Janssen Research & Development, B.V.*

Pharmacokinetics Written Summary

MODULE 2.6.4

VAC31518 JNJ-78436735

Prophylactic COVID-19 Vaccine

* Janssen Vaccines & Prevention B.V. is a Janssen pharmaceutical company of Johnson & Johnson and is hereafter referred to as the sponsor.

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LIST OF ABBREVIATIONS

Ad26	adenovirus type 26
Ad26 (b) (4)	Ad26 vector expressing (b) (4)
Ad26 (b) (4)	Ad26 vector encoding (b) (4)
COVID-19	coronavirus disease 2019
DNA	deoxyribonucleic acid
FDA	Food and Drug Administration
(b) (4)	
IM	intramuscular
LLOQ	lower limit of quantification
NZW	New Zealand white
OECD	Organization for Economic Co-operation and Development
(b) (4)	
qPCR	quantitative polymerase chain reaction
(b) (4)	
SARS	severe acute respiratory syndrome
SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
(b) (4)	
vp	virus particles

1. BRIEF SUMMARY

Ad26COVS1 (also known as VAC31518 or JNJ-78436735) is a monovalent, recombinant, replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Spike protein. It is being developed for prophylactic immunization against coronavirus disease 2019 (COVID-19), which has spread rapidly and globally since its emergence.

This summary provides an overview of the available pharmacokinetic data in support of the Ad26COVS1 development. No specific pharmacokinetic studies have been performed with Ad26COVS1. However, to assess the distribution, persistence, and clearance of the Ad26 vector (platform), biodistribution studies were conducted in rabbits using two other Ad26-based vaccines encoding (b) (4) and (b) (4) antigens. The Ad26 vector did not widely distribute following intramuscular (IM) administration in the animals. Vector DNA was primarily detected at the site of injection, draining lymph nodes and (to a lesser extent) the spleen. Clearance of the Ad26 vector from the tissues was observed. These data indicate that the Ad26 vector does not replicate and/or persist in the tissues following IM injection. In addition, both Ad26-based vaccines tested in the biodistribution studies showed a similar pattern of distribution and clearance when delivered via the IM route in the rabbit. Therefore, the available biodistribution results are considered sufficient to inform on the biodistribution profile of Ad26COVS1, for which the same Ad26 vector backbone is used.

The biodistribution studies were conducted in accordance with the GLP standards (OECD), which conform with Food and Drug Administration (FDA) regulations. The dates of study conduct, and location of the raw data are noted in the individual reports; these reports have been submitted previously as part of other Investigational New Drug Applications. Information on study GLP status and test facility identity are provided in the Pharmacokinetics Overview Table in Mod2.6.5.1.

2. BIODISTRIBUTION

To assess distribution, persistence, and clearance of the Ad26 viral vector (platform), IM biodistribution studies have been conducted in rabbits using an Ad26-based (b) (4) ie, Ad26 (b) (4) (Ad26 vector encoding (b) (4) (b) (4)) and an Ad26-based (b) (4) ie, Ad26 (b) (4) (Ad26 vector encoding (b) (4)); see Sections 2.1 and 2.2, respectively.

2.1. Ad26 (b) (4)

New Zealand white (NZW) rabbits were administered placebo or Ad26 (b) (4) at 1×10^{11} vp (Group 2) via a single IM injection on Day 1. In an additional study arm, Ad26 (b) (4) was dosed in combination with 150 µg (b) (4) as a single IM injection (Group 3). Necropsies were performed on 3 rabbits/sex in the placebo group and 5 rabbits/sex in the Ad26 (b) (4) groups on Days 11, 90, 120, and 180 to collect tissues for biodistribution analysis. The following tissues were collected to assess the presence of Ad26 (b) (4) using a quantitative polymerase chain reaction (qPCR) method: blood, ovaries/testes, liver, thymus,

heart, lung, kidney, spleen, mesenteric, iliac, and popliteal lymph nodes, bone marrow, brain, skin with subcutis at the injection site, and muscle at the injection site (b) (4)

In samples collected from Group 2 and 3 on Day 11, Ad26 (b) (4) vector DNA was primarily detected in the skin at the injection site, iliac lymph nodes, and spleen. The skin at the injection site and the iliac lymph nodes presented the highest number of vector copies. The popliteal lymph node showed a low signal (around or below the lower limit of quantification (LLOQ) of 28.6 copies/µg DNA) in 2 animals from Group 2. One animal from Group 3 showed a signal in the liver at a level below the LLOQ.

In both Group 2 and 3 on Day 90, Ad26 (b) (4) vector DNA was detected only in the skin at the injection site and in the iliac lymph nodes, but at a reduced incidence, as well as a lower maximum quantity of vector DNA than on Day 11.

On Day 120, Ad26 (b) (4) vector DNA was only detected at a low vector copy number (close to, or below the LLOQ) in a single spleen sample and iliac lymph nodes in 3 of 10 treated animals from Group 2.

