IND 075382
NDA 204790
NDA 213983

WRITTEN REQUEST – AMENDMENT 4

ViiV Healthcare Company
Attention: Stephen Hyatt
Associate Director, Global Regulatory Affairs
410 Blackwell Street
Durham, NC 27701

Dear Stephen Hyatt:[1]

Please refer to your correspondence dated May 2, 2024, requesting changes to FDA's March 3, 2010 Written Request for pediatric studies for dolutegravir.

We have reviewed your proposed changes to the subsection **Timeframe for submitting reports of the study(ies)** and are amending the Written Request. All other terms stated in our Written Request issued on March 10, 2010, and as amended on October 19, 2010, January 3, 2017, and July 16, 2020, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Background

Over the past decade, great progress has been made in preventing maternal-to-child transmission (MTCT) of HIV infection through early identification and treatment of the mother and providing prophylactic antiretroviral (ARV) treatment for the newborn. This has led to near elimination of MTCT of HIV. In the U.S. the epidemiology data provided by the CDC demonstrates the rare event of vertical transmission. For example, in 2011 only 53 infants were diagnosed with perinatally acquired HIV infection among the 50 states and 6 dependent areas. Globally, according to the WHO's 2013 data, among the 22 countries which account for 90% of new HIV infections, 8 have already reduced new HIV infections in children by over 50% since 2009.

The success in preventing MTCT of HIV has made conducting pediatric HIV trials to evaluate the pharmacokinetics, safety and antiviral/efficacy of ARVs difficult, especially in the U.S. and Western Europe. While transmission rates may be higher in other European countries such as Eastern Europe and Russia, there are significant logistical difficulties with conducting clinical studies in the infant population. For example, under

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

most circumstances, there is a time lag between identification of an infant born to an HIV-infected mother, collecting serum for PCR- confirmation of HIV infectivity in the infant, and getting the PCR result back. In addition, before treatment is initiated, the diagnosis has to be confirmed through an additional PCR test. This process can easily take up to 10 to 14 days. Furthermore, bringing the mother and infant back to a care center for initiation of therapy may add further delay. Therefore, even in the best settings, it can take 4-6 weeks to identify and initiate ARVs in HIV-positive infants. For this reason, the Division no longer requests efficacy/antiviral activity data in HIV-infected infants from birth to less than 4 weeks of age.

Neonates born to HIV-infected mothers should receive ARV prophylaxis to prevent HIV acquisition. According to the DHHS perinatal guideline, 'Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States'1, the recommended antiretroviral prophylaxis for neonates born to HIV-infected mothers includes zidovudine for 6-weeks. A shorter course – 4 weeks, can be considered if the newborn is full-term and the mother has received the standard HAART regimen during pregnancy with maintained viral suppression. If the newborn is considered to be at higher risk of HIV acquisition, in addition to the 6-week zidovudine course, a two-drug regimen is recommended in the first week of life, where a dose of nevirapine is given at birth, 48 hours later, and 96 hours post the second dose. HIV acquisition is considered 'higher-risk' for infants born to HIV-infected mothers who received only intrapartum ARV, or have received neither antepartum nor intrapartum ARVs, or have received antepartum ARVs without HIV RNA suppression near the time of delivery. The guideline also states that some experts recommend triple ARV prophylaxis for infants at higher risk of acquisition (as described above); however, there are 'no data demonstrating improved efficacy for a three-drug regimen over a two-drug regimen in prevention of transmission'. The guideline recommends consultation with HIV specialists if triple regimen is considered with full considerations for the potential risks and benefits of this approach.

Dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI) is among the newer antiretroviral drugs. Due to its mechanism of action, dolutegravir may be a good candidate for investigation as prophylaxis for infants who are HIV exposed and at risk of infection.

Accordingly, the Division would like the Sponsor to evaluate the PK and safety profile of dolutegravir in infants who are at high-risk for HIV infection. Such infants can include those born to HIV infected mothers with no or inadequate ARV therapy during antepartum and/or intrapartum periods. The PK and safety of dolutegravir can be evaluated while administered as part of the standard prophylactic regimen. To obtain needed pediatric information on dolutegravir, the Food and Drug Administration (FDA) is

hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the following study/studies:

Type of study(ies):
Study 1: Multiple-dose pharmacokinetic, safety and antiviral activity study(ies) of dolutegravir, in combination with other antiretroviral agents, in HIV-infected pediatric patients from 4 weeks to 18 years of age.

