CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213464Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 109901

MEETING PRELIMINARY COMMENTS

Bayer HealthCare Pharmaceuticals, Inc.
Attention: Bradley Jones, M.S., R.A.C.
Deputy Director, Global Regulatory Strategist
100 Bayer Boulevard
P.O. Box 915
Whippany, NJ 07981-0915

Dear Mr. Jones:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LAMPIT (nifurtimox) tablets.

We also refer to your May 17, 2019, correspondence, received May 17, 2019, requesting a Pre-NDA meeting to discuss your planned NDA submission.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Gregory F. DiBernardo
Senior Regulatory Project Manager
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: B

Meeting Category: Pre-NDA

Meeting Date and Time: August 13, 2019, 10:00 AM - 11:00 AM

Meeting Location: White Oak Campus Building 22, Room 1313

Application Number: IND 109901

Product Name: LAMPIT (nifurtimox) tablet

Indication: Treatment of Chagas disease caused by *Trypanosoma cruzi*

Sponsor Name: Bayer HealthCare Pharmaceuticals, Inc.

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for August 13, 2019, at 10:00 AM at the FDA White Oak Campus between Bayer HealthCare Pharmaceuticals, Inc. (Bayer) and the Division of Anti-Infective Products (DAIP). We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

On May 17, 2019, Bayer requested a Type B Pre-NDA meeting to discuss the planned NDA submission for LAMPIT (nifurtimox). FDA granted an August 13, 2019 meeting on June 5, 2019. Bayer submitted the meeting package on July 2, 2019.

2.0 DISCUSSION

Question 1

During development of the 30 mg and 120 mg scored tablets used in the clinical studies, (b) (4) *, a dissolution specification*

acceptance criteria of Q (b) (4)% after (b) (4) minutes was used. Although nifurtimox is a BCS-Class 2 compound for which a two-point specification option is recommended, given the results of Study 16007 which showed that pharmacokinetics of tablet batches with faster and slower dissolution profiles are equivalent to the clinical trial formulation, (i.e. AUC- and Cmax ratios fulfill the criteria of FDA bioequivalence guidelines), does the Agency agree to Bayer's proposed one-point specification Q (b) (4)@60 minutes for both, the 30 mg and 120 mg dose strengths?

FDA Response:
Please note that the acceptability of the dissolution acceptance criteria will be determined at the time of NDA review based on the totality of the information and, in addition, cannot be determined until the parameters of the dissolution method used to generate such data are deemed adequate by FDA. You may consider optimizing the current dissolution method parameters (b) (4) to achieve complete (b) (4) dissolution within 60 minutes for the slowest dissolving drug product batch(es) that is bioequivalent to the target product. The selection of the final parameters should be justified, and data regarding the final proposed method's discriminating power for changes/differences in critical quality attributes (b) (4) and stability indicating potential (b) (4) should be included in the dissolution method development report. For FDA's general recommendations regarding the content and format of the dissolution method development and validation report to be submitted during the IND or NDA stage, as well as, on the setting of the dissolution acceptance criteria/criterion, refer to the Biopharmaceutics Response to Question 4 in the Type C CMC Meeting Minutes dated February 28, 2013.

Until FDA approves/accepts the proposed dissolution method during the IND or NDA stage, and until we reach agreement regarding the dissolution acceptance criteria/criterion for both strengths of the proposed drug product during the NDA stage, we recommend that you collect and report full dissolution profile data for all the drug product lots used in clinical, registration/stability, and developmental studies. For comparative dissolution profiling and routine QC dissolution testing, we remind you to use single dosage units (tablets or split fractions thereof), regardless of tablet strength.

Since nifurtimox is a poorly soluble drug substance (by BCS criteria) and if QT prolonging potential and other Tmax-related adverse effects of the proposed drug product cannot be excluded, a second (earlier) dissolution specification (time point and tolerance limit) may be recommended for the routine QC testing of the proposed drug product (manufactured using the final formulation and process) to guard against release of tablet batches with faster-than-target dissolution rates, unless adequate clinical-based justification is provided in the NDA.

