CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214460Orig1s000
214461Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	214,460 and 214,461/S-0000
Drug Name:	TEMBEXA (brincidofovir)
Indication(s):	The treatment for human smallpox disease in adult and pediatric patients
Applicant:	Chimerix Inc.
Date(s):	Submitted: October 7, 2020
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Review Priority:	Priority
Biometrics Division:	Division of Biometrics IV
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Keywords: Smallpox, TEMBEXA, Animal model, Rabbitpox, and Mousepox

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1 EXECUTIVE SUMMARY

This is a statistical review of New Drug Application (NDA) 214460 and 214461 submitted by Chimerix Inc. (the Applicant) for TEMBEXA (brincidofovir (BCV)) administered by oral suspension or tablet. The proposed indication is for the treatment of human smallpox disease in adult and pediatric patients. Because smallpox is a potentially serious threat but does not occur naturally, clinical trials are not feasible and human challenge studies in healthy subjects are unethical. Therefore, animal models may provide important information for the evaluation of treatment effect and may contribute directly to drug approval under the Animal Rule (21 CFR part 314, subpart I). The main objective of this review is to evaluate whether the efficacy presented in the two pivotal animal studies submitted, one rabbit (rabbitpox) study and one mouse (mousepox) study, supports the indication sought by the Applicant under the Animal Rule.

The rabbit study, CMX-VIR-106, was a randomized, blinded, placebo-controlled study to evaluate the efficacy of a three-dose regimen (20/5/5 mg/kg) of TEMBEXA initiated at post inoculation day (PID) 3, 4, 5, or 6 as compared to a placebo control. The primary endpoint was the survival rate at PID 42. TEMBEXA demonstrated statistically significant difference on survival as compared to the placebo when initiated at PID 3, 4, 5, and 6.

The mouse study, CMX-VIR-044, was a randomized, placebo-controlled study to evaluate the efficacy of two dose levels of TEMBEXA as compared to a placebo control. The regimens are 3-dose (10/5/5 mg/kg) TEMBEXA initiated at PID 4, 5, or 6 and 3-dose (20/5/5 mg/kg) TEMBEXA initiated at PID 4, 5, 6, or 7. The primary endpoint was the survival rate at PID 42. CMX-VIR-044 showed that TEMBEXA 10/5/5 mg/kg initiated at PID 4 and PID 5 demonstrated statistically significant effect on survival; TEMBEXA 20/5/5 mg/kg initiated at PID 4, 5, 6, and 7 all demonstrated statistically significant effect on survival as compared to the placebo.

The rabbitpox model formed the basis of selecting the TEMBEXA dose of 200 mg once weekly for two doses for patients weighing 48 kg and above, and the dose selection was supported by the mousepox model with a TEMBEXA dose of 10/5/5 mg/kg. Dosing for pediatric patients weighing between 10 kg and less than 48 kg is 4 mg/kg of oral suspension once weekly for 2 doses and for those weighing less than 10 kg is 6 mg/kg of oral suspension once weekly for 2 doses, determined based on simulations (please refer to the clinical pharmacology review for details). Drug form of oral suspension was supported by bioequivalence studies (please refer to the clinical pharmacology review for details).

In conclusion, the findings from the two animal models demonstrated that TEMBEXA is efficacious as the treatment of human smallpox disease under the Animal Rule. A post marketing requirement (PMR) was issued to the Applicant to conduct a human field study to evaluate the efficacy and safety of TEMBEXA vs standard-of-care (SOC) vs TEMBEXA+ SOC.

Key statistical review issue: there was no major statistical review issue identified in this submission.

2 INTRODUCTION

2.1 Overview

Smallpox is an infectious human disease caused by variola virus. Although eradicated in 1980, the disease remains as a threat due to the potential use as a bioterrorism agent, the potential for accidental release, or re-mergence. Therefore, medical countermeasures, including antiviral therapies, are in need in the event of a smallpox virus outbreak.

TEMBEXA (brincidofovir) is a lipid-modified acyclic nucleotide that has activity against certain variola viruses and orthopoxviruses. Because human studies to evaluate the efficacy of BCV against smallpox disease is not ethical or feasible, TEMBEXA has been developed under the Animal Rule. Based on the discussion in the Antiviral Advisory Committee meeting in 2011, the FDA and the advisory committee agreed that data from animal models of orthopoxvirus infection utilizing rabbits, mice, and non-human primates could be used as evidence for an NDA. Please refer to the clinical review by Dr. Chan-Tack for more details regarding the Animal Rule for this NDA application.

In this NDA submission, the efficacy data from two independent animal models were submitted, which included one study of rabbits (rabbitpox) and one study of mice (mousepox). The Applicant also submitted studies for human safety evaluation, and they were not included in this statistical efficacy review.

2.1.1 Studies Reviewed

The detailed description of the two non-human studies is listed in Table 1. Study CMX001-VIR-106 was conducted using rabbitpox virus (RPXV) in New Zealand White (NZW) rabbits and Study CMX001-VIR-044 was conducted using mousepox (ectromelia virus (ECTV)) in mice.