Study 2: Multiple-dose pharmacokinetic and safety evaluation of dolutegravir in pediatric patients from birth to less than 4 weeks of age who are HIV-exposed and at-risk of infection.

These studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Indication(s) to be studied/Objective of each study:
Study 1
The objective of study 1 will be to determine the pharmacokinetic and safety profile of dolutegravir across the age range, identify an appropriate dose (or doses) for use in HIV-1- infected pediatric patients, and evaluate the activity of this dose (or doses) in treatment.
Efficacy will be extrapolated from adequate and well controlled studies in adults, and these studies are intended to provide additional information needed to support labeling this product for use in the pediatric population.

Study 2
The objective for Study 2 will be to characterize the PK and safety of dolutegravir in patients from birth to less than 4 weeks of age.

Age group in which study(ies) will be performed:
Study 1: HIV-1-infected pediatric patients from 4 weeks to 18 years of age.
Study 2: HIV-1-exposed and at-risk of infection pediatric patients from birth to less than 4 weeks of age.

Number of patients to be studied:
Study 1: Dolutegravir must be studied in an adequate number of pediatric subjects to characterize adverse events across the age range. A minimum of 100 subjects with at least 24-week safety data at the recommended dose or higher is required. The number of subjects should be approximately evenly distributed across the age range studied.

Study 2: A minimum of 7 subjects must be evaluated to characterize the pharmacokinetics and safety profile of dolutegravir in patients birth to less than 4 weeks of age.

Study endpoints
The following study endpoints must be evaluated:

Study 1
Pharmacokinetics: Parameters including Cmax, Cmin, Tmax, $t_{1/2}$, AUC, apparent systemic clearance and apparent volume of distribution.

Safety and tolerability: HIV-1-infected pediatric subjects must be followed for safety for a minimum of 24 weeks at the recommended dose or higher. In addition, plans for collecting long-term safety data for HIV-1 infected pediatric subjects who have received dolutegravir must be agreed upon with the Agency~~submit plans for collecting long-term safety data for HIV-1 infected pediatric subjects who have received dolutegravir~~.

Activity: Assessment of changes in plasma HIV RNA levels and in CD4 cell counts at a minimum of 24 weeks treatment.

Resistance: Collect and submit information regarding the resistance profile (genotypic and/or phenotypic) of clinical isolates at baseline and during treatment from pediatric subjects receiving dolutegravir, particularly from those who experience loss of virologic response.

Study 2
Pharmacokinetics: Parameters including Cmax, Cmin, Tmax, $t_{1/2}$, AUC, apparent systemic clearance and apparent volume of distribution.

Safety and tolerability: adverse events including laboratory toxicities.

Drug information
Dosage form: Age-appropriate formulation
Route of administration: Oral
Regimen: As agreed upon in the protocols for each study ~~To be determined by development program~~

The selected dose(s) for study(ies) must be agreed upon with the Division prior to initiating the necessary pediatric study(ies).

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-

appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Drug specific safety concerns:
Based on available toxicity information about your product, provide specific safety parameters that your pediatric program will monitor. Safety monitoring and data collection as provided in the protocol and agreed with the Agency must include, but not be limited to:

- Rash, including severe rash or hypersensitivity reactions
- Hepatotoxicity
- Malignancy
- Neuropsychiatric adverse events
- Effect on humoral and cellular immune system maturity

Statistical information, including power of study(ies) and statistical assessments:
Study 1

Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-1-infected pediatric subjects is required. Studies must include an adequate number of subjects to characterize pharmacokinetics for dose selection. The study must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for dolutegravir in the following age groups: 4 weeks to < 6 months, 6 months to < 2 years, 2 years to < 6 years, 6 years to < 12 years and 12 years to 18 years. Final selection of sample size for each age group must take into account ~~all~~ potential sources of variability, including inter-subject and intra-subject variability. As study data are evaluated, the sample size must be increased as necessary for characterization of pharmacokinetics across the intended age range.

