK Bioscience Co. Ltd (SK Bio) was assessed under the EUL procedure. Since AZ is the applicant and SK Bio is one of their manufacturing sites, the dossier submitted by AZ was used as the basis for the evaluation for non-clinical, clinical and quality information. Specific quality data generated by SK Bio were assessed, mainly focused on the validation of processes and analytical methods, genealogy of commercial scale batches and analytical comparability of such batches. No additional non-clinical or clinical data were submitted by AZ.

The product evaluation group (PEG) consisted of a several different experts. One focal person was designated by WHO for the quality review and one for the non-clinical and clinical assessment (including Risk Management Plan (RMP)). Clinical reviewers from the roster of experts of the WHO Prequalification unit as well as reviewers from National Regulatory Authority (NRA) from different regions were part of the assessment team. The reviewers were designated according to four areas of expertise: quality, non-clinical, clinical and RMP evaluation. In addition, as the Ministry of Food and Drug Safety (MFDS) of the Republic of Korea is the NRA of record for WHO, four reviewers from MFDS participated in the review. Through collaboration agreements with the European Medicines Agency (EMA), WHO assessors participated in meetings of the Committee for Medicinal Products for Human Use (CHMP) for AZ1222 in Europe and conducted scientific discussions with assessors of other NRAs prior to the preparation of the interim assessment report.

# 3 Scientific Review

## 3.1 Quality Overview

AZ advised WHO that there were several manufacturing nodes, including Contract Manufacturing Organizations (CMOs) to produce the Drug Substance (DS) and Drug Product (DP). AZ had submitted a dossier to EMA to support a conditional Marketing Authorization (cMA), which was granted on January 29th. AZ indicated that the manufacturing sites intended for supply through COVAX were not the same as those used to support the cMA in Europe. Therefore, WHO could receive the same submissions sent to EMA to start the review, and wait for the EMA approval of a variation to include those manufacturing sites for supply to COVAX. The first manufacturing node for the production of DS and DP submitted to WHO for listing in the context of supply through the COVAX facility was SK Bio. As a result, the assessment of the AZ vaccine manufactured by SK Bio, consisted of the evaluation of the core CMC data submitted by AZ based on other sites, plus specific data for process validation and analytical comparability of commercial scale batches manufactured by SK Bio.

AZ supplied the Working Cell Bank and Working Virus seeds to SK Bio. The identification of critical process parameters (CPPs) and critical quality attributes (CQAs) as well as validation protocols for processes and analytical methods were done by AZ.

Through the pharmaceutical development of the vaccine, AZ used 4 processes that evolved from Process 1 to Process 4. Processes 1, 2 and 3 were used for manufacture of clinical batches used in studies COV001, COV002, COV003 and COV005 and Process 4 is used for commercial scale production.

The information reviewed included core files generated by AZ as follows:

DRUG SUBSTANCE and DRUG PRODUCT

- List of manufacturing sites and responsibilities (in addition to CMOs in Europe responsible for manufacture of DS and DP, several others were responsible for the preparation of Master and Working Cell banks and Master and Working Virus Seeds)
- Description of the manufacturing process and process controls. This includes identification of CPPs and CQAs and analytical methods.
- Control of raw materials and starting materials of biological origin
- Source history and generation of AZD1222
- Establishment and characterization of Master and Working Host Cell Banks
- Preparation and testing of AZ Master and Working Virus Seed Lots
- Process validation for upstream and downstream processes. This included process validation protocols and Process Performance Qualification (PPQ) for commercial scale batches at different manufacturing sites.
- Manufacturing process history, including description of processes used for production of clinical batches used in clinical trials COV001, COV002, COV003 and COV005 and process changes leading to Process 4 used for commercial scale production in different AZ manufacturing sites
- Validation protocols for processes and analytical methods and protocols for stability studies for DS and DP

The information reviewed specific to the SK Bio manufacturing site is as follows:

- Manufacturing processes and associated quality control of DS and DP
- Validation protocols and validation reports for analytical methods and processes
- Batch analysis of pre-PPQ batches manufactured by SK Bio
- Preliminary stability data of the DS and DP (1 month)
- Suitability of use the primary and secondary containers filled with DS and DP at different real-time storage temperature and further during shelf life
- Suitability of shipping containers to be used for international shipments
- Review of Package inserts and labelling required for AZD1222 as per WHO EUL requirements.

## 3.2 Non-clinical overview

AZ has conducted the nonclinical studies submitted to support the EUL of AZD1222. AZD1222 was shown to be immunogenic in several animal models (mice, ferrets, pigs and non-human primates) either when administered in a single dose or in two doses, with better antigen-specific antibody (including neutralizing antibody) response and T cell responses after the latter. An important nonclinical study was a post-vaccination SARS-CoV-2 challenge in rhesus macaques in which a single administration of AZD1222 showed a significant reduction in viral load in bronchoalveolar lavage fluid and respiratory tract tissue of the vaccinated NHPs. No evidence of vaccine-associated enhanced respiratory disease (VAERD) was detected in the vaccinated NHPs.

Biodistribution studies in mice confirmed the findings of previous studies conducted with other ChAd vaccine candidates, having shown no evidence of replication of the adenovirus or presence of disseminated infection. The applicant proposed that given that AZD1222 is made with the same platform of other investigational vaccines, advantage can be taken from these toxicologic studies.

No AZD1222-related changes in arterial blood pressure, heart rate, body temperature or respiratory parameters were observed in a mouse cardiovascular and respiratory safety pharmacology study.