Table 1: List of Animal Studies Included in This Review

Study Number	**Design**	**Treatment**	**Endpoint/Analysis**	**Preliminary Findings (Survival Rate)**
CMX001-VIR-106 (GLP)	Randomized, blinded, placebo-controlled, parallel group study to evaluate the efficacy of 3-dose oral BCV 20/5/5 mg/kg in NZW rabbits infected with RPXV.	BCV at PID 3; N=29	The primary efficacy endpoint is the proportion of animals that survived through PID 42.	29/29 (100.0%)
		BCV at PID 4; N=29		26/29 (89.7%)
		BCV at PID 5; N=29		20/29 (69.0%)
		BCV at PID 6; N=29		20/29 (69.0%)

		Placebo; N=28		8/28 (28.6%)
CMX001-VIR-044^ (GLP)	Randomized, blinded, placebo-controlled, parallel group study to evaluate the efficacy of 3-dose oral BCV in the mousepox model for smallpox, when treatment of BCV 10/5/5 mg/kg is initiated at PID 4, 5, or 6, and treatment of BCV 20/5/5 mg/kg is initiated at PID 4, 5, 6, or 7	BCV 10/5/5 mg/kg at PID 4; N=32	The primary efficacy endpoint is the proportion of animals that survived through PID 42.	25/32 (78.1%)
		BCV 10/5/5 mg/kg at PID 5; N=32		21/32 (65.6%)
		BCV 10/5/5 mg/kg at PID 6; N=32		11/32 (34.4%)
		BCV 20/5/5 mg/kg at PID 4; N=32		27/32 (84.4%)
		BCV 20/5/5 mg/kg at PID 5; N=32		24/32 (75.0%)
		BCV 20/5/5 mg/kg at PID 6; N=32		15/32 (46.9%)
		BCV 20/5/5 mg/kg at PID 7; N=32		12/32 (37.5%)
		Placebo; N=32		4/32 (12.5%)

GLP, Good Laboratory Practices; PID, Post Inoculation Day.
^Groups 1-8 for efficacy evaluation
Source: Reviewer assembled.

The detailed design characteristics of the two studies are described in Section 3.2.1.

2.2 Data Sources

All studies submitted were animal studies and Standard for Exchange of Nonclinical Data (SEND) format datasets were submitted for the two studies under Module 4 instead of Module 5 for human clinical studies. This reviewer conducted efficacy analyses to verify the Applicant's results.

1. Reviewed protocols, statistical analysis plans, efficacy results, and conclusions in the following submitted documents:
    - Module 1- Labeling materials
    - Module 2- 2.7.3 Summary of Clinical Efficacy
    - Module 4- 4.2.1.1 Clinical Study Reports (CSRs) of the two animal studies
2. The SEND datasets are under CDER Electronic Document Room (EDR) directory.

Rabbit study: \\CDSESUB1\evsprod\nda214461\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\cmx001-vir-106

Mouse study: \\CDSESUB1\evsprod\nda214461\0001\m4\42-stud-rep\421-pharmacol\4211-prim-pd\cmx001-vir-044
\\CDSESUB1\evsprod\nda214461\0003\m4\datasets\cmx001-vir-044\tabulations\send
Note that the names of the efficacy datasets for the mouse study under both file path are the same. This reviewer compared the primary efficacy findings drawn from both datasets and they were the same. The analyses in this review were based on the data submitted in \\CDSESUB1\evsprod\nda214461\0001.

3 STATISTICAL EVALUATION

Two studies, one rabbit study and one mouse study, were reviewed separately in each of the following sections. All tables and figures were generated by the statistical reviewer unless otherwise cited.

3.1 Data and Analysis Quality

Overall, the quality of the data was acceptable. This reviewer was able to reproduce the primary efficacy results presented in the CSRs.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Rabbitpox Model – Study CMX001-VIR-106

Study CMX001-VIR-106 (further referred to as VIR-106) was a randomized, blinded, placebo-controlled, parallel group study to evaluate the efficacy of brincidofovir (BCV) orally administered in New Zealand White (NZW) rabbits infected with rabbitpox virus (RPXV). The study treatments were blinded to the Applicant, Study Director, staff, and virologists; they were unblinded to 3 individuals at the test facility: quality assurance auditor, randomization statistician, and unblinded Subject Matter Expert (SME). The randomization group assignment was confidential to the SME until the study was officially unblinded.

This study evaluated a three-dose regimen, BCV 20/5/5 mg/kg. The animals were challenged with RPXV (600 plaque forming units [pfu]) via intradermal route on Study Day 0 and were randomized by weight and sex into 5 groups to receive BCV 20/5/5 mg/kg every other day beginning on Study Day 3 (Post Inoculation Day (PID) 3), 4 (PID 4), 5 (PID 5), 6 (PID 6), or placebo. Clinical observations occurred from Study Day -7 to Study Day 42. Morbidity and mortality check, including determination on whether an animal met the criteria for euthanasia and determination on weight loss, occurred from Study Day 4 through Study Day 11. Body temperature and respiratory rate were observed on Study Days -2, -1, 0, 1, through Study Day 42. Body weight was observed on Study Days -7, -3, -1, 0, 1, through Study Day 42. Lesion was

assessed from Study Day 0 through Study Day 42. Challenge site was monitored from Study Day 0 through Study Day 42.