Study 2
Because Study 2 will only provide descriptive analyses of multiple-dose pharmacokinetic and safety data in HIV-exposed neonates, no formal statistical power calculation is required. However, the proposed number of patients for studying the pharmacokinetic of dolutegravir in birth to less than 4-weeks old age group must be agreed upon with the Agency~~Division~~.

Labeling that may result from the study(ies):
You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that GSK1349572 is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

Format and types of reports to be submitted:
You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to

you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*
at http://www.fda.gov/Cder/guidance/7087rev.htm.

Timeframe for submitting reports of the study(ies):
Reports of the above studies must be submitted to the Agency on or before ~~October 31, 2024~~August 31, 2026. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request:
Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated March 3, 2010, as amended by this letter and by previous amendments dated October 19, 2010, ~~and~~ January 3, 2017, and July 16, 2020 must be submitted to the Agency on or before

~~October 31, 2024~~August 31, 2026, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[2]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

[2] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

If you have any questions, call Kevin Allen, Regulatory Project Manager, at 301-837-7467.

Sincerely,

{See appended electronic signature page}

John Farley, MD, MPH
Director
Office of Infectious Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Complete Copy of Written Request as Amended

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WRITTEN REQUEST – AMENDMENT 4

Background

Over the past decade, great progress has been made in preventing maternal-to-child transmission (MTCT) of HIV infection through early identification and treatment of the mother and providing prophylactic antiretroviral (ARV) treatment for the newborn. This has led to near elimination of MTCT of HIV. In the U.S. the epidemiology data provided by the CDC demonstrates the rare event of vertical transmission. For example, in 2011 only 53 infants were diagnosed with perinatally acquired HIV infection among the 50 states and 6 dependent areas. Globally, according to the WHO's 2013 data, among the 22 countries which account for 90% of new HIV infections, 8 have already reduced new HIV infections in children by over 50% since 2009.

The success in preventing MTCT of HIV has made conducting pediatric HIV trials to evaluate the pharmacokinetics, safety and antiviral/efficacy of ARVs difficult, especially in the U.S. and Western Europe. While transmission rates may be higher in other European countries such as Eastern Europe and Russia, there are significant logistical difficulties with conducting clinical studies in the infant population. For example, under most circumstances, there is a time lag between identification of an infant born to an HIV-infected mother, collecting serum for PCR- confirmation of HIV infectivity in the infant, and getting the PCR result back. In addition, before treatment is initiated, the diagnosis has to be confirmed through an additional PCR test. This process can easily take up to 10 to 14 days. Furthermore, bringing the mother and infant back to a care center for initiation of therapy may add further delay. Therefore, even in the best settings, it can take 4-6 weeks to identify and initiate ARVs in HIV-positive infants. For this reason, the Division no longer requests efficacy/antiviral activity data in HIV-infected infants from birth to less than 4 weeks of age.

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nevirapine is given at birth, 48 hours later, and 96 hours post the second dose. HIV acquisition is considered 'higher-risk' for infants born to HIV-infected mothers who received only intrapartum ARV, or have received neither antepartum nor intrapartum ARVs, or have received antepartum ARVs without HIV RNA suppression near the time of delivery. The guideline also states that some experts recommend triple ARV prophylaxis for infants at higher risk of acquisition (as described above); however, there are 'no data demonstrating improved efficacy for a three-drug regimen over a two-drug regimen in prevention of transmission'. The guideline recommends consultation with HIV specialists if triple regimen is considered with full considerations for the potential risks and benefits of this approach.

Dolutegravir (DTG), an integrase strand transfer inhibitor (INSTI) is among the newer antiretroviral drugs. Due to its mechanism of action, dolutegravir may be a good candidate for investigation as prophylaxis for infants who are HIV exposed and at risk of infection.

Accordingly, the Division would like the Sponsor to evaluate the PK and safety profile of dolutegravir in infants who are at high-risk for HIV infection. Such infants can include those born to HIV infected mothers with no or inadequate ARV therapy during antepartum and/or intrapartum periods. The PK and safety of dolutegravir can be evaluated while administered as part of the standard prophylactic regimen. To obtain needed pediatric information on dolutegravir, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the following study/studies:

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These studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Indication(s) to be studied/Objective of each study:
Study 1

The objective of study 1 will be to determine the pharmacokinetic and safety profile of dolutegravir across the age range, identify an appropriate dose (or doses) for use in HIV-1- infected pediatric patients, and evaluate the activity of this dose (or doses) in treatment.
Efficacy will be extrapolated from adequate and well controlled studies in adults, and these studies are intended to provide additional information needed to support labeling this product for use in the pediatric population.