Question 2

Clinical efficacy and safety data in the pediatric population

A total of 330 pediatric subjects with Chagas' disease were treated with nifurtimox during the CHICO part of the Phase 3 clinical study (16027). CHICO was successfully completed, confirming superiority of the 60-day nifurtimox treatment over historical placebo control.

Does the Agency agree that the results from the CHICO part of the Phase 3 study provide adequate evidence on efficacy and safety of nifurtimox for treatment of Chagas' disease (American trypanosomiasis) caused by Trypanosoma cruzi in pediatric patients 0 to <18 years of age?

FDA Response:
The adequacy of the evidence to support the proposed indication will be determined during the NDA review. However, based on the study summary, the CHICO part of Study 16027 has the potential to be adequate to demonstrate the safety and efficacy of nifurtimox in pediatric patients with Chagas disease. One issue that will need further consideration during the review is whether a 20% sero-reduction in optical density values can be considered a success for the primary endpoint. This is an important issue as the primary endpoint was driven by sero-reduction. In your NDA, please include a justification to support this endpoint. Additionally, we recommend that you consider submitting information on the assays, that includes the details of the methods and data supporting the performance characteristics of the assays in the laboratories where testing of clinical specimens was performed, prior to submission of the NDA. This will facilitate the review and also allow sufficient time to seek input from the Center for Devices and Radiologic Health.

Question 3

Treatment duration in younger children

Efficacy of the 60-day and the 30-day nifurtimox treatment regimens, measured as ≥20% seroreduction or seroconversion to negative at 12-month post-treatment follow-up, was investigated as a secondary objective in the CHICO part of the Phase 3 study (16027). In the overall study population, the efficacy of the 30-day treatment regimen was lower compared to the 60-day nifurtimox treatment regimen. However, subgroup analyses revealed that the cure rates of the two treatment regimens appear to be similar in subjects younger than 2 years of age at randomization.

FDA Response:

Question 4

Pediatric dosing recommendations

Based on the results of the Phase 3 clinical study 16027, CHICO part, and considering the dose schemes used in CHICO, new dosing recommendations for nifurtimox are proposed for the pediatric population.

Does the Agency agree that the data package adequately supports the proposed dosing in pediatric patient age groups?

FDA Response:
It is premature to provide a definitive answer at this time. The adequacy of the data package and the proposed nifurtimox dosing will be evaluated during the NDA review.

Question 5

(b) (4)

Question 6

Indication

The clinical data package will be comprised of the CHICO part of the Phase 3 clinical study 16027 in pediatric subjects with Chagas' disease, supportive literature, (b) (4)

Does the Agency agree that the clinical data package will provide sufficient data to support the FDA review of the planned NDA for nifurtimox tablets with the proposed indication: Treatment of Chagas' disease (American Trypanosomiasis) caused by Trypanosoma cruzi?

FDA Response:
The CHICO part of Study 16027 may support the efficacy and safety of nifurtimox in pediatric patients with supporting evidence provided by the literature and from the chart review. (b) (4)

Question 7

Proposed strategy for safety and efficacy data presentation

Demonstration of the efficacy and safety of nifurtimox in the pediatric population will be based on a single study, i.e. the Phase 3 clinical study 16027, CHICO part. (b) (4)

Does the Agency agree with this approach?

FDA Response: Your proposal is acceptable.

Question 8

Electronic dataset format

The nifurtimox eCTD submission for the CHICO part of the Phase 3 clinical study 16027 will contain both SDTM datasets and Analysis datasets, to be submitted electronically in SAS Version 5 transport file format with corresponding documentation.

Does the Agency agree with the proposed scope, format, and documentation of the electronic datasets to be submitted?

FDA Response: We agree.

Question 9

Case Report Forms (CRFs)

The NDA will be supported by the data from one Phase 3 clinical study (16027), CHICO part. Bayer proposes to provide copies of individual CRFs for all subjects whose narratives have been provided. These are for subjects with the event of death, serious adverse events, and other significant adverse events (including CRFs for subjects who discontinued, with adverse events of special interest [AESIs] and pregnancies during the study). CRFs for all other subjects in the study would be available upon request.

Does the agency agree with this approach?

FDA Response:
Please clarify whether the CRFs were generated on paper initially and then transferred to an electronic format. If so, we would request a 10% random sample of the CRFs in addition to the ones from subjects outlined above.

