Approval Date: October 15, 2019

Product: Adenovirus Type 4 and Type 7 Vaccine, Live Oral

Proper Name: None

Indication: Active immunization for the prevention of febrile acute respiratory disease caused by Adenovirus Type 4 and Type 7.

Description: Adenovirus Type 4 and Type 7 Vaccine, Live, Oral contains viable, selected strains of human adenovirus Type 4 and human adenovirus Type 7 prepared in human-diploid fibroblast cell cultures (strain WI-38).

BLA: BL 125296

Regulatory Milestone:

Duramed Research, Inc., a subsidiary of Barr Laboratories, Inc., submitted biologics license application (BLA) 125296 on September 30, 2008 for licensure of Adenovirus Type 4 and Type 7 Vaccine, Live, Oral, Enteric Coated Tablets, to prevent febrile acute respiratory disease in military populations caused by Adenovirus Type 4 and Type 7. Efficacy and safety data in the BLA are from two clinical studies conducted under IND (b)(4), which was first submitted in July 2004. A Complete Response letter was sent to the applicant on July 16, 2009. In 2010, Barr Laboratories, Inc. was purchased by Teva Pharmaceuticals and Duramed's name was changed to Teva Women's Health, Inc. However, the manufacturing facility that produces the drug substance and drug product retained the name of the original company, Barr Laboratories. The applicant

submitted a complete response to the Complete Response letter on September 13, 2010. The response reset the review clock to a due date of March 16, 2011.

PDUFA Date: March 16, 2011

Package Insert: Package Insert – Adenovirus Type 4 and Type 7 Vaccine, Live, Oral

Summary Basis for Regulatory Approval: Summary Basis for Regulatory Action - Adenovirus

European Public Assessment Report:

Advisory Committee:

The application was not referred to the Vaccines and Related Biological Products Advisory Committee because the review of information submitted in the Biologics License Application (BLA), including the clinical study design and trial results, did not raise concerns or controversial issues which would have benefited from an advisory committee discussion

Safety:

No safety signal was noted in either the Phase 1 or the Phase 3 studies. Shedding was confirmed to occur in the treatment recipients in the Phase 1 study but only one out of 1009 placebo recipients had a positive throat swab for the vaccine strain of ADV-4, demonstrating the efficacy of the vaccine and highlighting the need for the vaccine in vulnerable populations.

The percentage of AEs and serious adverse events (SAEs) were comparable in both the treatment and placebo recipients in both studies. No specific event was identified as being caused by receipt of the vaccine, including pyrexia or viremia. Five pregnancies occurred during the Phase

3 study, 4 were vaccine recipients, and 1 received the placebo. All 5 pregnancies resulted in healthy babies.

The only safety concern associated with the vaccine is the possibility of infection of the unprotected population. A risk-management plan includes an education program for all recruits to explain the importance of personal hygiene during the 28-day shedding period. Prior to receipt of the vaccine and, if necessary, again prior to leaving the military during the 28-day shedding period, the recruits will be educated of the possibility of infecting vulnerable populations, such as children under the age of 7 years old, pregnant women, and immunocompromised individuals.

NCT Numbers:

- NCT03160339
- NCT01584037
- NCT00382408

EudraCT Numbers:

- 2011-001788-36
- 2017-003169-82
- 2019-001154-26
- 2014-004714-28
- 2018-000853-29
- 2007-001657-26
- 2006-005795-41
- 2019-001890-98
- 2011-005889-38

Publications:

- Li, J. X., Hou, L. H., Meng, F. Y., Wu, S. P., Hu, Y. M., Liang, Q., Chu, K., Zhang, Z., Xu, J. J., Tang, R., Wang, W. J., Liu, P., Hu, J. L., Luo, L., Jiang, R., Zhu, F. C., & Chen, W. (2017). Immunity duration of a recombinant adenovirus type-5 vector-based Ebola vaccine and a homologous prime-boost immunisation in healthy adults in China: final report of a randomised, double-blind, placebo-controlled, phase 1 trial. *The Lancet. Global health*, *5*(3), e324–e334. https://doi.org/10.1016/S2214-109X(16)30367-9
- Milligan, I. D., Gibani, M. M., Sewell, R., Clutterbuck, E. A., Campbell, D., Plested, E., Nuthall, E., Voysey, M., Silva-Reyes, L., McElrath, M. J., De Rosa, S. C., Frahm, N.,

Cohen, K. W., Shukarev, G., Orzabal, N., van Duijnhoven, W., Truyers, C., Bachmayer, N., Splinter, D., Samy, N., … Snape, M. D. (2016). Safety and Immunogenicity of Novel Adenovirus Type 26- and Modified Vaccinia Ankara-Vectored Ebola Vaccines: A Randomized Clinical Trial. *JAMA*, *315*(15), 1610–1623. https://doi.org/10.1001/jama.2016.4218