AZD1222 was well tolerated in a repeat dose toxicity study in CD-1 mice. Anti S glycoprotein antibodies were raised and maintained throughout the dosing and recovery periods in all the animals exposed to AZD1222. In these animals, higher spleen weights were observed but with no histological changes. At the vaccine administration sites inflammatory findings were observed, consistent with those anticipated following intramuscular injections.

No AZD1222-related effects were observed in a preliminary developmental and reproductive toxicology (DART) study conducted in mice.

In brief, AZD1222 (and similar ChAd vaccines) were well tolerated and shown to be immunogenic in several animal models. Rhesus macaques vaccinated with AZD1222 had significantly reduced viral load when challenged with SARS-CoV-2 and there is no evidence of VAERD in these animals.

## 3.3 Clinical overview

### 3.3.1 Vaccine efficacy

AZ submitted an interim pooled analysis conducted in the primary efficacy population of one phase 2/3 clinical trial conducted in the UK (COV002) and another phase 2/3 trial conducted in Brazil (COV003). There was a median follow-up of 19 weeks after Dose 1 and 9 weeks after Dose 2. In the pooled analysis, an overall vaccine efficacy of 70.42% (95.84% confidence interval [CI]: 54.84, 80.63) against symptomatic COVID-19, calculated for two standard doses of the vaccine (SDSD regimen) or for one low dose followed by a standard dose (LDSD regimen) was observed. The vaccine efficacy when the analysis was restricted to individuals who received two standard doses of AZD1222 was 62.10% (95.84% CI: 39.96, 76.08). Vaccine efficacy estimates for the UK and Brazil were, 73.52% (95% CI: 55.50, 84.24), and 64.17 (95% CI: 30.65, 81.49) respectively. Complete protection was observed against COVID-19 hospital admission (WHO Severity Grading ≥ 4) ≥22 days after the first vaccine dose (0 versus 9 cases in the control group, two of which were considered severe cases and one was fatal). For the participants who received the SD regimen of AZD1222 protection was shown to begin from 22 days after the first dose and to extent at least until 12 weeks, allowing for flexibility for the second vaccine dose to be given 4 to 12 weeks.

Vaccine efficacy could not be reliably determined in older adults (≥65 years) given that the number of events was too low for that age group in the available follow-up time. Adults with pre-existing comorbidity had similar vaccine efficacy as the general population. The available efficacy data together with the immunogenicity data (see 3.3.3 Immunogenicity, below) support the use of an AZD1222 vaccine regimen of two standard doses (SDSD) given between 4 and 12 weeks apart in the elderly (≥65 years) and people with comorbidities.

### 3.3.2 Vaccine safety

An interim pooled analysis was conducted with data from COV001 and COV002 trials (both carried out in the UK), COV003 (conducted in Brazil) and COV005 (conducted in South Africa). The safety database included 23 745 participants, of whom 12 021 received at least 1 dose of AZD1222, and of whom 11 724 received at least one dose of control. The median follow-up for the AZD1222 and the control groups were, respectively, 105 and 104 days. AZD1222 was well tolerated, with most local and systemic adverse events (AEs) being mild to moderate, and even milder and less reported after the second dose compared to the first one. Among the solicited AEs (considered as adverse drug reactions - ADRs) the most commonly observed were headache, nausea, myalgia, arthralgia, injection site tenderness, injection site pain, injection site warmth, injection site pruritus, fatigue, malaise, pyrexia, and chills, . According to the applicant, unsolicited AEs were consistent with those commonly observed following vaccination. Preferred terms (PTs) not commonly associated with vaccination were relatively balanced in the vaccine and control groups.

The incidence of serious adverse events (SAEs) was <1% in both the AZD1222 and the control groups, and the frequency and type of SAE also did not differ between them. A total of 6 fatal SAEs were observed (2 of them in the AZD1222 group), none of them considered by the investigators as causally related to the study interventions. Few adverse events of special interest (AESIs) were registered, 0.8% and 1.1% in the

AZD1222 and the control groups, respectively. No clear imbalance in the incidence of AESIs by category or PT was observed that could suggest an association with AZD1222.

Paresthesia, hypoaesthesia, and muscular weakness were the most frequently observed PTs within the categories of neurologic events and potential immune-mediated neurologic conditions, and were less common in the AZD1222 group. Facial paralysis was reported in 3 patients in each group. Three SAEs of demyelinating events were reported, 2 in the AZD1222 group (1 case of transverse myelitis and 1 case of multiple sclerosis in a patient who already had the disease before enrolment in the study, which was unrecognized at the time).

There was no evidence of an association of AZD1222 and PTs related to possible vaccine-associated enhanced disease (VAED), which were reported in a slightly smaller percentage of participants in the AZD1222 group than in the placebo group.

The safety profile was comparable when the participants were stratified by comorbidity, country or serostatus subgroup. This was also comparable in older adults and in adults aged 18 to 64 years, but older adults reported milder and less frequent solicited reactogenic AEs.

### 3.3.3 Immunogenicity

AZD1222 was highly immunogenic, with a seroconversion of binding antibodies >97% and of live virus neutralizing antibodies >80% after a single standard dose (SD) or low dose (LD), and >99% of both antibodies after a second SD. Seroconversion for both binding and neutralizing antibodies increased with increasing dose interval between the first and second vaccine dose. The applicant has interpreted this finding as supportive of the finding of increased efficacy across the dosing interval of 4 to 12 weeks.