On Day 180, detection of the vector was limited to the iliac lymph nodes in 3 of 10 treated animals in Group 2 and 2 out of 10 animals in Group 3 at a level close to, or below the LLOQ and was below the limit of detection in all other examined tissues or animals.

Animals from Group 2 and Group 3 showed a similar distribution pattern, indicating that addition of a recombinant (b) (4) protein does not impact on the distribution pattern of the Ad26 vector.

2.2. Ad26 (b) (4)

NZW rabbits were administered placebo or Ad26 (b) (4) at 5 x 10^{10} vp via a single IM injection on Day 1. Necropsies were performed on 3 rabbits/sex in the placebo group and 5 rabbits/sex in the Ad26 (b) (4) group on Days 11, 61, and 91 to collect tissues for biodistribution analysis. The following tissues were analyzed for the presence of Ad26 (b) (4) using a qPCR method: blood, ovaries/testes, liver, thymus, heart, lung, kidney, spleen, mesenteric and iliac lymph nodes, bone marrow, brain, and skin, subcutis, and muscle at the injection site (b) (4)

Analysis on Day 11 indicated that the Ad26 (b) (4) vaccine was primarily localized in the injection site muscle, draining (iliac) lymph nodes and to a lesser extent the spleen. Ad26 (b) (4) vector DNA was below limit of detection in all other organs, except for one animal that showed a low signal in the injection site skin at a level below the lower limit of quantification (50 copies/µg DNA).

In the animals sacrificed on Day 61, the Ad26 vector DNA was no longer detected in the spleen while vector DNA in the injection site muscle and iliac lymph nodes was detected at a reduced incidence and quantity compared to Study Day 11.

On Day 91, detection of the vector was limited to the injection site muscle and iliac lymph nodes in 2 of 10 treated animals and was below the limit of detection in all other examined tissues or animals.

3. DISCUSSION AND CONCLUSIONS

As a general pattern, both Ad26 vectors (i.e. Ad26 (b) (4) and Ad26 (b) (4)) showed a similar and limited biodistribution profile following IM administration, as they were primarily detected at the site of injection, regional (iliac) lymph nodes and (to a lesser extent) the spleen.

Comparing the various necropsy timepoints following IM administration (ie, Days 11, 61, and 91 for Ad26 (b) (4) Days 11, 90, 120 and 180 for Ad26 (b) (4)), a downward trend in the number of positive tissues and/or vector copy number was observed, to levels close to, or below the respective limits of detection, indicating clearance of the Ad26 vector from the tissues. These data further indicate that the Ad26 vector does not replicate and/or persist in the tissues following IM injection.

Comparing the injection site tissues, Ad26 (b) (4) vector DNA was mostly detected in the injection site muscle, while Ad26 (b) (4) vector DNA was mostly detected in the injection site skin. While there is no clear explanation for this difference, it has no apparent impact on the (systemic) distribution and clearance profile of the Ad26 vector. Therefore, despite differences in the expressed transgene insert, it can be concluded that both Ad26 vectors showed a similar pattern of (systemic) biodistribution and clearance when delivered via the IM route at full human doses in the rabbit.

The Ad26 vector backbone used for Ad26COVS1 is identical to the vector backbone of the Ad26-based vaccines that were tested in the available biodistribution studies (ie, Ad26 (b) (4) and Ad26 (b) (4)). Ad26COVS1 contains a (b) (4) in the cytomegalovirus promoter sequence of the transgene expression cassette (for details, see (b) (4)). This (b) (4) was not present in Ad26 (b) (4) and Ad26 (b) (4) Insertion of the (b) (4) is not considered to impact the biodistribution profile of the Ad26 vector. Adenoviruses are non-enveloped viruses whose cell entry, and therefore tropism, is dictated via interactions of structural capsid proteins (mainly the fiber and penton base) with specific cellular receptors [1]. The transgene expression cassette itself, which is inserted into the site where the E1 gene was previously located, is not involved in the formation or the composition of the Ad26 vector capsid. Different antigen transgenes/expression cassettes are therefore not expected to alter cell tropism. As a consequence, the biodistribution profile of the Ad26 vector is considered independent of the antigen transgenes/expression cassette, which is supported by the comparable distribution profile observed for Ad26 (b) (4) and Ad26 (b) (4) Therefore, the biodistribution profile observed for Ad26 (b) (4) and

Ad26 (b) (4) is considered sufficient to inform on the biodistribution profile of the Ad26COVS1 construct when administered via the same route of administration (IM).

4. LIST OF LITERATURE CITATIONS

Literature references are located in Mod4.3.

1. Sharma A, Li X, Bangari Ds, Mittal SK. Adenovirus receptors and their implications in gene delivery. Virus Res. 2009;143(2):184–194.