- Kuschner, R. A., Russell, K. L., Abuja, M., Bauer, K. M., Faix, D. J., Hait, H., Henrick, J., Jacobs, M., Liss, A., Lynch, J. A., Liu, Q., Lyons, A. G., Malik, M., Moon, J. E., Stubbs, J., Sun, W., Tang, D., Towle, A. C., Walsh, D. S., Wilkerson, D., … Adenovirus Vaccine Efficacy Trial Consortium (2013). A phase 3, randomized, double-blind, placebo-controlled study of the safety and efficacy of the live, oral adenovirus type 4 and type 7 vaccine, in U.S. military recruits. *Vaccine*, *31*(28), 2963–2971. https://doi.org/10.1016/j.vaccine.2013.04.035
- Ledgerwood, J. E., DeZure, A. D., Stanley, D. A., Coates, E. E., Novik, L., Enama, M. E., Berkowitz, N. M., Hu, Z., Joshi, G., Ploquin, A., Sitar, S., Gordon, I. J., Plummer, S. A., Holman, L. A., Hendel, C. S., Yamshchikov, G., Roman, F., Nicosia, A., Colloca, S., Cortese, R., … VRC 207 Study Team (2017). Chimpanzee Adenovirus Vector Ebola Vaccine. *The New England journal of medicine*, *376*(10), 928–938. https://doi.org/10.1056/NEJMoa1410863
- Lyons, A., Longfield, J., Kuschner, R., Straight, T., Binn, L., Seriwatana, J., Reitstetter, R., Froh, I. B., Craft, D., McNabb, K., Russell, K., Metzgar, D., Liss, A., Sun, X., Towle, A., & Sun, W. (2008). A double-blind, placebo-controlled study of the safety and immunogenicity of live, oral type 4 and type 7 adenovirus vaccines in adults. *Vaccine*, *26*(23), 2890–2898. https://doi.org/10.1016/j.vaccine.2008.03.037
- Takafuji, E. T., Gaydos, J. C., Allen, R. G., & Top, F. H., Jr (1979). Simultaneous administration of live, enteric-coated adenovirus types 4, 7 and 21 vaccines: safety and immunogenicity. *The Journal of infectious diseases*, *140*(1), 48–53. https://doi.org/10.1093/infdis/140.1.48
- Dudding, B. A., Bartelloni, P. J., Scott, R. M., Top, F. H., Jr, Russell, P. K., & Buescher, E. L. (1972). Enteric immunization with live adenovirus type 21 vaccine. I. Tests for safety, infectivity, immunogenicity, and potency in volunteers. *Infection and immunity*, *5*(3), 295–299. https://doi.org/10.1128/IAI.5.3.295-299.1972

- Ouédraogo, A., Tiono, A. B., Kargougou, D., Yaro, J. B., Ouédraogo, E., Kaboré, Y., Kangoye, D., Bougouma, E. C., Gansane, A., Henri, N., Diarra, A., Sanon, S., Soulama, I., Konate, A. T., Watson, N. L., Brown, V., Hendriks, J., Pau, M. G., Versteege, I., Wiesken, E., … Sirima, S. B. (2013). A phase 1b randomized, controlled, double-blinded dosage-escalation trial to evaluate the safety, reactogenicity and immunogenicity of an adenovirus type 35 based circumsporozoite malaria vaccine in Burkinabe healthy adults 18 to 45 years of age. *PloS one*, *8*(11), e78679. https://doi.org/10.1371/journal.pone.0078679
- Top, F. H., Jr, Buescher, E. L., Bancroft, W. H., & Russell, P. K. (1971). Immunization with live types 7 and 4 adenovirus vaccines. II. Antibody response and protective effect against acute respiratory disease due to adenovirus type 7. *The Journal of infectious diseases*, *124*(2), 155–160. https://doi.org/10.1093/infdis/124.2.155
- van Zyl-Smit, R. N., Esmail, A., Bateman, M. E., Dawson, R., Goldin, J., van Rikxoort, E., Douoguih, M., Pau, M. G., Sadoff, J. C., McClain, J. B., Snowden, M. A., Benko, J., Hokey, D. A., Rutkowski, K. T., Graves, A., Shepherd, B., Ishmukhamedov, S., Kagina, B., Abel, B., Hanekom, W. A., … Bateman, E. D. (2017). Safety and Immunogenicity of Adenovirus 35 Tuberculosis Vaccine Candidate in Adults with Active or Previous Tuberculosis. A Randomized Trial. *American journal of respiratory and critical care medicine*, *195*(9), 1171–1180. https://doi.org/10.1164/rccm.201603-0654OC