Immunogenicity in vaccinated participants with comorbidities was similar to that observed in the general population. In older adults (≥65 years) the rates of seroconversion to binding and to live neutralising antibodies were similar to those found in younger adults, however their absolute titres tended to be lower.

The applicant took into consideration the immunogenicity data together with the efficacy data, to support their recommendations for the use of AZD1222 (see 3.3.1 Vaccine efficacy, above).

### 3.3.4 Special populations

Regarding special populations, as mentioned above, efficacy in individuals over 65 years of age could not be assessed due to small numbers. AEs were generally milder and less frequent in older participants. Older adults reported milder and less frequent solicited reactogenic AEs.

Persons with severe immunodeficiency, severe underlying disease, and pregnant/lactating women were excluded from the studies, therefore efficacy, immunogenicity and safety of AZD1222 in these groups is currently unknown. Although data from Brazil and South Africa have been submitted by the applicant, not all available data may be generalizable to populations in low and middle-income countries (LMIC) who have profiles that can impact on the efficacy of this vaccine (for example, ethnicity, concomitant infections and malnutrition).

## 3.4 Risk Management Plan

### 3.4.1 Product description

Acceptable.

### 3.4.2 Nonclinical information

Acceptable.

There are two ongoing studies, with no impact expected in the safety profile. No additional information is required.

### 3.4.3 Clinical information

a. Important identified risks:

| Identified risks proposed by | AZ | WHO |
|---|---|---|
| None | √ | √ |

b. Important potential risks:

| AZ | WHO | Comments |
|---|---|---|
| Immune-mediated neurological conditions | Neurological System disorders, including Immune-mediated neurological conditions | Immune-mediated neurological conditions have been changed to nervous system disorders including Immune-mediated neurological conditions in the last evaluation by CHMP Rapp team (AR dated 17.01.2021) |
| Vaccine-associated enhanced disease (VAED) | Vaccine-associated enhanced disease (VAED) including vaccine-associated enhanced respiratory disease (VAERD) | There is a theoretical concern that vaccination against SARS-CoV-2 may be associated with enhanced severity of COVID-19 episodes which would manifest as VAED. Although available data have not identified VAED as a concern for AZD1222, the risk of VAED cannot be ruled out. VAED may be potentially serious or life-threatening, and requires early detection, careful monitoring, and timely medical intervention. |
| | Anaphylaxis | Anaphylaxis is known to be possible with any injectable vaccine. Anaphylaxis can be upgraded to an identified risk based on the outcome of the assessment of the clinical data of ongoing studies or post-marketing information. |

| | | |
|---|---|---|
| | | A minimum period of 15-minutes of observation is recommended for each vaccinee after vaccination, given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions |
| | Programmatic errors | Vaccine administration errors were a protocol deviation during clinical trials, such errors were noted to be relatively infrequent by the sponsor. However, it may be necessary to minimize this situation in advance under real use conditions. |

c. Missing information:

| **AZ** | **WHO** | **Comments** |
|---|---|---|
| Use during pregnancy and while breastfeeding | Use during pregnancy and while breastfeeding | Pregnant and lactating women not included in the clinical trials |
| Use of AZD1222 in subjects with severe immunodeficiency or requiring immunosuppressive medications. | Use in immunocompromised patients, including people living with HIV | Immunocompromised individuals not included in the clinical trials. The data in this population is limited and it is possible that immune response to the vaccine may be different and compromise the effectiveness. |
| Use of AZD1222 in subjects with severe and/or uncontrolled underlying disease | Use of AZD1222 in subjects with severe and/or uncontrolled underlying disease | These individuals have not been included in the clinical studies but are theoretically likely to be at risk for severe COVID-19. |
| | Use of AZD1222 in frail patients with comorbidities (e.g. chronic obstructive pulmonary disease, diabetes, chronic neurological disease, cardiovascular disease) | Frail individuals have not been included in the clinical studies, but old frail individuals have been prioritized for vaccination in practice |
| Interchangeability and interactions with other vaccines | Interaction with other vaccines | The safety, immunogenicity, and efficacy of this vaccine when co-administered with other vaccines (e.g. influenza) has not been evaluated. |

| | | |
|---|---|---|
| | Interchangeability or sequential use with other vaccines | The evidence to support interchangeability or sequential use of AZD1222 with other* COVID-19 vaccines is still not available. There are proposed heterologous prime/boost studies with vaccines already approved for emergency use in some countries.<br>*The SIIPL vaccine (COVISHIELD), which is a technology transfer of AZD1222, is not considered a different vaccine. |
| | Use in pediatric population <18 years of age | There are some ongoing studies in this age group, but the results are not yet available and AZ1222 is currently not recommended for this population. |
| | Use in patients with autoimmune or inflammatory disorders | Use in patients with autoimmune or inflammatory disorders should also be considered missing information. Although patients with autoimmune or inflammatory disorders were not explicitly excluded from the clinical studies, the use in this subgroup of patients should be described as one of the subgroups with severe co-morbidities as recommended |
| | Long-term safety | Long-term safety profile of AZD1222 is currently limited and it is recognized that further follow-up for all vaccines is required. Additional activities will be needed to obtain such information. |
| | Vaccine effectiveness and safety in very old (e.g. 85+) individuals; | Vaccine effectiveness and safety in very old individuals (e.g. 85+) has not been demonstrated but may be addressed by observational studies [e.g "A post-authorization/post-marketing retrospective cohort study to evaluate the effectiveness of the AZD1222 vaccine to prevent serious COVID-19 infection in conditions of usual care (D8111R00005 [EU/UK])"]. |
| | Impact of the emergence of variants on vaccine efficacy/effectiveness and safety | AZ should provide to WHO any data on new emerging variants particularly from vaccine breakthrough cases as soon as available, irrespective of source. |

### 3.4.4 Pharmacovigilance Plan

Routine pharmacovigilance activities: Acceptable in general, adverse reaction reporting, and signal detection are in accordance with national and international Good Pharmacovigilance (GPV) guidelines. The spontaneous reporting needs preferably be harmonized in most of the countries and with the sharing system with the VigiBase platform.

