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MEDICAL REVIEW

HFD-530 / DGillivan

NDA 20-154/SE-08 - 033

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Medical Review
(Supplemental NDA)

Date Submitted:	**March 21, 2000**
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Applicant:	Bristol Myers-Squibb Company 5 Research Parkway Wallingford, CT 06492
Drug: Generic	didanosine (ddI)
Trade	Videx®
Dosage form:	Chewable/dispersible tablet
Indication:	Once-daily dosing in the treatment of HIV-1 infection
Related NDAs:	20-155 Videx® Buffered powder for oral solution 20-156 Videx® Pediatric powder for oral solution 21-183 Videx® Enteric Coated capsules

1.0 Executive Summary

1.1 Recommendation

This supplemental application containing the 48-week final results of study AI454-148 that reinforce twice-daily administration of Videx® (didanosine, ddI) as the recommended dosing frequency should be approved.

So that clinicians and their patients can make informed decisions about their antiretroviral therapy, a detailed description of the 48-week final results of study AI454-148 will be included in the ddI label, the patient package insert, and the applicant will issue a Dear Healthcare Professional letter.

2.0 Summary of Clinical Findings

Once-daily administration of ddI was approved based on the results of a 24-week interim analysis of study AI454-148. Study AI454-148 compared the combination of once-daily didanosine (ddI)+stavudine (d4T)+nelfinavir (NLF) to zidovudine (ZDV)+lamivudine (3TC)+NLF in 756 antiretroviral naïve HIV-infected adult patients. The 24-week analysis demonstrated that the two regimens produced similar antiviral and immunologic activity, 61% and 56%, respectively.

The 48-week final analysis, however, demonstrated that the regimen containing once-daily ddI produced inferior antiviral activity compared to the ZDV+3TC+NLF regimen. Specifically, the proportion of patients with HIV RNA <400 c/mL was 50% in the ddI+d4T+NLF arm and 59% in the ZDV+3TC+NLF arm. Of more concern was the proportion of patients with HIV RNA <50 c/mL: 34% in the ddI-containing arm and 47% in the ZDV arm, respectively.

Although the study was not designed to determine the specific contribution of each individual drug to outcome, it appears that administration of ddI once per day may not provide sufficient additive activity to the other two drugs in the regimen to result in a high rate durable antiviral response.

Although once-daily administration of ddI is an approved dosing frequency and may be more convenient for patients, the results of study AI454-148 raise concerns about its continued utility as the preferred frequency for dosing ddI. Because once daily administration is enjoying widespread use among HIV infected patients and because there may be some patients for whom a once daily regimen might be necessary, it was decided to retain the once daily dosing frequency as an option in the approved label.

In order to ensure that patients and clinicians are aware that the convenience of once daily administration of ddI must be balanced by a significant risk of less than optimal antiviral outcome, the ddI label and patient package insert will be revised to include the final results of study AI454-148. In addition, the applicant will issue a Dear Healthcare Professional letter to reinforce twice-daily administration as the recommended dosing frequency for ddI.

There were no new safety issues raised by this study. Fatal and non-fatal pancreatitis, peripheral neuropathy, gastrointestinal disturbances, and abnormalities in liver function remain the most common and serious adverse events related to treatment with ddI+d4T+NLF.

3.0 Study AI454-148

"A Randomized Study of the Long Term Suppression of Plasma HIV RNA Levels by Triple Combination Regimens in Treatment-Naïve Subjects."

Study AI454-148 was initiated in March 1998 and was completed on September 22, 1999. In April 1999, the applicant submitted an interim efficacy analysis of 387 of 756 enrolled patients through 24 weeks of therapy that supported approval of once-daily ddI. The applicant has now submitted the final 48-week report for all 756 patients enrolled in the study.

3.1 Design

Study AI454-148 was a multinational, open-label, 48-week, randomized, phase 3 study comparing the antiviral activity and tolerability of ddI dosed once daily in combination with d4T+NLF versus the combination of ZDV+3TC+NLF. The study population was HIV-infected antiretroviral-naïve patients with a screening CD4 cell count of at least 100 cells/mm^3 and plasma HIV RNA $\geq$2,000 c/mL.