The primary endpoint was the proportion of animals survived through PID 42. The survival rate in each of the BCV group was compared to that in the placebo group. The overall type I error rate of 0.05 was controlled utilizing a stepdown testing procedure, following a trend test on the treatment efficacy across regimens. The stepdown testing procedure compared each BCV group to the placebo at a pre-specified order of PID 3 vs placebo, PID 4 vs placebo, PID 5 vs placebo, and PID 6 vs placebo.

The primary analyses were performed based on the intent-to-treat (ITT) set, defined as all randomized animals that meet the eligibility criteria, challenged and assigned to a blinded dosing kit. Per the Statistical Analysis Plan (SAP), the monotonicity of treatment efficacy on survival rate was established using a Cochran Armitage trend test, followed by the primary efficacy analysis using a Boschloo's exact unconditional test to compare the survival rate between each BCV group and the placebo. Multiplicity was handled utilizing a sequential testing procedure with a fixed sequence, starting from the earliest treatment initiation day compared to the placebo continuing to the second earliest initiation day, until there was no significant difference.

The planned sample size was 150 (30 animals in each group). The sample size calculation assumed a survival rate of 85% and 40% for BCV and the placebo, respectively. Based on the reviewer's calculation, this study had over 93% power to demonstrate superiority of BCV over the placebo with 26 subjects in each group. The sample size calculation was based on a Boschloo's exact unconditional test for difference between proportions at a one-sided alpha of 0.025 and was carried out using Cytel Studio 11. The actual sample size was 144 (29 animals in each of the BCV groups and 28 animals in the placebo group). Six (6) animals were excluded or not challenged, of which 3 were euthanized because the inclusion criteria were not met, 1 died prior to challenge, 1 was euthanized after being found with a broken leg, and 1 was found dead. The study group assignment was summarized in Table 2.

Reviewer comment: The Applicant calculated sample size based on a Boschloo's exact unconditional test at a one-sided alpha of 0.05 and the proposed power was >95%.

This study began at 09/28/2018 and was unblinded at 01/22/2019, conducted at (b) (4) (b) (4) VIR-106 was conducted in accordance with Good Laboratory Practices (GLP).

Table 2. Summary of Group Assignment, Study VIR-106

Group	Planned Number of Animals	Actual Number of Animals	Challenge Study Day 0 Target Challenge Dose	Timing of BCV and Control Article Administration Per Blinded Kit Study Day 3 Blinded Dosing Kit Dose Vial 1	Study Day 4 Blinded Dosing Kit Dose Vial 2	Study Day 5 Blinded Dosing Kit Dose Vial 3	Study Day 6 Blinded Dosing Kit Dose Vial 4	Study Day 7 Blinded Dosing Kit Dose Vial 5	Study Day 8 Blinded Dosing Kit Dose Vial 6	Study Day 9 Blinded Dosing Kit Dose Vial 7	Study Day 10 Blinded Dosing Kit Dose Vial 8
1	30 (15/sex)	29 (14 M, 15 F)	600 PFU	**BCV (20 mg/kg)**	Control Article	**BCV (5 mg/kg)**	Control Article	**BCV (5 mg/kg)**	Control Article	Control Article	Control Article
2	30 (15/sex)	29 (15 M, 14 F)		Control Article	**BCV (20 mg/kg)**	Control Article	**BCV (5 mg/kg)**	Control Article	**BCV (5 mg/kg)**	Control Article	Control Article
3	30 (15/sex)	29 (14 M, 15 F)		Control Article	Control Article	**BCV (20 mg/kg)**	Control Article	**BCV (5 mg/kg)**	Control Article	**BCV (5 mg/kg)**	Control Article
4	30 (15/sex)	29 (15 M, 14 F)		Control Article	Control Article	Control Article	**BCV (20 mg/kg)**	Control Article	**BCV (5 mg/kg)**	Control Article	**BCV (5 mg/kg)**
5	30 (15/sex)	28 (14 M,14 F)		Control Article	Control Article	Control Article	Control Article	Control Article	Control Article	Control Article	Control Article

Source: Table 1 in Study VIR-106 CSR

3.2.1.2 Mousepox Model – Study VIR-044

This was a randomized, placebo-controlled, parallel group study to investigate BCV in the mousepox model for smallpox. This study consisted of 3 cohorts: Cohort 1 with 8 groups (Groups 1-8) for efficacy evaluation, Cohort 2 with 1 group (Group 9) assessing viral load, and Cohort 3 with 3 groups (Groups 10-12) assessing resistance. All the animals were challenged with ECTV. The randomization was blinded in Cohort 1 and was unblinded in Cohorts 2 and 3. For the randomization in Cohort 1, study treatments were blinded to the Applicant, Study Director, staff, and virologists; they were unblinded to 3 individuals at the test facility: quality assurance auditor, randomization statistician, and unblinded SME. This review will focus on efficacy evaluations in Cohort 1 as the efficacy findings were supported by the data in Cohort 1.