The monitoring of adverse events (AEs) of interest should consider Bell's palsy, transverse myelitis, multisystem inflammatory syndrome following vaccination and all serious adverse events, as included in routine pharmacovigilance in the submitted Risk Management Plan.

For signal detection a mechanism for traceability and cold chain information needs to be established. Routine pharmacovigilance activities should be implemented in all WHO regions, including at least a card with the date when the recipient needs to return for the vaccine second dose, the name of the recipient, the name of the vaccine, batch number, and a telephone number where to report side effects. Signal detection by batch will be performed by AstraZeneca as described in the RMP. Any investigations by lot will include cold chain traceability (a WHO approved electronic temperature monitoring device is included in the temperature-controlled shipping system). AZ will provide templated vaccination card electronically, that can be modified if required. The vaccination card will include the MAH website where AEs can be reported. Methods for vaccinees to contact AZ are available on the website.

There is a general concern about the collection of AEs in low- and middle-income countries (LMICs) of certain regions, because of the need for adequate pharmacovigilance systems. A hyperlink to the AZ website for reporting adverse events and requesting medical information will be made available (on carton, package leaflet, vaccination card). An adverse event reporting form is available on this AZ website; a telephone number is also available. AZ will conduct appropriate follow-up on any AEs reported.

AstraZeneca is considering non-interventional and interventional studies as additional pharmacovigilance activities. The additional pharmacovigilance activities described in the EU RMP are intended for implementation in the European Economic Area (EEA) only. No additional pharmacovigilance activities are planned for other WHO regions.

The applicant proposes five non-Interventional studies in the pharmacovigilance plan:

1. Enhanced Active Surveillance.
2. AZD1222 Pregnancy Registry. At least one country of each WHO region would preferably be included.
3. Post-marketing observational study using existing secondary health data sources.
4. Post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency.
5. Post-marketing Effectiveness Study. If feasible, countries from the different WHO regions should be included.

### 3.4.5 Risk minimization activities

The routine risk minimization activities are sufficient to manage the safety concerns of the medicinal product. The applicant should implement these in all WHO regions and ensure the feasibility to measure these in all countries

# 4 Outcome of review

## 4.1 Quality

The assessment of the manufacturing process focused mainly on the comparability of the commercial scale batches manufactured by SK Bio, using Process 4 established by AZ and used in other manufacturing sites in Europe.

Although the applicant has not submitted results of the analytical comparability of PPQ DS batches, the 5 pre-PPQ batches were manufactured at the same scale as the commercial batches. The list of tests included in the comparability studies includes all the CQAs identified by AZ and the results were satisfactory.

The CPPs indicated by SK Bio for the DP manufacturing process steps are identical to the ones described and carried out by AZ and other manufacturing sites. Three process validation (PV) runs have been completed for the primary DP manufacturing process along with one GMP pre-PPQ batch in order to confirm the consistency of the DP formulation and filling process. In this validation study conducted as per the defined AZ PPQ protocol, all CPPs were considered because of the potential impact on CQAs. Additional auxiliary validations studies were conducted by SK Bio to support the manufacturing process.

Regarding the stability, the studies are ongoing for both the DS and the DP. So far, data for only 1-month timepoint at real-time and accelerate conditions are available.

The applicant needs to submit the following information as a post-listing commitment:

1) Results of updated stability data for the 3 DS pre-PPQ and 3 DP PPQ batches that were placed on the stability study, should be submitted as they become available for each time point in the stability protocol.

2) In order to achieve final demonstration of comparability, studies and data related to the PPQ DS batches that have been manufactured in December and January are awaited. The applicant has reported that this information will be available on 19 February. These should be submitted by **February 25th .**

3) The validation reports for the analytical methods carried out by SK Bio for testing of COVID-19 Vaccine AstraZeneca DP should be provided.

4) The package insert/leaflet needs to be updated in order to be in line with the WHO Multidose Vial Policy (MDVP) specifying that the vaccine should be discarded within six hours after opening or at the end of the immunization session, whichever comes first. It should also be specified that opened

multidose vaccine vials that do not contain preservative should be kept cooled at temperatures between +2°C and +8°C during the immunization session, or within six hours after opening, whichever comes first.

## 4.2 Clinical

This clinical assessment raised a series of queries and comments from the reviewers on different aspects of the nonclinical and clinical submitted evidence, as well as on issues related to the RMP. These have either been considered covered by the AZ answers to the EMA CHMP list of questions, or have been incorporated into the recommendations listed below and in the conclusion section of this document.