Patients were randomized in a 2:1 ratio to receive ddI once daily (2 x 200 mg tablets)+d4T (40 mg BID)+NLF (750 mg TID). Randomization was stratified according to baseline HIV RNA levels (<30,000 copies/mL and $\geq$30,000 copies/mL). Treatment continued for 48 weeks after enrollment of the last patient.

The protocol permitted patients who were unable to tolerate d4T (e.g., Grade $\geq$2 peripheral neuropathy, elevated hepatic transaminases, or headache) to substitute ZDV for d4T, and allowed patients unable to tolerate ZDV (e.g., Grade $\geq$2 anemia, neutropenia, thrombocytopenia, myalgia, nausea, or headache) to switch from ZDV to d4T.

3.2 Patient Population and Disposition

The 756 patients enrolled in the study were relatively healthy HIV-infected white (56%) males (76%) with median baseline HIV RNA levels of 4.69 $\log_{10}$ c/mL (range 2.6 to 6.5 $\log_{10}$ c/mL) and median CD4 cell counts of 340 cells/mm^3 (range 80 to 1568 cells/mm^3).

The disposition of study patients and the reasons for premature study discontinuations are presented in Tables 1 and 2.

Table 1. Patient Disposition

	ddI+d4T+NLF	ZDV+3TC+NLF
Total number randomized	503	253
Received at least one dose of study medications*	482	248
Completed study	322	173

*Twenty-one patients in the ddI+d4T+NLF arm and five patients in the ZDV+3TC+NLF arm did not initiate study medications due to personal choice not to continue with the trial.

Table 2. Reasons for Premature Discontinuation

	ddI+d4T+NLF	ZDV+3TC+NLF
Received at least one dose of study medications	482	248
Discontinuations	160 (33%)	75 (30%)
-Adverse events[a]	53	13
-Withdrew consent	13	11
-Non-compliance	10	10
-Lost to follow-up	52	26
-Disease progression/relapse[b]	25	12
-Death	4	2
-Pregnancy	3	1

a: Does not include patients who substituted d4T for ZDV or ZDV for d4T due to protocol defined toxicities.
b: Includes patients who discontinued due to virologic failure and CDC Class C events.

Thirty-six patients (20 ddI+d4T+NLF and 16 ZDV+3TC+NLF) substituted d4T for ZDV or ZDV for d4T for protocol defined adverse events. In the protocol, patients who underwent these substitutions for protocol defined toxicities were to be analyzed as if they had remained on their initially assigned therapy. The applicant examined the frequency and timing of the switches and concluded that the variations in timing and the imbalance in the number of patients who switched violated the assumption of the planned analysis, i.e., that therapy substitutions would be balanced, infrequent and random. In response to these findings, the applicant conducted additional analyses classifying patients who switched from d4T to ZDV and ZDV to d4T as treatment failures. Tables 3 and 4 present timing and outcomes information on the patients who substituted d4T for ZDV, and vice versa.

Table 3. Patients who switched from ZDV to d4T

Patient ID	Day	Reason	Outcome
04-0159	80	Nausea, diarrhea	Completed study, success*
05-0292	252	Myalgia, arthritis	Completed study, success
08-0399	56	Neutropenia	Discontinued day 56,
09-0400	59	Nausea	Lost To Follow-Up day 121
17-0185	169	Headache, belching	Completed study, success
17-0211	67	Neutropenia	Completed study, failure
17-0553	57	Joint pain	Completed study, success
20-0383	23	Nausea	Completed study, failure
21-0140	57	Nausea, vomiting	Discontinued day 365, viral rebound
34-0679	112	Anemia, leukopenia	Completed study, failure
41-0258	85	Anemia	Completed study, success
44-0413	63	Neutropenia	Discontinued day 133, Grade 4 LFTs
45-0808	24	Vomiting	Completed study, success

52-0764	86	Anemia	Completed study, success
54-0618	57	Neutropenia	Completed study, success
62-0445	57	Anemia	Completed study, success
63-0474	75	Neutropenia	Completed study, success
78-0266	193	Anemia	Completed study, failure
81-0422	142	Anemia	Completed study, success
100-0341	64	Anemia, fatigue	Completed study, success

*Success= <400 c/mL at week 48.