Study 2
The objective for Study 2 will be to characterize the PK and safety of dolutegravir in patients from birth to less than 4 weeks of age.

Age group in which study(ies) will be performed:
Study 1: HIV-1-infected pediatric patients from 4 weeks to 18 years of age.
Study 2: HIV-1-exposed and at-risk of infection pediatric patients from birth to less than 4 weeks of age.

Number of patients to be studied:
Study 1: Dolutegravir must be studied in an adequate number of pediatric subjects to characterize adverse events across the age range. A minimum of 100 subjects with at least 24-week safety data at the recommended dose or higher is required. The number of subjects should be approximately evenly distributed across the age range studied.

Study 2: A minimum of 7 subjects must be evaluated to characterize the pharmacokinetics and safety profile of dolutegravir in patients birth to less than 4 weeks of age.

Study endpoints
The following study endpoints must be evaluated:

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Pharmacokinetics: Parameters including Cmax, Cmin, Tmax, $t_{1/2}$, AUC, apparent systemic clearance and apparent volume of distribution.

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Activity: Assessment of changes in plasma HIV RNA levels and in CD4 cell counts at a minimum of 24 weeks treatment.

Resistance: Collect and submit information regarding the resistance profile (genotypic and/or phenotypic) of clinical isolates at baseline and during treatment from pediatric subjects receiving dolutegravir, particularly from those who experience loss of virologic response.

Study 2
Pharmacokinetics: Parameters including Cmax, Cmin, Tmax, $t_{1/2}$, AUC, apparent systemic clearance and apparent volume of distribution.

Safety and tolerability: adverse events including laboratory toxicities.

Drug information
Dosage form: Age-appropriate formulation
Route of administration: Oral
Regimen: As agreed upon in the protocols for each study

The selected dose(s) for study(ies) must be agreed upon with the Division prior to initiating the necessary pediatric study(ies).

Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents,

suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

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Drug specific safety concerns:
Based on available toxicity information about your product, provide specific safety parameters that your pediatric program will monitor. Safety monitoring and data collection as provided in the protocol and agreed with the Agency must include, but not be limited to:

- Rash, including severe rash or hypersensitivity reactions
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- Malignancy
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- Effect on humoral and cellular immune system maturity

Statistical information, including power of study(ies) and statistical assessments:
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Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-1-infected pediatric subjects is required. Studies must include an adequate number of subjects to characterize pharmacokinetics for dose selection. The study must be prospectively powered to target a 95% CI within 60% and 140% of the point estimate for the geometric mean estimates of clearance and volume of distribution for dolutegravir in the following age groups: 4 weeks to < 6 months, 6 months to < 2 years, 2 years to < 6 years, 6 years to < 12 years and 12 years to 18 years. Final selection of sample size for each age group must take into account potential sources of variability, including inter-subject and intra-subject variability. As study data are evaluated, the sample size must be increased as necessary for characterization of pharmacokinetics across the intended age range.

Study 2
Because Study 2 will only provide descriptive analyses of multiple-dose pharmacokinetic and safety data in HIV-exposed neonates, no formal statistical power calculation is required. However, the proposed number of patients for studying the pharmacokinetic of dolutegravir in birth to less than 4-weeks old age group must be agreed upon with the Agency.

Labeling that may result from the study(ies):
You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that GSK1349572 is safe and effective, or whether such study results are

inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

Format and types of reports to be submitted:
You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document “Study Data Specifications,” which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*
at http://www.fda.gov/Cder/guidance/7087rev.htm.

Timeframe for submitting reports of the study(ies):
Reports of the above studies must be submitted to the Agency on or before August 31, 2026. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request:
Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

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Reports of the studies that meet the terms of the Written Request dated March 3, 2010, as amended by this letter and by previous amendments dated October 19, 2010, January 3, 2017, and July 16, 2020 must be submitted to the Agency on or before August 31, 2026, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
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FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[1]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

[1] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN J FARLEY
08/28/2024 05:27:48 PM