From the clinical point of review the Product Evaluation Group (PEG) recommended that an EUL may be granted by WHO to AstraZeneca COVID-19 Vaccine provided that AstraZeneca commits to meet the following conditions post-EUL:

1. The applicant should submit to WHO further interim analyses and the final clinical study reports of the ongoing studies (COV001, COV002, COV003 and COV005, whose interim analyses have been presented as part of this application, as well as COV004, conducted in Kenya, D8110C00001, conducted in the United States, Chile and Peru, and D8111C00002, conducted in Japan) once they are completed.
2. The applicant is urged to encourage participants, especially those not prioritized for vaccine access, to remain in the ongoing randomized controlled clinical trials as originally randomized for as long as possible, in order to accumulate at least 6 months of safety follow-up data after Dose 2 of the vaccine
3. The Risk Management Plan should also include/address the following:
    - Safety specifications:
        - Potential risks: add *anaphylaxis* and *programmatic error*
        - Missing information: add *people living with HIV*, *frail subjects*, *use in paediatric population <18 years of age, use in patients with autoimmune or inflammatory disorders,* and *long-term safety data.*
        - *Interaction with other vaccines* and *interchangeability* should be considered separately from each other.
    - Pharmacovigilance plan
        - The applicant is urged to conduct additional pharmacovigilance activities (non-interventional and interventional studies as those intended for implementation in the EEA) in other WHO regions
    - Risk minimization activities
        - A minimum period of 15-minutes of observation for each vaccinee after vaccination given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions should be recommended in the product insert.

In addition, in light of the recent evidence of vaccine escape of some emerging SARS-Cov-2 variants, the applicant is requested to closely monitor and evaluate the impact of these emerging SARS-CoV-2 variants (such as B.1.1.7, B.1.351 and P.1, and others that may appear in the future) on the effectiveness of AZD1222 and to discuss with WHO in case of plans to make changes to the vaccine to address this issue.

# 5 Technical considerations

## 5.1 Vaccine characteristics

One dose (0.5 ml) contains:
COVID-19 Vaccine (ChAdOx1-S* recombinant) $5 \times 10^{10}$ viral particles (vp)
*Recombinant, replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2 Spike (S) glycoprotein. Produced in genetically modified human embryonic kidney (HEK) 293 cells.

Solution for injection. The solution is colourless to slightly brown, clear to slightly opaque and particle free with a pH of 6.6.

No diluent is required.

COVID-19 Vaccine AstraZeneca is for intramuscular (IM) injection only, preferably in the deltoid muscle.

**List of presentations available to UN Agencies/COVAX Facilities – multidose vials ***

| Presentation | Pharmaceutical form | Dose | Container | Pack Size |
|---|---|---|---|---|
| 5 ml | solution for injection | 0.5 ml | Vial: 5mL Clear Glass (Type 1)<br>Stopper: 20 mm, elastomeric<br>Seal: 20 mm Aluminum flip-off plastic button | 10 multidose vials (10 doses per vial - 0.5 ml per dose) |

* fill overage is not intended to increase the number of doses to be extracted from the vial.

## 5.2 Special precautions for storage and handling proposed by the applicant

Unopened multidose vial is stable for 6 months when stored at 2°C - 8°C.

After first opening, chemical and physical in-use stability has been demonstrated from the time of vial puncture to the administration for no more than:

- 6 hours at room temperature, up to 30°C, or
- 48 hours in a refrigerator (2 to 8°C).

The vial can be re-refrigerated, but the cumulative storage time at room temperature must not exceed 6 hours, and the total cumulative storage time must not exceed 48 hours.[5]

Unopened multidose vial should be stored in a refrigerator (2 to 8°C). Do not freeze.

Keep vials in outer carton to protect from light.

These recommendations are not in compliance with the WHO Multi-Dose Vial Policy (MDVP). The vaccine should be discarded within six hours after opening or at the end of the immunization session, whichever comes first. It should also be specified that opened multidose vaccine vials that do not contain preservative should be kept cooled at temperatures between +2°C and +8°C during the immunization session, or within six hours after opening, whichever comes first. (See Outcome of the review and Conclusions)

## 5.3 Indication, warnings and contraindications

**Therapeutic indications**
COVID-19 Vaccine AstraZeneca is indicated for active immunisation of individuals ≥18 years old for the prevention of coronavirus disease 2019 (COVID-19) (see sections 4.4 and 5.1 [of the Summary of Product Characteristics]).
The use of the vaccine should be in accordance with official recommendations.

**Contraindications**
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 [of the Summary of Product Characteristics].

**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.

Hypersensitivity
As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event 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 COVID-19 Vaccine AstraZeneca. [4]

Concurrent illness
As with other vaccines, administration of COVID-19 Vaccine AstraZeneca should be postponed in individuals suffering from an acute severe febrile illness. However, the presence of a minor infection, such as cold, and/or low-grade fever should not delay vaccination.

Thrombocytopenia and coagulation disorders
As with other intramuscular injections, COVID-19 Vaccine AstraZeneca should be given with caution to individuals with thrombocytopenia, any coagulation disorder or to persons on anticoagulation therapy, because bleeding or bruising may occur following an intramuscular administration in these individuals.

Neurological events
Very rare events of demyelinating disorders have been reported following vaccination with COVID-19 Vaccine AstraZeneca. A causal relationship has not been established.
As with other vaccines, the benefits and potential risks of vaccinating individuals with COVID-19 Vaccine AstraZeneca should be considered.

[4] This text is not in the insert and is a recommendation from WHO

Immunocompromised individuals
It is not known whether individuals with impaired immune responsiveness, including individuals receiving immunosuppressant therapy, will elicit the same response as immunocompetent individuals to the vaccine regimen.

Duration and level of protection
The duration of protection has not yet been established.
As with any vaccine, vaccination with COVID-19 Vaccine AstraZeneca may not protect all vaccine recipients.

Interchangeability
There are no safety, immunogenicity or efficacy data to support interchangeability of COVID-19 Vaccine AstraZeneca with other COVID-19 vaccines.