Table 4. Patients who switched from d4T to ZDV

Patient ID	Day	Reason	Outcome
02-0157	246	Neuropathy	Completed study, success
12-0377	207	Neuropathy	Completed study, success
22-0117	288	Neuropathy	Completed study, success
25-0695	238	Neuropathy	Completed study, success
32-0421	117	Neuropathy	Discontinued day 225, neuropathy
35-0815	172	Neuropathy	Discontinued day 227, neuropathy
36-0615	229	Neuropathy	Completed study, failure
37-0206	15	Neuropathy	Discontinued day 367, high viral load
37-0229	224	Neuropathy	Completed study, success
38-0248	134	Neuropathy	Completed study, failure
40-0218	153	Neuropathy	Discontinued day 201, neuropathy
43-0510	199	Neuropathy	Discontinued day 230, neuropathy
44-0373	168	Neuropathy	Completed study, failure
45-0513	111	Neuropathy	Discontinued day 167, neuropathy
53-0500	245	Neuropathy	Completed study, success
55-0801	195	Neuropathy	Lost To Follow-Up day 298

Comment: ZDV and d4T are both thymidine analogues and are generally interchangeable as part of routine management of adverse events. Therefore it was unlikely that the substitution of one of these drugs for the other would have had a significant impact on efficacy. Further, the permissibility of these substitutions was prospectively defined in the protocol and these patients were to be analyzed based on their initially assigned therapy. The efficacy analyses presented below treat these patients based on their initially assigned therapy, as outlined in the protocol.

The timing of substitutions appears to reflect the early adverse events due to tolerability of ZDV while the later switches from d4T to ZDV for peripheral neuropathy implies more prolonged/cumulative exposure to d4T is required to cause this toxicity.

3.3 Results: Efficacy

For an in-depth analysis of efficacy in study 148, please refer to Dr. Greg Soon's statistical review. The protocol specified primary virologic endpoint was the proportion of patients who initiated study medications with HIV RNA <400 c/mL (Roche Amplicor HIV-1 Monitor® assay) within an eight week window surrounding week 48 (day 274 to 365). The applicant powered the study to demonstrate that ddI+d4T+NLF was as least as

effective as ZDV+3TC+NLF if the lower limit of the 95% confidence interval (CI) for the differences between regimens was not below –12%.

Secondary analyses included assessments of the proportion of patients with HIV RNA <50 c/mL, the proportion of patients with HIV RNA <400 and 50 c/mL who entered with baseline HIV RNA < and ≥30,000 c/mL, changes from baseline in CD4 cell counts, and time to virologic failure (including AIDS and death).

Comment: The applicant's definition of the all-treated population ignored the disproportionate number of patients in ddI+d4T+NLF who did not initiate study medications, 21 compared to 5 in the ZDV+3TC+NLF arm. FDA's preferred analysis population is all randomized patients because it represents the intent-to-treat population, and maintains balance between the treatment arms for statistical analyses.

The analyses of all randomized patients, not classifying d4T and ZDV substitutions as treatment failures, conducted by the applicant and FDA produced similar results. The following tables present the FDA's 48-week analyses.

Table 5. Sustained response through week 48, all randomized patients

	ddI+d4T+NLF (n=503)	ZDV+3TC+NLF (n=253)	95% CI
Proportion <400 c/mL	50%	59%	-17.0%, -2.1%, p=0.012
Proportion <50 c/mL	34%	47%	-20.8%, -6.0%, p<0.001
Median change in CD4	+188 cells/mm^3	+188 cells/mm^3	

Table 6. Sustained response through week 48, patients with <30,000 c/mL at baseline

	ddI+d4T+NLF (n=181)	ZDV+3TC+NLF (n=92)
Proportion <400 c/mL	58%	66%
Proportion <50 c/mL	39%	52%

Table 7. Sustained response through week 48, patients with ≥30,000 c/mL at baseline

	ddI+d4T+NLF (n=322)	ZDV+3TC+NLF (n=161)
Proportion <400 c/mL	45%	55%
Proportion <50 c/mL	30%	44%

Table 8 provides a summary of the outcome of all randomized patients through week 48.