This study evaluated two dose levels of BCV with a three-dose regimen, BCV 10/5/5 mg/kg (initiated at PID 4, 5, 6) and BCV 20/5/5 mg/kg (initiated at PID 4, 5, 6, 7). The animals were challenged intranasally with ECTV (200 pfu) on Study Day 1 and were randomized by weight and sex into eight groups to receive the study treatments every other day at the pre-specified treatment initiation day or the placebo. Clinical observation occurred during quarantine, and from Study Day -7 to Study Day 43. Morbidity and mortality were observed from Study Day 5 to Study Day 12. Body weight was observed once during quarantine, and on Study Days -7, -3, -1, and from Study Day 1 to Study Day 43. Body temperature was observed from Study Day -7 to Study Day 43.

The primary endpoint was the proportion of animals survived through PID 42. The Applicant compared the survival rate in each of the BCV group to that in the placebo group. Because two dose levels were evaluated, the Applicant split the nominal alpha level between the two dose levels to control the overall type I error rate. Within each dose group, a Cochran-Armitage trend test was used to assess the monotonicity of efficacy. The survival rates were compared using a one-sided Boschloo's exact unconditional test, the familywise error rate within each dose level was controlled utilizing a sequential testing procedure.

The planned sample size for the efficacy cohort was 168 (32 animals in each group). Assuming the survival rate was up to 20% in the placebo group, based on the reviewer's calculation, the study with 26 animals per group would have >93% power with a risk difference of 50% and have >78% power with a risk difference of 40%. The sample size calculation was based on a

Boschloo's exact unconditional test for difference between proportions at a one-sided alpha of 0.0125, carried out using Cytel Studio 11. The actual sample size was the same as planned. The study group assignment was summarized in Table 3.

Reviewer Comment: The Applicant calculated the sample size based on a one-sided Boschloo's exact unconditional test at a one-sided alpha of 0.025, and the study would have >95% power with a risk difference of 50% and >85% power with a risk difference of 40%.

This study began at 01/18/2019, and was unblinded at 04/26/2019, conducted at (b) (4) (b) (4) VIR-044 was conducted in accordance with Good Laboratory Practices (GLP).

Table 3. Summary of Group Assignment, Study VIR-044

Arm	Group	n (M/F)	ECTV Challenge Day[a]	Blinded or Unblinded	BCV First/ Second/ Third/ Dose (mg/Kg)	BCV/ Placebo Dosing[b] Days								Blood, Liver, Spleen Collection Days	Number of Mice per Collection Time Point (M/F)
						Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12		
Efficacy Evaluation	1	16/16	1	Blinded	10 / 5 / 5	BCV	P	BCV	P	BCV	P	P	P	T[c]	16/16
	2	16/16	1	Blinded	10 / 5 / 5	P	BCV	P	BCV	P	BCV	P	P	T[c]	16/16
	3	16/16	1	Blinded	10 / 5 / 5	P	P	BCV	P	BCV	P	BCV	P	T[c]	16/16
	4	16/16	1	Blinded	20 / 5 / 5	BCV	P	BCV	P	BCV	P	P	P	T[c]	16/16
	5	16/16	1	Blinded	20 / 5 / 5	P	BCV	P	BCV	P	BCV	P	P	T[c]	16/16
	6	16/16	1	Blinded	20 / 5 / 5	P	P	BCV	P	BCV	P	BCV	P	T[c]	16/16
	7	16/16	1	Blinded	20 / 5 / 5	P	P	P	BCV	P	BCV	P	BCV	T[c]	16/16
	8	16/16	1	Blinded	0 / 0 / 0	P	P	P	P	P	P	P	P	T[c]	16/16
Viral Load	9	20/20	1	Unblinded	None	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3, 4, 5, 6, 7, T[d]	4/4
Resistance	10	7/7	1	Unblinded	20 / 5 / 5	N/A	BCV	P	BCV	P	BCV	P	N/A	8, 9, 10, 11, 12, 13, 16, T[e]	1/1
	11	7/7	1	Unblinded	20 / 5 / 5	N/A	P	BCV	P	BCV	P	BCV	N/A		1/1
	12	7/7	1	Unblinded	0 / 0 / 0	N/A	P	P	P	P	P	P	N/A		1/1

[a] Intranasal challenge for the first animal was initiated at 0900 ± 2 hours.
[b] Doses were administered by oral gavage. The first dose of each blinded treatment (BCV or placebo, P) for Groups 1 through 8 was administered on Day 5 (post-infection day 4 or PID4). The first dose of each unblinded treatment (BCV or P) for Groups 10 through 12 was administered on Day 6 (post-infection day 5 or PID5). Daily doses (blinded and unblinded) were administered at 1000 ± 2 hours.
[c] "T" refers to terminal for survivors on Day 43 (last day on study), unscheduled euthanasia or animals found dead. Blood was not to be collected from animals found dead; only liver and spleen were to be collected.
[d] "T" refers to unscheduled euthanasia or animals found dead. Blood was not to be collected from animals found dead; only liver and spleen were to be collected. NOTE: last day on study for Group 9 was Day 7.
[e] "T" refers to unscheduled euthanasia or animals found dead. Blood was not to be collected from animals found dead; only liver and spleen were to be collected. NOTE: last day on study for Groups 10, 11, and 12 was Day 16.

