ZKBS
Zentrale Kommission
für die **Biologische Sicherheit**

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Recommendation of the ZKBS for the risk assessment of the recombinant Adenovirus Ad26.COVS1 according to § 5 paragraph 1 GenTSV

General

Ad26.COVS1 is a replication-defective human adenovirus of serotype 26 (Ad26) that contains the *severe acute respiratory syndrome coronavirus* (SARS-CoV-2) spike protein gene. Ad26 belongs to the species *human mastadenovirus D* and was first isolated in 1956 from an anal swab of a nine-month-old boy [1] . In the few studies published to date, gastrointestinal and conjunctival infections have been described for viruses of the species *human mastadenovirus D.* [2] . Ad26 is assigned to risk group 2.

Ad26.COVS1 is replication defective due to the deletion of the E1 gene region (bp 463 - 3364). In addition, the E3 gene region (bp 26,690 - 30,682) is deleted, whose transcription units are not required for *in vitro replication of* the virus but encode immunomodulatory factors. The *open reading frame 6* (ORF6) of the E4 region was replaced with the corresponding region from adenovirus 5 (Ad5). A synthetic nucleic acid segment for the spike protein of SARS-CoV-2 was inserted into the E1 region. This was slightly modified to stabilize the formed protein in the pre-fusion conformation. The spike nucleic acid section is under the control of a cytomegalovirus TetO promoter and an SV40 poly(A) signal. To produce Ad26.COVS1, a recombinant complementing cell line is used, which provides the E1 gene region of Ad5 required for replication and contains a TetR element [3]

Ad26 vectors are widely used to produce vaccine candidates and have been tested in clinical trials involving more than 59,000 subjects. Potential vaccines used for this purpose include: Ad26.ZEBOV (against Zaire Ebola virus), Ad26.ENVA01, Ad26.Mos.HIV, Ad26.Mos4.HIV (all against human immunodeficiency virus, HIV), Ad26.CS.01 (against *Plasmodium falciparum*), Ad26.RSV.FA2, Ad26.RSV.preF (against respiratory syncytial virus, RSV), Ad26.HPV.16, Ad26.HPV.18 (against human papillomavirus) and Ad26.Filo (against filovirus). There are currently 51 clinical trials investigating Ad26-based vaccine candidates worldwide, including a trial with Ad26.COVS1 being conducted in the U.S. and Belgium [4] .

The first clinical trial with an Ad26-based vaccine (Ad26.ENVA.0 with a Nu-small acid section for a modified gp140 protein of HIV) was conducted with doses ranging from ^{109} to ^{1011} viral particles (vp). No *serious adverse events* (SAEs) occurred in this first study. At a dose of ^{1011} vp, adverse events such as malaise, muscle pain, fatigue, chills, and lymphopenia occurred and were rated as moderate to severe, but were only transient [5] . In further studies with Ad26.ENVA.01 and Ad26.Mos.HIV (trivalent vaccine consisting of Ad26.Mos1.Gag-Pol, Ad26.Mos2.Gag-Pol and Ad26.Mos.Env), most adverse events at a dose of 5 x ^{1010} vp were mild to moderate, in a few cases severe, and disappeared after a few days. Observed reactions included injection site reactions such as warmth, redness, swelling, pain, itching, rash, and/or induration, and systemic reactions such as headache, muscle and limb pain, fatigue, chills, fever, malaise, diffuse pruritus, nausea, vomiting, abdominal pain, and/or diarrhea [6–9] . The

RSV vaccine Ad26.RSV.preF elicited the same adverse events at a dose of 5 x ^{1010} vp or ^{1011} vp, almost all of which were mild or moderate and all of which were transient [10] .

Extensive clinical data are available for the Ebola vaccine Ad26.ZEBOV, which received marketing authorization from the European Commission on July 1, 2020. [11] extensive clinical data are available. Ad26.ZEBOV carries the glycoprotein of the Zaire Ebola virus and is administered in a two-dose vaccination model with a modified vacciniavirus Ankara-based preparation (vaccinations with several weeks interval). In clinical trials, adverse events were mostly mild to moderate and consistent with those for other Ad26-based vaccines [12, 13] . In one study, 24 of the 75 subjects experienced a decreased neutrophil count as an unanticipated adverse event. This normalized after seven days [14] . *Serious adverse events* also did not occur with Ad26.ZEBOV . The Committee for Medicinal Products for Human Use of the European Medicines Agency evaluated data from 3367 subjects in its positive opinion. [15] .

Recommendation

According to § 5 paragraph 1 GenTSV in conjunction with the criteria in Annex I GenTSV, the recombinant adenovirus Ad26.COVS1 is assigned to **risk group 1** as a genetically modified organism.

Justification

The recombinant adenovirus Ad26.COVS1 is a replication-deficient virus carrying a gene from SARS-CoV-2 without its own hazard potential and will be tested as a vaccine against SARS-CoV-2. An Ad26-based vaccine against the Zaire Ebola virus was recently approved by the EU Commission. This and other Ad26-based vaccines were well tolerated in clinical trials and mostly caused only mild or moderate adverse events.

Literature

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