Table 8. Outcomes of randomized patients through week 48, <400 c/mL(<50 c/mL)

	ddI+d4T+NLF (n=503)	ZDV+3TC+NLF (n=253)
Responder[a]	50% (34%)	59% (47%)
Virologic failure[b]	36% (57%)	32% (48%)
Death or disease progression	<1 (<1%)	1% (<1%)
Discontinued due to AE	4% (2%)	2% (<1%)
Discontinued for other reasons[c]	6% (3%)	4% (2%)
Never initiated treatment	4% (4%)	2% (2%)

a: Two consecutive HIV RNA <400 (<50) c/mL maintained through week 48.
b: Includes viral rebound and failure to achieve confirmed <400 (<50) c/mL byt week 48.
c: Includes lost to follow-up, non-compliance, withdrawal and pregnancy.

Comment: There were significantly more ddI+d4T+NLF-treated patients who experienced virologic rebound, and whose last on study HIV RNA level was >400 c/mL, raising the concern that a regimen containing ddI administered once-daily may not be sufficiently potent to provide durable long-term virologic suppression. There were too few AIDS-defining events to assess the impact of treatment with either regimen on disease progression.

The results for the ZDV+3TC+NLF arm were expected based on other studies in which treatment naïve patients received this combination. There are no 48-week data on the combination of d4T+NLF in treatment naïve patients, so it was not possible to determine what the contribution of once-daily administration of ddI to these two agents might have been.

The finding of inferiority raises significant concerns about the appropriateness of dosing ddI once daily.

According to the applicant, the results of study 148 are not of such concern that once-daily dosing of ddI should be removed from the labeling as a recommended dosing frequency. Rather, once daily should be retained so that clinicians and patients can make an informed choice considering ease of administration versus the risk for a loss of activity when used long-term.

According to the applicant, the intracellular half-life of ddATP, the active moiety of ddI, is >24 hours. The applicant submitted pharmacokinetic data showing that the proportional absorption and total daily exposure of ddI was similar whether administered as a single 400 mg dose or 200 mg administered twice-daily. Finally, the applicant provided data demonstrating the time over which the plasma concentration of ddI exceeds the EC_{50} and EC_{90} of a panel of recombinant viruses containing the RT gene found in clinical isolates. Following administration of a 400-mg dose, ddI plasma concentrations over 24 hours exceed the EC_{50} for 5.1 hours and the EC_{90} for 1.9 hours. Following administration of 200 mg twice daily, ddI plasma concentrations exceed the EC_{50} for only 8.1 hours and the EC_{90} for only 1.5 hours. It is important to note that these duration data are based on mean pharmacokinetic profiles; data for individual patients may vary.

Comment: The direct quantification of ddATP is not possible as there is no assay available to measure intracellular levels of the activated triphosphate.

The possible explanation for the inferiority of the ddI-containing regimen was that ddI needs to be administered more frequently in order to contribute to higher rates of antiviral activity, such as those seen in Start 2. Because there was a significant portion of a 24-hour period when ddI plasma levels were below the EC_{50} and EC_{90}, there was continued low-level viral replication that the combination of d4T+NLF was not sufficiently powerful to compensate. Unfortunately the applicant has not conducted any long-term studies comparing once daily to twice daily, or more frequent, administration of ddI.

The applicant also submitted data to support the short-term (12-24 week) antivirial activity of the combination of ddI QD+d4T compared to ddI BID+d4T. The results of these studies demonstrated similar reductions from baseline in HIV RNA for the two dosing frequencies with the proportion of patients with HIV RNA below the limit of detection of the assay used ranging from 30-90%.

Comment: The two studies submitted, AI454-143 and AI454-146 have been previously reviewed. It was determined that they were small, short duration, and not sufficient to assess the durability of antiviral activity of ddI administered once daily.

Finally, the applicant proposed a number of factors that could have contributed to the differences observed between the study arms. First, the choice of nelfinavir may have influenced patient compliance/adherence leading to poorer outcome due to overlapping GI intolerance. Second, the applicant assumed that switches from d4T to AZT or vice versa would be equally distributed by both number and time-to-switch. Third, there was an unexpectantly high dropout rate (30% from each arm) that may have disallowed an adequate sample size for the planned statistical analyses. Finally, the high number of subjects who did not initiate study treatment may have compromised the analysis.

Comments: There are no data to support the applicant's supposition that nelfinavir significantly increased the frequency of GI adverse events seen in this study. This combination, ddI+d4T+NLF, has been used in other clinical trials without such conclusions being drawn. Further, there were no assessments of tolerability conducted in the study so it is unknown if there were any issues of non-compliance or adherence to nelfinavir.