Source: Table 1 in Study VIR-044 CSR

3.2.2 Statistical Methodologies

Reviewer Comment: The Applicant conducted statistical tests and concluded the efficacy findings using a one-sided alpha of 0.05. It is recommended that inferences should be made using a two-sided alpha of 0.05 or a one-sided alpha of 0.025. Therefore, the reviewer will make efficacy inferences based on a one-sided alpha of 0.025, or one-sided adjusted alpha levels as applicable.

The Applicant did not specify the nuisance parameter, Gamma, for the Boschloo's test. The reviewer analyzed the primary efficacy endpoint using a Boschloo's exact test with gamma = 0 and was able to reproduce the results presented in the CSRs.

3.2.2.1 Study VIR-106

The Applicant used a Cochran Armitage trend test to demonstrate the monotonicity of treatment efficacy, followed by the Boschloo's test to compare the survival rate between each BCV group and the placebo at a pre-specified order. The Applicant also provided the exact 95% CI of difference in survival rate between each BCV regimen and the placebo, along with the 95% CI of survival rate in each treatment group.

In the SAP, the Applicant proposed to adjust multiplicity utilizing a sequential testing procedure that the subsequent test will be performed only when statistical significance is demonstrated. The test between each BCV group and the placebo group was ordered by treatment initiation day, earliest first. The CSR reported a stepdown version of Bonferroni adjusted p-values (also known as Holm's procedure) in addition to the unadjusted p-values.

The reviewer conducted a Cochran-Armitage trend test to assess the monotonicity of efficacy across the 4 BCV groups, and the Boschloo's test with gamma = 0. The reviewer calculated the 95% CIs of difference based on inverting two one-sided tests, carried out using Cytel Studio, and the 95% of survival rate using a Clopper-Pearson method. This reviewer made inferences based on the Applicant proposed sequential testing procedure, and conclusions based on the Holm's procedure were also discussed.

3.2.2.2 Study VIR-044

To control the overall type I error rate, the Applicant split the alpha level, allocating 0.025 to the BCV 10/5/5 mg/kg groups and 0.025 to the BCV 20/5/5 mg/kg groups. The Applicant further controlled the familywise error rate within each dose group utilizing a sequential testing procedure, ordered by treatment initiation day, earliest first. The testing procedure described below applies to each of the dose levels.

The Applicant used a Cochran-Armitage trend test to demonstrate the monotonicity of efficacy for the treatment groups ordered by treatment initiation day, earliest first. After monotonicity of efficacy was demonstrated at the adjusted alpha level, the Applicant used a one-sided Boschloo's test to compare the survival rate between each of the BCV regimen and the placebo. The Applicant provided the exact 95% CIs of difference in survival rate between each BCV group and the placebo, and the proportion of animals survived at PID 42 and its associated 95% CI.

The reviewer performed the Cochran-Armitage trend test to assess monotonicity of efficacy across BCV regimens within the same dose groups, and the Boschloo's test using gamma = 0. The reviewer calculated the 95% exact CIs of difference in survival rate between each BCV group and the placebo, and the 95% CI of survival rate in each group using the same methods as specified in Study VIR-106. The conclusions will be made based on the sequential testing procedure; and be discussed based on the Holm's procedure.

3.2.3 Demographic Characteristics

This section summarizes the randomization factors of sex and weight at baseline.

3.2.3.1 Study VIR-106

Table 4 captures the baseline demographic characteristics of the animals in Study VIR-106. Sex was balanced in each of the treatment group. Baseline body weight at Study Day 0 was similar across all groups, with a mean weight of 2.0 kg.

Table 4. Summary of Baseline Demographic Characteristics, Study VIR-106

	Sex, n (%)		Study Day 0 Body Weight (kg)		
Group	**Male**	**Female**	**Mean**	**Median**	**Range**
BCV 20/5/5 mg/kg at PID 3	14 (48.3)	15 (51.7)	2.0	2.0	1.8 - 2.3
BCV 20/5/5 mg/kg at PID 4	15 (51.7)	14 (48.3)	2.0	2.0	1.8 - 2.3
BCV 20/5/5 mg/kg at PID 5	14 (48.3)	15 (51.7)	2.0	2.0	1.7 - 2.4
BCV 20/5/5 mg/kg at PID 6	15 (51.7)	14 (48.3)	2.0	2.0	1.8 - 2.4
Placebo	14 (50.0)	14 (50.0)	2.0	2.0	1.8 - 2.4

Source: Reviewer's analyses

3.2.3.2 Study VIR-044

Table 5 presents the baseline demographic characteristics of the animals in Study VIR-044. Sex was balanced in all treatment groups. Baseline body weight was similar across groups, with a mean of 19-20 g.