Question 10

Advisory Committee Meeting

Based on current information, does the Agency believe they would plan to convene an Advisory Committee meeting for discussion of nifurtimox?

FDA Response:
It is premature to comment on the need for an Advisory Committee meeting. A decision on whether to convene an Advisory Committee will be made during the review of the NDA.

Question 11

Priority Review designation

Does the Agency have any comments on Bayer's rationale for seeking a Priority Review Designation?

FDA Response:
A decision on whether the application qualifies for Priority Review will be made at the time of NDA filing.

Additional comments

Chemistry Manufacturing and Controls

- We note that several issues in your CMC development program remain unsettled (e.g., designation of the starting materials) and warrant further discussion (e.g., NDA stability data package). In addition, you have proposed several changes for the commercial product, such as a site transfer for the manufacturing of nifurtimox tablets commercial supplies, a formulation change (i.e., addition of (b) (4) magnesium stearate), and a change in the drug product manufacturing process (as indicated in nifurtimox tablets manufacturing flow diagram, page 76 of the briefing package). Therefore, as stated in our previous correspondences (dated December 30, 2014 and November 1, 2018), we strongly recommend that you request a CMC-dedicated Pre-NDA meeting to discuss the changes outlined above and to come to agreements on various aspects of product quality information (including a stability data package) to be submitted in your NDA.

Clinical Microbiology

- Specify the location of the information for the serological, molecular and parasitological assays, supporting the intended context of use, in the NDA. As previously communicated, the information should include the following:

  - Package insert(s) for the FDA cleared test(s). We note that all the FDA cleared assays are available for qualitative and not quantitative use. If the assay was used for quantitative purpose, e.g., measuring antibody levels, then the data supporting the performance of the assay for quantitative use, in the laboratory where testing of clinical specimens was performed, should be provided.
  - Details of the experimental methods (i.e., not cleared by the FDA) and data supporting performance characteristics of the assays supporting the intended context of use (qualitative/quantitative), in the laboratory where testing of clinical specimens was performed.
  - As your intent is to compare the study results with the historical studies, specify whether the serological assays used are the same as in the historical studies and performed in the same laboratory. If not, provide any differences in the procedure and performance of the current assay compared to that in the historical study.
  - Details of the concentration technique used for detection of parasites.

- It has been reported that different strains and lineages of *T. cruzi* parasites can affect serological test performance. Your study spans multiple sites across Argentina, Bolivia, and Colombia, and the approach focuses on serological test results. As part of your submission, please provide a summary of the circulating *T. cruzi* parasite lineages expected for each patient population based on available epidemiological information for the study period. Note any differences between the expected parasite lineages for each population and the parasite antigens used in the serology tests, as well as, comment on any serology result trends that appear to associate with population/circulating parasite lineages.

- We acknowledge that you intend to submit publications to support the activity of nifurtimox against different lineages of *T. cruzi*. It will aid in our review if you could summarize the information in a tabular form that includes the information source (reference), the name of the *T. cruzi* strain, the distinct typing unit, the stage of the parasite used for culture, a brief summary of the experimental method used for determining drug sensitivity, as well as, a brief finding of the results (please see Appendix-1 for details.

- It will aid our review if the data for a subset of patients that were positive by direct examination of parasites by the concentration test prior to treatment is summarized as shown in Appendix-2. If there were any patients ≥8 months of age that were parasitologically positive by the concentration test prior to treatment, a separate table should be created.

- We note that several of the articles referenced in the proposed application are written in non-English languages. In your application, please provide English translations of any submitted non-English articles.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 5, 2019, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

In addition, we note that a chemistry pre-submission meeting is not currently scheduled or planned . If this meeting is scheduled then a summary of agreements reached at that meeting will be documented in the respective meeting minutes.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding,

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively

[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[4]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[5]

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

[4] http://www.fda.gov/ectd
[5] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[6]

[6] https://www.fda.gov/media/85061/download

Appendix-1: Summary of studies supporting the *in vitro* activity of nifurtimox against *T. cruzi*