The applicant offered no specific reasons that there were a disproportional number of patients who did not initiate study medications in the ddI-containing arm. One hypothesis is that once patients were informed of their treatment assignment in this open-label trial, they decided not to receive ddI because of its long history of intolerability and the numerous dietary restrictions associated with its use.

The issue of the timing and frequency of treatment switches between d4T and ZDV, or vice versa, is discussed in detail above. Briefly, the criteria for these switches were pre-specified and only in post-hoc analyses was the applicant able to demonstrate a smaller difference in the proportion of patients with HIV RNA <400 c/mL between treatment arms when these switches were treated as treatment failures.

According to the applicants' statistical analysis plan, if the proportion of patients with HIV RNA <400 c/mL at week 48 is 50%, the study still had 85% power to demonstrate that the two treatment regimens were similar. The applicant offered no sensitivity analyses to assess the impact of the 30% dropout rates on the overall results of the study. Finally, the applicant failed to consider that significantly more patients in the ddI-containing arm experienced virologic failure (see Table 8, above).

In conclusion, study 148 was conducted under Good Clinical Practices and the results clearly demonstrated that the regimen containing ddI administered once daily produced inferior antiviral activity compared to the reference regimen. There are no data available to refute this conclusion.

4.0 Review of Safety

The review of safety included all patients who received at least one dose of study medication. Fatal and non-fatal pancreatitis, peripheral neuropathy, gastrointestinal problems, and elevated hepatic transaminases continue to be the most common significant adverse events related to treatment with ddI in combination with other antiretroviral agents.

4.1 Deaths and Non-fatal Serious Adverse Events

A total of six patients died, four in the ddI+d4T+NLF arm and two in the ZDV+3TC+NLF arm. Two deaths in the ddI+d4T+NLF arm were probably related to study medications, one due to drug-induced pancreatitis, and one due to aspiration and upper airway obstruction as complications of neuropathy.

One patient in the ZDV+3TC+NLF arm died as a result of injuries sustained in a motor vehicle accident. The second death occurred in a 26-year old black male who sustained facial and spinal injuries with residual weakness in his left upper and lower extremities as a result of an assault that occurred around study day 186. The patient remained on study medications and on study day 306, he was "found dead."

Non-fatal serious adverse events were reported by significantly more patients in the ddI+d4T+NLF arm, 13%, compared to 7% in the ZDV+3TC+NLF arm (applicant's p=0.02); the majority of these SAEs were not drug-related.

In the ddI+d4T+NLF arm, there were three patients who exhibited study drug-related serious adverse events: one with clinical pancreatitis, one with asymptomatic elevated

lipase, and one with peripheral neuropathy. There were seven additional patients who complained of similar gastrointestinal adverse events, including abdominal pain, nausea, vomiting, gastroesophageal reflux, and cholecystitis.

In the ZDV+3TC+NLF arm, one patient with elevated LFTs and one patient with nausea and vomiting were judged by this reviewer to be probably drug-related.
Comment: Although already included in the ddI label, neuropathy, fatal and non-fatal pancreatitis, and gastrointestinal events continue to be of serious concern for patients treated with treatment regimens including ddI+d4T.

4.2 Adverse Events Leading to Study Discontinuation

Significantly more patients discontinued the study due to adverse events from the ddI+d4T+NLF arm (n=42) than from the ZDV+3TC+NLF arm (n=12).[1]

The adverse events leading to study discontinuation from the two study arms were generally consistent with the known adverse event profiles of the study drugs. In the ddI+d4T+NLF arm, peripheral neuropathy, elevated liver function tests, elevated lipase levels alone and with clinical pancreatitis, gastrointestinal complaints (i.e., nausea, vomiting, diarrhea, abdominal distention/bloating, loss of appetite), and rash were the main reasons for discontinuations. In the ZDV+3TC+NLF arm, gastrointestinal complaints and rash were the most frequent study medication related events leading to discontinuations.

4.3 Adverse Clinical and Laboratory Events

Selected adverse events are presented in Table 9.