Table 5. Summary of Baseline Demographic Characteristics, Study VIR-044

	Sex, n (%)		Study Day 1 Body Weight (g)		
Group	**Male**	**Female**	**Mean**	**Median**	**Range**
BCV 10/5/5 mg/kg at PID 4	16 (50.0)	16 (50.0)	19.7	19.1	15.8, 26.2
BCV 10/5/5 mg/kg at PID 5	16 (50.0)	16 (50.0)	19.9	19.2	16.2, 25.5
BCV 10/5/5 mg/kg at PID 6	16 (50.0)	16 (50.0)	19.5	18.9	15.3, 24.9
BCV 20/5/5 mg/kg at PID 4	16 (50.0)	16 (50.0)	19.8	18.8	16.7, 24.7
BCV 20/5/5 mg/kg at PID 5	16 (50.0)	16 (50.0)	19.8	19.6	15.0, 25.2
BCV 20/5/5 mg/kg at PID 6	16 (50.0)	16 (50.0)	19.7	18.4	15.2, 27.6
BCV 20/5/5 mg/kg at PID 7	16 (50.0)	16 (50.0)	19.3	18.3	15.6, 25.1
Placebo	16 (50.0)	16 (50.0)	19.8	19.5	15.7, 25.4

Source: Reviewer's analyses

3.2.4 Results and Conclusions

3.2.4.1 Primary Efficacy Results in Rabbitpox Model (Study VIR-106)

The Cochran Armitage trend test showed that the survival rate decreased as the initiation of BCV was delayed for longer (one-sided p = 0.0002).

Reviewer Comment: The CSR presented the same conclusion that a trend in survival rate across BCV regimens was observed based on the Cochran Armitage trend test, but the p-value was different (p < 0.0001).

The survival rate at PID 42 in each of the treatment groups was summarized in Table 6. All the BCV regimens were superior to the placebo in terms of survival rate, at a one-sided significance level of 0.025 based on the sequential testing procedure. The conclusions remained the same based on the Holm's procedure.

Table 6. Summary of Survival Rate at PID 42, ITT population, Study VIR-106

Group	Survival Rate, % (n/N)	95% CI[a] (%)	Rate Difference[b] & 95% CI[c] (%)	Boschloo's one-sided p-value[d]	
				Unadjusted	Adjusted[e]
BCV 20/5/5 mg/kg at PID 3	100.0 (29/29)	88.1, 100.0	71.4 (51.3, 86.8)	<0.0001	<0.0001
BCV 20/5/5 mg/kg at PID 4	89.7 (26/29)	72.7, 97.8	61.1 (35.7, 79.3)	<0.0001	<0.0001
BCV 20/5/5 mg/kg at PID 5	69.0 (20/29)	49.2, 84.7	40.4 (12.5, 62.8)	0.0014	0.0028
BCV 20/5/5 mg/kg at PID 6	69.0 (20/29)	49.2, 84.7	40.4 (12.5, 62.8)	0.0014	0.0028
Placebo	28.6 (8/28)	13.2, 48.7	-	-	-
Cochran-Armitage Trend Test[f]	p = 0.0002				

[a] Clopper-Pearson 95% CI; [b] Difference in survival rate, BCV – placebo; [c] The exact confidence interval for difference in survival rate was based on inverting two one-sided tests, carried out using Cytel Studio; [d] P-value was based on a one-sided Boschloo's exact test with gamma=0 as compared to the placebo; [e] Adjusted p-values using the Holm's procedure; [f] Cochran-Armitage trend test across BCV groups.
Source: Reviewer's analyses

This reviewer conducted a sensitivity analysis to assess the impact of different testing methods on the statistical inference for efficacy. A Bernard's exact unconditional test was used to compare the survival rate between groups, and multiplicity was adjusted utilizing the sequential testing procedure and the Holm's procedure. The conclusion on efficacy remained unchanged

based on both approaches (presented in Table 7), suggesting that the survival rates at PID 42 were significantly higher in all the BCV 20/5/5 mg/kg regimens than that in the placebo group.

Table 7. Sensitivity Analysis of the Survival Rate at PID 42 using One-sided Bernard's Exact Unconditional Test, ITT Population, Study VIR-106

Group	One-sided Bernard's exact unconditional test of superiority	
	Unadjusted p-value	Adjusted p-value[a]
BCV 20/5/5 mg/kg at PID 3	<0.0001	<0.0001
BCV 20/5/5 mg/kg at PID 4	<0.0001	<0.0001
BCV 20/5/5 mg/kg at PID 5	0.0014	0.0028
BCV 20/5/5 mg/kg at PID 6	0.0014	0.0028

[a] Adjusted p-values using the Holm's procedure
Source: Reviewer's analyses

3.2.4.2 Primary Efficacy Results in Mousepox Model (Study VIR-044)

For the BCV 10/5/5 mg/kg groups, the Cochran Armitage trend test showed that the rate of survival decreased as the initiation of BCV was delayed for longer (one-sided p = 0.0003). The survival rates at PID 42 and associated difference between groups (BCV – placebo), were presented in Table 8. The results suggested that BCV 10/5/5 mg/kg started at PID 4 and PID 5 were superior to the placebo in terms of survival rate at a one-sided significance level of 0.0125. However, the survival rate for BCV 10/5/5 mg/kg initiated at PID 6 was not statistically significantly higher than that for the placebo at a one-sided alpha = 0.0125, utilizing the sequential testing procedure. The conclusion was the same using the Holm's procedure.