Sodium
This medicinal product contains less than 1mmol sodium (23mg) per dose, and is considered to be essentially sodium-free.

## 5.4 Posology and method of administration

Posology
The COVID-19 Vaccine AstraZeneca vaccination course consists of two separate doses of 0.5 ml each. The second dose should be administered between 4 and 12 weeks after the first dose (see section5.1 [of the Summary of Product Characteristics]).
It is recommended that individuals who receive a first dose of COVID-19 Vaccine AstraZeneca complete the vaccination course with COVID-19 Vaccine AstraZeneca (see section 4.4[of the Summary of Product Characteristics]).

*Elderly population*
No dosage adjustment is required in elderly individuals ≥65 years of age.

*Paediatric population*
The safety and efficacy of COVID-19 Vaccine AstraZeneca in children and adolescents (aged <18 years old) have not yet been established. No data are available.

Method of administration
COVID-19 Vaccine AstraZeneca is for intramuscular (IM) injection only, preferably in the deltoid muscle. For instructions on administration, see section 6.6 [of the Summary of Product Characteristics].

## 5.5 Safety profile

Summary of the safety profile

The overall safety of COVID-19 Vaccine AstraZeneca is based on an interim analysis of pooled data from four clinical trials conducted in the United Kingdom, Brazil, and South Africa. At the time of analysis, 23,745 participants ≥18 years old had been randomised and received either COVID-19 Vaccine

AstraZeneca or control. Out of these, 12,021 received at least one dose of COVID-19 Vaccine AstraZeneca.

Demographic characteristics were generally similar among participants who received COVID-19 Vaccine AstraZeneca and those who received control. Overall, among the participants who received COVID-19 Vaccine AstraZeneca, 90.3% were aged 18 to 64 years and 9.7% were 65 years of age or older. The majority of recipients were White (75.5%), 10.1% were Black and 3.5% were Asian; 55.8% were female and 44.2% male.

The most frequently reported adverse reactions were injection site tenderness (>60%); injection site pain, headache, fatigue (>50%); myalgia, malaise (>40%); pyrexia, chills (>30%); and arthralgia, nausea (>20%). The majority of adverse reactions were mild to moderate in severity and usually resolved within a few days of vaccination. When compared with the first dose, adverse reactions reported after the second dose were milder and reported less frequently.

Adverse reactions were generally milder and reported less frequently in older adults (≥65 years old). Analgesic and/or anti-pyretic medicinal products (e.g. paracetamol-containing products) may be used to provide symptomatic relief from post-vaccination adverse reactions.

Tabulated list of adverse reactions

Adverse drug reactions (ADRs) are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data).

**Table 1 Adverse drug reactions**

| MedDRA SOC | Frequency | Adverse Reactions |
|---|---|---|
| Nervous system disorders | Very common | Headache |
| Gastrointestinal disorders | Very common | Nausea |
| Musculoskeletal and connective tissue disorders | Very common | Myalgia, arthralgia |
| General disorders and administration site condition | Very common | Injection site tenderness, injection site pain, injection site warmth, injection site pruritus, fatigue, malaise, pyrexia[a], chills |
| | Common | Injection site swelling, injection, site erythema |

[a] Pyrexia includes feverishness (very common) and fever ≥38°C (common)

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 via the national reporting system listed in www.covax.azcovid-19.com.

# 6 Monitoring of performance of the vaccine in the field

AZ proposes a series of activities for post-authorization safety monitoring, focused on Europe, including a proposed effectiveness study.

These post-authorization activities do not focus on populations and special groups that may be commonly found in LMICs supplied with WHO recommended COVID-19 vaccines. Available clinical data may not fully represent all populations.

## 6.1 Vaccine efficacy/effectiveness

AZ is conducting a series of clinical trials with AZ1222. Part of these studies have been initiated by the University of Oxford, and others have AstraZeneca as the sponsor. An interim pooled analysis of studies COV002 (conducted in the United Kingdom) and COV003 (conducted in Brazil) has been submitted in this application to support vaccine efficacy and immunogenicity. Five other clinical trials (COV001, conducted in the UK, COV004, conducted in Kenya, COV005, conducted in South Africa, D8110C00001, conducted in the United States, Chile and Peru, and D8111C00002, conducted in Japan) are ongoing. D8110C00001, a double-blind randomized, placebo-controlled clinical trial is of major interest as it involves ~30000 participants, and its results are expected to be used to support Emergency Use Authorization and, eventually, licensure in the United States.

AZ has also indicated, in its RMP, that an effectiveness study will be conducted. Given the recent concern with new variants, case-control studies are already being conducted in the United Kingdom in order to assess whether these variants may impact on vaccine effectiveness. The fact that the UK has an excellent genomic surveillance puts that country in a unique position to conduct such assessment.

## 6.2 Safety Monitoring

In addition to the collection and monitoring of spontaneous reports from healthcare professionals and vaccinees, AstraZeneca has proposed, in the Risk Management Plan, an Enhanced Active Surveillance, a AZD1222 Pregnancy Registry, a post-marketing observational study using existing secondary health data sources, and a post-marketing safety study in patients receiving immunosuppressant medication or with primary immunodeficiency.

### 6.3 Programmatic aspects

The programmatic suitability of vaccine candidates for WHO Prequalification (PSPQ) of COVID-19 Vaccine AstraZeneca has been assessed as per the PSPQ WHO recommendations[5].