Table 9. Selected Clinical Adverse Events, All Grades, N(%)

EVENT	ddI+d4T+NLF	ZDV+3TC+NLF
Any event	451 (94)	228 (92)
Diarrhea	340 (70)	150 (60)
Nausea	136 (28)	99 (40)
Abdominal pain	98 (20)	42 (17)
Headache	103 (21)	77 (30)
Neuropathy	124 (26)	20 (8)
Rash	62 (13)	40 (16)
Vomiting	56 (12)	34 (14)
Pancreatitis	5 (1)*	-

* One fatal case

Comment: Adverse events were similar in type and frequency across the two treatment arms and represent the known adverse event profiles associated with these combinations. Peripheral neuropathy continues to be a frequently observed adverse event associated with the combination of ddI+d4T. Rash and diarrhea are

[1] Does not include patients who underwent protocol-defined substitutions of d4T for ZDV and ZDV for d4T.

adverse events attributable to nucleoside analogues, but NLF was likely a contributor.

4.4 Selected Abnormal Laboratory Tests

The proportions of all randomized patients with selected laboratory abnormalities are presented in Table 10.

Table 10. Selected Laboratory Abnormalities, (%).

PARAMETER	ddI+d4T+NLF	ZDV+3TC+NLF
SGOT (AST)		
-All Grades	42	24
-Grade 3-4	3	2
SGPT (ALT)		
-All Grades	37	25
-Grade 3-4	3	4
Bilirubin		
-All Grades	7	4
-Grade 3-4	1	<1
Lipase		
-All Grades	18	13
-Grade 3-4	7	2
Uric acid		
-All Grades	13	5
-Grade 3-4	2	2

Comment: Elevated lipase levels, AST and ALT were observed more frequently in patients treated with ddI+d4T+NLF; however, the rates were similar to those seen in other studies of this combination and reported in the current ddI label.

5.0 Review of Package Insert

The label submitted by the applicant proposed to simply state that the two regimens produced similar antiviral and immunologic activity. This proposal was deemed unacceptable given the clear inferiority of the ddI+d4T+NLF regimen. The applicant was instructed to provide a more detailed description of the study results, as well as precautionary statements to inform clinicians and patients of the potential trade-off of convenience of once daily dosing versus inferior antiviral activity. Also, the applicant was instructed to revise the patient labeling to reinforce twice-daily administration of ddI as the recommended dosing frequency for the majority of patients. A draft label submitted by the applicant on July 24, 2000, included all the revisions requested and was found to be acceptable.

6.0 Conclusions

The final 48-week results of this study demonstrated that the combination of once-daily ddI+d4T+NLF produced significantly inferior sustained virologic suppression compared to the reference regimen used in this study, ZDV+3TC+NLF.

The relative contribution of each component of the regimen to efficacy could not be evaluated. However, previous studies that included ddI dosed twice-daily resulted in higher proportions of patients with HIV RNA <400 c/mL. Based on available pharmacokinetic data, it was likely that there were significant periods of each day during which circulating levels of ddI were absent thus potentially leading to insufficient antiviral pressure by all three drugs in the regimen throughout a 24 hour period.

There were no new safety concerns raised by the 48-week data. In general the patterns and frequencies of adverse events were consistent with other studies and data already contained in the ddI label. Fatal and non-fatal pancreatitis, peripheral neuropathy, gastrointestinal problems, and elevated hepatic transaminases continue to be the most important adverse events related to treatment with ddI+d4T+NLF.

Once daily administration of ddI is an approved dosing option. Although once daily dosing of ddI may be convenient, twice-daily administration of ddI appears to be associated with higher rates of durable virologic response. Thus patients and clinicians must be aware that the convenience of using ddI once daily must be balanced by the risk of a less than optimal antiviral outcome. The ddI label and patient package insert will be revised to include the final results of study AI454-148. In addition, the applicant will issue a Dear Healthcare Professional letter to reinforce twice-daily administration as the recommended dosing frequency for ddI.

Finally, the applicant is currently investigating an enteric-coated formulation of ddI in clinical trials. The early results of a study that directly compares once-daily administration of ddI as either a once daily 400 mg enteric-coated capsule versus a once-daily 400 mg dose of ddI's currently approved formulation in combination with d4T+ NLF suggest, again, that both regimens produce similar antiviral activity. In order to ensure that the enteric-coated formulation again does not produce inferior antiviral responses compared to the currently approved formulation and to determine the optimal dosing frequency, final study data from this and other ongoing trials will need to be thoroughly reviewed.

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