Reviewer Comment: In the CSR, it was concluded that monotonicity of treatment efficacy was demonstrated across regimens at BCV 10/5/5 mg/kg dose level at a smaller p-value (p <0.0001). The Applicant concluded that all the BCV 10/5/5 mg/kg regimens were superior to the placebo at a one-sided significance level of 0.025. The inconsistency in conclusion was due to the use of a larger significance level, which is not a recommended approach.

For the BCV 20/5/5 mg/kg groups, the Cochran Armitage trend test showed that the survival rate decreased as the BCV regimens were delayed (one-sided p <0.0001). As presented in Table 8, all the BCV 20/5/5 mg/kg regimens were superior to the placebo in terms of survival rate at PID 42, at a one-sided significance level of 0.0125. The conclusion was the same using the Holm's procedure.

Table 8. Summary of Survival Rate at PID 42, ITT Population, Study VIR-044

Group	Survival Rate, % (n/N)	95% CI[a] (%)	Rate Difference[b] & 95% CI[c] (%)	Boschloo's one-sided p-value[d]	
				Unadjusted	Adjusted[e]
BCV 10/5/5 mg/kg at PID 4	78.1 (25/32)	60.0, 90.7	65.6 (43.6, 81.9)	<0.0001	<0.0001

BCV 10/5/5 mg/kg at PID 5	65.6 (21/32)	46.8, 81.4	53.1 (28.9, 71.6)	<0.0001	<0.0001
BCV 10/5/5 mg/kg at PID 6	34.4 (11/32)	18.6, 53.2	21.9 (0.7, 43.0)	0.02334[h]	0.02334[h]
Cochran-Armitage Trend Test[f]	0.0003				
BCV 20/5/5 mg/kg at PID 4	84.4 (27/32)	67.2, 94.7	71.9 (50.0, 86.7)	<0.0001	<0.0001
BCV 20/5/5 mg/kg at PID 5	75.0 (24/32)	56.6, 88.5	62.5 (40.3, 79.4)	<0.0001	<0.0001
BCV 20/5/5 mg/kg at PID 6	46.9 (15/32)	29.1, 65.3	34.4 (10.6, 54.6)	0.0014	0.0028
BCV 20/5/5 mg/kg at PID 7	37.5 (12/32)	21.1, 56.3	25.0 (3.2, 45.8)	0.0118	0.0118
Placebo	12.5 (4/32)	3.5, 29.0	-	-	-
Cochran-Armitage Trend Test[g]	<0.0001				

[a] Clopper-Pearson 95% CI; [b] Difference in survival rate, BCV – placebo; [c] The exact confidence interval for difference in survival rate was based on inverting two one-sided tests, carried out using Cytel Studio; [d] P-value was based on a one-sided Boschloo's test with gamma=0 as compared to the placebo; [e] Adjusted p-values using the Holm's procedure; [f] One-sided Cochran-Armitage trend test across groups with BCV 10/5/5 mg/kg; [g] One-sided Cochran-Armitage trend test across groups with BCV 20/5/5 mg/kg; [h] P-value is not significant at the one-sided alpha of 0.0125

This reviewer conducted a sensitivity analysis to compare the survival rates through PID 42 between each BCV regimen and the placebo, using a one-sided Bernard's exact unconditional test. The unadjusted p-values utilizing the sequential testing procedure and the adjusted p-values using the Holm's procedure are presented in Table 9. The conclusion was consistent with that using the Boschloo's test, all the BCV regimens were superior to the placebo in terms of survival rate, at a one-sided alpha level of 0.0125, except that superiority was not demonstrated statistically for BCV 10/5/5 mg/kg initiated at PID 6.

Table 9. Sensitivity Analysis of the Survival Rate at PID 42, ITT population, VIR-044

	One-sided Bernard's exact unconditional test of superiority	
Group	**Unadjusted p-value**	**Adjusted p-value[a]**
BCV 10/5/5 mg/kg at PID 4	<0.0001	<0.0001
BCV 10/5/5 mg/kg at PID 5	<0.0001	<0.0001

BCV 10/5/5 mg/kg at PID 6	0.02256[b]	0.02256[b]
BCV 20/5/5 mg/kg at PID 4	<0.0001	<0.0001
BCV 20/5/5 mg/kg at PID 5	<0.0001	<0.0001
BCV 20/5/5 mg/kg at PID 6	0.0014	0.0028
BCV 20/5/5 mg/kg at PID 7	0.0118	0.0118

[a] Adjusted p-values using the Holm's procedure; [b] p-value is not significant at the one-sided alpha of 0.0125
Source: Reviewer's analyses