COVID-19 Vaccine AstraZeneca meets most of the mandatory characteristics as it is to be stored at +2°C to +8°C, does not require an intravenous route of administration and the dose volume (0.5 mL) is not more than 1 mL. However, the vaccine does not meet one mandatory characteristic as it is presented in a 10 dose vial without a preservative.

The majority of the critical characteristics are either met (the vaccine does not require storage below +2°C, the dose volume corresponds to standardized volume) or not applicable (no constraint on vaccination visits given that the vaccine is for use in pandemic, vaccine not presented in a pre-filled device). One critical characteristic is not met as the vaccines does not bear a vaccine vial monitor (VVM).

## 7 SAGE recommendations

The Strategic Advisory Group of Experts on Immunization (SAGE) issues recommendations for use on vaccines of public health importance, including investigational products considered for use during a public health emergency. A SAGE working group on COVID-19 vaccination was set up in spring 2020 to develop the basis for recommendations once vaccines become authorized. Based on advice provided by SAGE, the initial use of vaccine is prioritized for health workers with high and very high risk of exposure and older adults, with the intention of preserving the most essential services and reducing mortality and morbidity from disease.

On February 8, 2021, SAGE reviewed the available data on COVID-19 AstraZeneca AZD1222, previously known as ChAdOx1 nCoV-19, with a specific view of addressing the above-mentioned use scenario. The resulting interim recommendations were released by WHO on 10 February 2021. WHO recommends the use of the vaccine in accordance to the prioritization roadmap in individuals above 18 years of age, without an upper age limit. A two-dose schedule should be used, with an interval of preferentially 8-12 weeks. The vaccine maintains high level of efficacy against variant B.1.1.7 strain, while preliminary findings suggest the vaccine may be less effective against B.1.351. Awaiting additional data on vaccine effectiveness, in particular against severe disease, WHO also recommends the use of the vaccine in countries were variant strains are circulating. Benefit risk assessment and continued monitoring of variant epidemiology are recommended.

The interim recommendations apply to AZD1222 (ChAdOx1-S [recombinant]) vaccine against COVID-19 developed by Oxford University (United Kingdom) and AstraZeneca as well as to ChAdOx1-S [recombinant] vaccines against COVID-19 produced by other manufacturers that rely on the AstraZeneca core clinical data, following demonstrated equivalence in their regulatory review and once emergency use listing (EUL) has been obtained from WHO.

[5] Assessing the programmatic suitability of vaccine candidates for WHO prequalification, Revision 2014

# 8 Regulatory oversight

The Ministry of Food and Drug Safety (MFDS) of the Republic of Korea, which granted a conditional marketing authorisation to COVID-19 Vaccine AstraZeneca under its local name 'Korea AstraZeneca COVID-19 Vaccine Inj.', is the NRA of record for this vaccine as per the EUL procedure. The WHO Vaccine Prequalification Team will continue to rely on the regulatory oversight of MFDS and will continue fostering participation in MFDS' decision making process, as possible and when possible.

# 9 Benefit/Risk Assessment

According to WHO, the COVID-19 pandemic has caused, as of 9 February 2021, over 106 million cases of the disease and over 2.3 million deaths (https://covid19.who.int/). COVID-19, caused by a novel coronavirus, SARS-CoV-2, transmitted easily worldwide to a naïve population and has become a major cause of morbidity and mortality given the inexistence of a vaccine and of proved specific treatment. SARS-CoV-2 transmission continues to occur with an increasing rate. Hopes that herd immunity be achieved by natural infection have not been borne out because a large proportion of the population remains seronegative, which supports the hypothesis that they are susceptible to the virus. This scenario has been complicated by the recognition of new SARS-CoV-2 variants, whose increased transmissibility has caused concern. The development of effective and safe vaccines and their deployment worldwide may decrease the spread of the disease and its morbidity and mortality.

AZD1222 has demonstrated protection against symptomatic COVID-19, and no severe cases of COVID-19 or COVID-19 hospitalisations were observed 10 days after the first dose in two clinical trials conducted in the UK (COV002) and in Brazil (COV003). The applicant claims that AZD1222 has the potential to be a critical intervention both for the individual and for public health in preventing COVID-19 and its associated risk of severe morbidity and of mortality.

AZ also claims that the need for an effective COVID-19 vaccine is highest among older people and individuals with comorbidities, and that the available results support the use of AZD1222 in individuals with these co-morbidities. The small number of events in the available clinical data does not allow for a reliable estimate of vaccine efficacy in older adults, in particular regarding protection against severe disease. The applicant claims that there is adequate seroconversion in the elderly, but the absence of an established immunological correlate of protection limits interpretation of immunogenicity data relative to efficacy. Lower antibody titres may also translate to shorter duration of immunity. Although vaccine efficacy and its duration are yet to be established in older adults, the overall safety profile and seroconversion rates in this age group are good and suggest that the benefit of vaccine outweighs the risk. Therefore, the current benefit/risk assessment in older adults is positive.

According to the applicant, the safety profiles in individuals with comorbidities were similar to those in the overall population, and that therefore the benefit-risk profile in the subgroups with comorbidities can be considered similar to that in the general adult population. However, as individuals with severe diseases were not included in clinical trials, the same inference about the benefit-risk profile is not applicable to them.

