

Addendum to the statistical memo dated April 20, 2020

<b>Application Type</b>	Original BLA
<b>STN</b>	125700/0/54
<b>CBER Received Date</b>	September 3, 2019 (original submission) June 30, 2022 (resubmission)
<b>PDUFA Goal Date</b>	December 30, 2022
<b>Division / Office</b>	DCGT/OTAT
<b>Committee Chair</b>	Anurag Sharma, PhD
<b>Clinical Reviewer(s)</b>	Laronna Colbert, M.D.
<b>Project Manager</b>	Adriane Fisher, M.P.H., M.B.A.
<b>Priority Review</b>	Yes
<b>Reviewer Name(s)</b>	Jiang Hu, Ph.D.
<b>Review Completion Date / Stamped Date</b>	
<b>Supervisory Concurrence</b>	Boguang Zhen, Ph.D. Branch Chief, Therapeutics Evaluation Branch 1
<b>Applicant</b>	Ferring Pharmaceuticals A/S
<b>Established Name</b>	Nadofaragene firadenovec
<b>(Proposed) Trade Name</b>	ADSTILADRIN
<b>Pharmacologic Class</b>	
<b>Dosage Form(s) and Route(s) of Administration</b>	Administered by intravesical instillation every three months.
<b>Dosing Regimen</b>	2.25 x 10 <sup>13</sup> virus particles (vp) /mL in a total volume of 75 mL
<b>Indication(s) and Intended Population(s)</b>	Treatment of high-grade, Bacillus Calmette- Guérin (BCG) unresponsive non-muscle invasive bladder cancer.

## 1. Executive Summary

This Biologics License Application (BLA) seeks licensure of ADSTILADRIN for the treatment of high-grade, Bacillus Calmette-Guérin (BCG) unresponsive non-muscle invasive bladder cancer (NMIBC).

The original BLA, 125700/0, was submitted on September 3, 2019. I completed the statistical review and submitted the signed memo on April 20, 2020 with the conclusion that the statistical analysis results support the safety and effectiveness of ADSTILADRIN in the proposed indication for this BLA. For detailed statistical evaluation, please refer to the statistical memo.

Due to Chemistry, Manufacturing, and Controls issues, a Complete Response letter was issued on April 24, 2020. The BLA was resubmitted on April 11, 2022, and an incomplete response letter was issued on May 10, 2022. The applicant resubmitted the second time on June 30, 2022. This addendum presents the re-analysis results for the updated data of Study rAd-IFN-CS-003 submitted in 125700/0/54.

For the resubmission, the clinical team would like to exclude five (5) subjects from the efficacy population for Study rAd-IFN-CS-003 due to the uncertainty of their complete response (CR) status. I re-analyzed the data without the five subjects and found that the results are consistent with those with the five subjects. Overall, the statistical analysis results support the safety and effectiveness of ADSTILADRIN in the proposed indication for this BLA.

## 2. Statistical Evaluation

The efficacy of ADSTILADRIN was evaluated in CS-003 (NCT02773849), an open-label, multicenter, single-arm trial in 157 adults with BCG-unresponsive, high risk, non-muscle invasive bladder cancer with carcinoma in situ (CIS) with or without papillary tumors following transurethral resection, of whom 103 were considered evaluable for response. For the resubmission in 125700/0/54, the clinical team reviewed the data from the 55 responders and feel that some subjects should be excluded from the efficacy population as the definition of complete response (CR) used by the applicant is not consistent with the definition of CR in the 2018 FDA guidance-BCG-Unresponsive Non-muscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment. The team also found that two subjects for whom the sponsor could not provide any documentation regarding the cystoscopy method used at screening so they cannot confirm that the same cystoscopy method was used at the time of CR. Therefore, the clinical team recommends excluding the five subjects and re-analyzing the data.

In the statistical memo of 125700/0, the primary efficacy endpoint, the CR rate, was observed as 53.4% (55/103) with a 95% CI (43.3%, 63.3%). After excluding five subjects from the efficacy population, the CR rate was observed as 51.0%

(50/98) with a 95% CI (40.7%, 61.3%). The null hypothesis of a true response rate of less than 27% is rejected and the study met its pre-specified success criterion. Among the 50 subjects who achieved CR, the median durability of CR is 9.7 months (range:3, 52+), and 46% (23/50) had the CR duration  $\geq$  12 months.

The 98 evaluable CIS study population characteristics were median age of 70 (range 44-89) with 32%  $>75$  years of age; 88% male, 92% white. Tumor pattern at study entry was CIS with T1 (5%), CIS with high-grade Ta (19%), and CIS (76%). The median number of instillations of prior BCG was 12 (range 8 to 18).

### 3. CONCLUSION

With the updated datasets submitted in 125700/0/54, the CR rate was observed as 51.0% (50/98) with a 95% CI (40.7%, 61.3%) and the median durability of CR is 9.70 months (range:3, 52+). The pre-specified success criterion has been met. The statistical analysis results provide evidence to support the safety and effectiveness of ADSTILADRIN in the proposed indication for this BLA.