Parasite stage (Reference) and experimental design	Strain (DTU)!	IC_{50} µM (µg/mL)
Epimastigote used for culture (Reference) For example, $5x10^6$ cells (mainly epimastigotes; about 20% trypomastigotes) were cultured in SGH medium with different concentrations of nifurtimox and morphological evaluations performed at different time points for up to 3 days by phase contrast microscopy. Growth and viability of the parasite were reported.	Y (II)	
	Sonya clone* (not known)	
	Colombiana* (I)	
Epimastigote used for culture (Reference) Add a few relevant details of experimental design	Tulahuen** (VI)	
	Y** (II)	
	Peru** (not known)	
List a study as needed	Sonya clone* (not specified)	
	Colombiana* (I)	
	Tulahuen** (VI)	
	Y** (II)	
	Peru** (Not specified)	
List a study as needed	CL tdTomato	Microscopically!! µM (.. µg/mL) Flow cytometry µM (…µg/mL)
Amastigote (Reference) For example, metacyclic trypomastigotes grown in gamma irradiated Vero cells and medium replaced. Different concentrations of BZN added and cultured for up to 4 days. The change in fluorescence intensity was determined.	CL tdTomato	
Amastigote (Reference) #Represent strains susceptible - for which nifurtimox susceptibility had been measured in infected mice. The strains were classified as follows: • susceptible (cure rates > 66%) – Berenice 62 and CL. • partially susceptible (cure rates between 33-66%) – Y. • resistant (cure rates < 33%) - Colombiana, VL10 and YuYu.	115 (V)	
	BE-62 (II)#	
	CL Brener (VI)#	
	SC2005 ()	
	YuYu (I)#	
Amastigote (Reference)	28 strains from different regions of Colombia (haplotypes I and II)	
List a study as needed	Silvio X 10 cl1 TcI	
	Colombiana TcI	
	CL Brenner TCVI	
	793 Tcbat	

DTU-discrete typing units. BE-Berenice; Vero cells- African Green monkey cells
[!]Add names of the strains and DTU as needed
[!!]If more than one method used for determining sensitivity, show results separately
*Nonresponsive strains and **Responsive strains based on long-term treatment of mouse (CD1 mice) infections with nifurtimox or benznidazole (if information is available).

Appendix-2

Summary of parasitological and serological findings in a subset of patients that were positive by direct examination of parasites by the concentration test prior to initiation of treatment

Group	Baseline		Treatment phase						Follow-up						Clinical[!!]	
			Day 3 (Visit 3)		Day 30 (Visit 6)		Day 60 (Visit 8)		Day 90 (Visit 9)		Day 240 (Visit 10)		Day 420 (Visit 11)		Signs and Symptoms (Day)	Resolution (Day)
	Parasite +ve*	Serology	Parasite +ve*	Serology!	Parasite +ve*	Serology!	Parasite +ve*	Serology!	Parasite +ve*	Serology!	Parasite +ve*	Serology!	Parasite +ve*	Serology!		
Chagatest ELISA recombinant v3.0 (Weiner)																
60 days (n=12)		+ve/ OD (n=)														
		-ve/OD (n=)														
30 days (n=7)		+ve/OD (n=)														
		-ve / OD (n=)														
Chagatest lysate ELISA (Weiner)																
60 days (n=12)		+ve/ OD (n=)														
		-ve/OD (n=)														
30 days (n=7)		+ve/OD (n=)														
		-ve / OD (n=)														
F29 ELISA																
60 days (n=12)		+ve/ OD (n=)														
		-ve/OD (n=)														
30 days (n=7)		+ve/OD (n=)														
		-ve / OD (n=)														
IHA																
60 days (n=12)		+ve/ OD (n=)														
		-ve/OD (n=)														
30 days (n=7)		+ve/OD (n=)														
		-ve / OD (n=)														

*Parasite +ve by direct examination; if quantitation of the parasites was conducted then the data should be included in ().

**Provide the threshold for characterizing the samples as sero-positive or sero-negative.

[!]Serology results should be expressed as positive or negative, as well as, OD for ELISA tests and antibody dilution titer for IHA.

[!!]Include details on the occurrence of any clinical signs (e.g., cardiac, GI) and symptoms, the number of patients in which it occurred, as well as, the day signs and symptoms resolved.

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/

GREGORY F DIBERNARDO
08/09/2019 01:07:05 PM