The safety database presented by AZ included data from studies COV002 and COV003, mentioned above, and also from studies COV001 (conducted in the United Kingdom) and COV005 (conducted in South Africa). No important identified risks with AZD1222 vaccination have been detected by the clinical trials so far. Very rare events of demyelinating disorders have been recognized in the AZD1222 and the control groups, though without evidence of a causal relationship between the vaccine and these disorders. AZ, however, has included immune-mediated neurological conditions as an important potential risk in the RMP, due to theoretical concerns about the association of these disorders with vaccines, notwithstanding the fact that demyelinating diseases occur more frequently with infections than with vaccination. The applicant argues that studies have not conclusively shown a causal relation between contemporary vaccines (in general) and acute demyelinating events.

AZ argues that the benefits of AZD1222, both from the individual and public health standpoints, outweigh the potential risks, including VAED/VAERD, which remain theoretical and not supported by empirical nonclinical and clinical data for this vaccine. In AZ's opinion the benefits extend to older adults ≥ 65 years and those with comorbidities. Vaccination with AZD1222 is anticipated to have a major impact in the prevention of severe COVID-19 disease, hospitalisations and deaths, with the advantages of being a vaccine with a good safety profile provided in a formulation that allows easy storage and handling.

# 10 Conclusion

Considering the public health need to halt COVID-19 morbidity and mortality and to continue immunizing the world's population to the largest extent possible, the introduction of new vaccines that would protect the population from disease and, whenever possible, from SARS-CoV-2 infection is needed.

Based on assessment of the available evidence, the TAG finds that sufficient data is available on AstraZeneca COVID-19 vaccine for an EUL recommendation, subject to the post-listing commitments as indicated in the below sections.

Should new evidence become available that change the benefit-risk assessment (e.g. as a result of the new variants) the EUL recommendation could be reconsidered.

## 10.1 Quality (CMC) perspective

The PEG has prepared a detailed report that includes some questions for AZ. No major concerns exist regarding the manufacturing and quality control of the vaccine. The questions from EMA to the applicant and their responses were evaluated and compared with the WHO list of questions, in order to avoid duplication. In addition, a consultation was conducted with Quality assessors of Health Canada and the observations and conclusions from both assessment teams were aligned.

In general, based on the evaluation, the PEG concluded that no major concerns arose that would warrant a delay in the decision to list the vaccine. The TAG however highlighted the need to finalize comparability data as soon as possible to confirm that the manufacturing at SK Bio is comparable to production elsewhere, in order to alleviate any concerns regarding the quality of the product irrespective of site of production. Since the manufacture of commercial scale batches is recent, few batches have been

manufactured by SK Bio and the comparability and stability of PPQ batches is still ongoing, the conditions for listing of the vaccine manufactured by AZ/ SK Bio are as follows:

1) AZ should provide the results of stability data for the 3 pre-PPQ batches of DS placed on the stability study, as well as the stability data for PPQ batches of DS and PPQ batches of DP manufactured by SK Bio as soon as they are available for timepoints established in the stability protocol

2) In order to achieve final demonstration of comparability, studies and data related to the PPQ DS batches that have been manufactured in December and January are awaited. AZ is thus requested to submit information on the PPQ batches manufactured by SK Bio in December 2020 and January 2021 by **February 25th 2021.**

3) The validation reports for the analytical methods carried out by SK Bio for testing of COVID-19 Vaccine AstraZeneca DP must be submitted.

4) The applicant must commit to address all pending issues generated from the CMC review.

5) The package insert/leaflet should be updated in order to be in line with the MDVP.

## 10.2 Clinical perspective

From the clinical point of review the PEG recommended that an EUL may be granted by WHO to AstraZeneca COVID-19 Vaccine provided that AstraZeneca commits to providing the following requested information post-EUL as soon as such information becomes available:

- The applicant should submit to WHO further interim analyses and the final clinical study reports of the ongoing studies (COV001, COV002, COV003 and COV005, whose interim analyses have been presented as part of this application, as well as COV004, conducted in Kenya, D8110C00001, conducted in the United States, Chile and Peru, and D8111C00002, conducted in Japan) once they are completed.
- The expectation is that the continued analysis of these studies will provide evidence of vaccine efficacy in the 65+ age group, in particular for the prevention of severe cases. Once available information (or any relevant data coming from post EUL effectiveness studies) should be shared with WHO, as this might change the benefit/risk profile of the vaccine in this population.
- The applicant should investigate and provide to WHO, on a regular basis or whenever relevant information is available, updated data on the efficacy of the vaccine against severe disease caused by emerging SARS-CoV-2 variants such as B.1.1.7, B.1.351 and P.1. This is important information given that decreasing effectiveness may change the benefit/risk assessment in countries where these variants are predominant

- The applicant is urged to encourage participants, especially those not prioritized for vaccine access, to remain in the ongoing randomized controlled clinical trials as originally randomized for as long as possible, in order to accumulate at least 6 months of safety follow-up data after Dose 2 of the vaccine
- The Risk Management Plan should include/address the following:

- Safety specifications:
  - Potential risks: text should be aligned with the table in section 3.4.3 and add *anaphylaxis* and *medication error*
  - Missing information: text should be aligned with the table in section 3.4.3 and add *people living with HIV*, *frail subjects*, *use in paediatric population <18 years of age, use in patients with autoimmune or inflammatory disorders,* and *long-term safety data.*
  - *Interaction with other vaccines* and *interchangeability* should be considered separately from each other.
- Pharmacovigilance plan
  - The applicant is urged to conduct additional pharmacovigilance activities (non-interventional and interventional studies as those intended for implementation in the EEA) in other WHO regions

- Risk minimization activities
  - A minimum period of 15-minutes of observation for each vaccinee after vaccination given the risk of potentially life-threatening anaphylactic/anaphylactoid reactions should be recommended in the product insert.