3.3 Evaluation of Safety

Please see the clinical review for the evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Due to limited sample sizes in these animal studies, no subgroup analyses were conducted.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There was one statistical issue. A one-sided Boschloo's test was used to analyze the primary endpoint in both animal models. The Applicant concluded the efficacy findings using a one-sided alpha level of 0.05 in Study VIR-106 and a one-sided alpha level of 0.025 for each dose level in Study VIR-044. However, the efficacy findings should be based on a one-sided alpha level of 0.025 in Study VIR-106 and a one-sided alpha level of 0.0125 within each dose level in Study VIR-044. The conclusions remained the same for Study VIR-106. However, in Study VIR-044, superiority was not demonstrated statistically for BCV 10/5/5 mg/kg initiated at PID 6.

5.2 Collective Evidence

In the rabbitpox model (Study VIR-106), statistically significant survival benefit of BCV 20/5/5 mg/kg over placebo was demonstrated in all the regimens studied; the survival rates at PID 42 was 100%, 89.7%, 69.0%, 69.0% when BCV was initiated at PID 3, PID 4, PID 5, and PID 6, respectively.

In the mousepox model (Study VIR-044), statistically significant survival benefit of BCV 20/5/5 mg/kg over placebo was demonstrated when BCV was initiated at PID 4, PID 5, PID 6, and PID 7 and the survival rate at PID 42 was 84.4%, 75.0%, 46.9%, and 37.5%, respectively. Statistically significant survival benefit was demonstrated when BCV 10/5/5 mg/kg was initiated at PID 4 and PID 5, with a PID 42 survival rate of 78.1% and 65.6%, respectively; however, statistically significant survival benefit was not demonstrated when BCV 10/5/5 mg/kg was initiated at PID 6, with a survival rate of 34.4% at PID 42.

5.3 Conclusions and Recommendations

Based on the review, it is concluded that BCV demonstrated efficacy in the two animal models, mousepox infection in mice and rabbitpox infection in rabbits. Based on the Animal Rule, these results support the recommendation of approving TEMBEXA as a treatment for adult and pediatric patients infected with smallpox.

5.4 Labeling Recommendations

The dose regimen for human subjects is 200 mg once weekly for 2 doses in those ≥48 kg of weight.

For human dose selection, a BCV dose of 20/5/5 mg/kg was selected in the rabbitpox study to provide exposures that exceed those associated with the fully effective dose. A BCV dose of 10/5/5 mg/kg was selected in the mousepox study to provide exposures that exceed those associated with fully effective dose for human dose selection. For these reasons, groups treated with BCV dose of 20/5/5 mg/kg in the rabbitpox study and with BCV dose of 10/5/5 mg/kg in the mousepox study were selected to be presented in Section 14 of the label. The following table is the current table in the label, which has not been finalized by now and is subject to change.

Survival Rates in Brincidofovir Treatment Studies in the Rabbitpox and Mousepox Models

Dose Regimen (mg/kg)	**Treatment Initiation Day**	**Survival % (# survived/n)**		**Survival Rate Difference (95% CI)[a]**	**p-value[b]**
		Placebo	**BCV**		
Rabbitpox[c]					
Study 1	Day 4	29% (8/28)	90% (26/29)	61% (36%, 79%)	<0.0001
	Day 5		69% (20/29)	40% (12%, 63%)	0.0014
	Day 6		69% (20/29)	40% (12%, 63%)	0.0014
Mousepox[d]					
Study 2	Day 4	13% (4/32)	78% (25/32)	66% (44%, 82%)	<0.0001
	Day 5		66% (21/32)	53% (29%, 72%)	<0.0001
	Day 6		34% (11/32)	22% (1%, 43%)	0.0233[e]

[a] Survival percentage with brincidofovir-treated animals minus survival percentage in placebo-treated animals. Exact confidence intervals are presented.
[b] P-value is from 1-sided Boschloo test compared with placebo.
[c] 20/5/5 mg/kg (fully effective dose in the rabbitpox model)
[d] 10/5/5 mg/kg (fully effective dose in the mousepox model)
[e] P-value is not significant at the one-sided alpha of 0.0125.

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Statistical Review and Evaluation

NDA #	214461
SDN #	21
Received Date	01/29/2021
Drug	Tembexa (Brincidofovir, BCV)
Indication	Treatment for Smallpox
Sponsor	Chimerix, Inc
Documents Reviewed	Protocol Synopsis
Document location	\\CDSESUB1\evsprod\NDA214461\0021

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1 Introduction and Background

Tembexa (Brincidofovir, BCV) is under review for NDA for the treatment of smallpox infection under the Animal Rule. The Applicant is required to conduct a post market field human study to evaluate the efficacy and safety of Tembexa.

An initial protocol was submitted in SDN 644 under IND 67681 dated 02/19/2020, and the Agency provided feedback. The Applicant submitted a revised protocol synopsis in SDN 21 under NDA214461. Section 2 will summarize the protocol synopsis. Section 3 will include the statistical comments.

2 Summary of Protocol Synopsis

(b) (4)

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