DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205123

NDA APPROVAL

Janssen Research & Development, LLC
Attention: Michele Dias, MS
Manager, Global Regulatory Affairs
920 Route 202
Raritan, NJ 08869

Dear Ms. Dias:

Please refer to your New Drug Application (NDA) dated and received March 28, 2013, submitted under 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Olysio™ (simeprevir) 150 mg capsules.

We also refer to our approval letter dated November 22, 2013, which contained the following errors:

1. Language regarding Section 505(o)(3) of the FDCA was included under the Required Pediatric Assessment paragraph and PREA is not subject to 505(o); and

2. The language italicized below was not included under the header **POSTMARKETING REQUIREMENTS UNDER 505(o),** in the paragraphs preceding PMRs 2105-3 and 2105-4:

    a. We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient *to assess a signal of a serious risk of the emergence of substitutions and* to identify rare emergent variants and their potential for conferring resistance to Olysio™ (simeprevir).

    b. Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess *signals of* the serious risk of increased frequency of adverse events (including rash, photosensitivity, pruritus, dyspnea, and increased bilirubin) in chronic hepatitis C patients of East Asian ancestry.

This replacement approval letter incorporates the correction of the errors. The effective approval date will remain November 22, 2013, the date of the original approval letter.

We acknowledge receipt of your amendments dated March 28, 2013, March 29, 2013, April 4, 2013, April 12, 2013, April 23, 2013, April 29, 2013, May 2, 2013, May 9, 2013, May 13, 2013, May 24, 2013, May 28, 2013, June 12, 2013, June 14, 2013, June 24, 2013, June 26, 2013, July 3, 2013, July 22, 2013, July 23, 2013, July 24, 2013, July 26, 2013, August 1, 2013, August 5, 2013, August 8, 2013, August 9, 2013, August 14, 2013, August 16, 2013, August 20, 2013, August 21, 2013 (2), August 23, 2013, August 27, 2013 (2), August 29, 2013, September 4, 2013, September 9, 2013 (2), September 13, 2013 (2), September 25, 2013, September 30, 2013, October 1, 2013, October 18, 2013, October 28, 2013, October 31, 2013, November 8, 2013, November 15, 2013, November 18, 2013, November 20, 2013, November 21, 2013(2).

This new drug application provides for the use of Olysio™ (simeprevir) 150 mg capsules, for the treatment of chronic hepatitis C (CHC) infection, as a component of a combination antiviral treatment regimen.

Olysio™ (simeprevir) 150 mg capsules have been granted a 24 month shelf life, when stored below 30 ºC (86 ºF) in the approved container closure system.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text and with the minor revisions listed below:

Package Insert:

Highlights and Full Prescribing Information

WARNINGS AND PRECAUTIONS

- Embryofetal Toxicity (Use with Ribavirin and Peginterferon Alfa): Ribavirin may cause birth defects and fetal death *and animal studies have shown interferons have abortifacient effects;*

Table 5:

(b) (4)-deleted
Fluconazole-added

Table 6 and 7:

(b) (4)-deleted

Patient Package Insert:

(b) (4)-deleted

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry SPL Standard for Content of Labeling Technical Qs and As, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed immediate container labels that are identical to the enclosed immediate container labels submitted on November 21, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 205123**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

MARKET PACKAGE

Please submit one market package of the drug product when it is available to the following address:

Victoria Tyson
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 6392
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code 20903 if shipping via United States Postal Service (USPS).
Use zip code 20993 if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages less than 3 years because necessary studies are impossible or highly impractical. Chronic hepatitis C infection is relatively benign in this age group, spontaneous clearance is possible and the risk-benefit balance would not favor treatment.

We are deferring submission of your pediatric study for ages 3 through 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. The required studies are listed below.

2105-1 Conduct a study to evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of Olysio™ (simeprevir) as a component of a combination antiviral treatment regimen in pediatric subjects 3 through 17 years of age with chronic hepatitis C.

Final Protocol Submission:	05/18
Study Completion:	07/21
Final Report Submission:	12/21

2105-2 Collect long-term safety data for subjects enrolled in the pediatric simeprevir safety, pharmacokinetics and efficacy study. Data collected should include at least 3 years of follow-up in order to characterize the long-term safety of Olysio™ (simeprevir) in pediatric subjects, including growth assessment, sexual maturation and characterization of Olysio™ (simeprevir) resistance-associated substitutions in viral isolates from subjects failing therapy.

Final Protocol Submission:	08/19
Study Completion:	07/24
Final Report Submission:	01/25

Submit the protocols to your IND 75391, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling

changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission **"SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS"** in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of the emergence of substitutions and to identify rare emergent variants and their potential for conferring resistance to Olysio™ (simeprevir).

Emergence of the substitutions R24W, K213R, L356F, T358F, V406I, P574A, P574S, T610I, or V629I was observed in clinical trial virologic failure isolates. However, their emergence was infrequent and the association between these substitutions and the serious risk of resistance or virologic failure is unclear and requires further investigation.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2105-3 Conduct a study to determine the phenotypic susceptibility of TMC435 against:

L356F, V406I, or V629I expressed in genotype 1a replicon cultures, individually and in combination with Q80K

R24W, K213R, T358F, P574A, P574S, T610I, or V629I expressed in genotype 1b replicon cultures

The timetable you submitted on November 8, 2013, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/14

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess signals of the serious risk of increased frequency of adverse events (including rash, photosensitivity, pruritus, dyspnea, and increased bilirubin) in chronic hepatitis C patients of East Asian ancestry. Existing clinical data indicate that there is a positive relationship between Olysio™ (simeprevir) exposures and the frequency of adverse events. Substantial increases in mean exposures to Olysio™ (simeprevir) were observed in Asian

patients in Phase 3 trials due to physiological characteristics (e.g. lower hepatic levels of the metabolizing enzyme CYP3A).

Therefore, based on the relevant scientific data, FDA has determined that you are required to conduct the following:

2105-4 Submit the final report and datasets from the ongoing clinical trial TMC435HPC3005 entitled "A Phase 3, Randomized, Double-Blind, Double Dummy, Placebo-Controlled Study Conducted in the Asia-Pacific Region to Investigate the Efficacy, Pharmacokinetics, Safety and Tolerability of TMC435 vs. Placebo as Part of a Treatment Regimen Including Peginterferon alfa-2a and Ribavirin in Treatment-naïve, Genotype 1 Hepatitis C-Infected Subjects."

The timetable you submitted on November 8, 2013, states that you will conduct this trial according to the following schedule:

Trial Completion:	02/15
Final Report Submission:	07/15

Please be reminded that final protocol submission implies that a draft protocol has been submitted to and commented on by FDA in order that the protocol can be revised as needed to meet the goal of the clinical trial (See Guidance for Industry: Postmarketing Studies and Clinical Trials – Implementation of Section 505(o)(3) of the Federal Food, Drug and Cosmetic Act).

Submit the protocol(s) to your IND 75391, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)".**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2105-5 Submit the final report and datasets for trial HPC3001, entitled, "A Phase 3, Randomized, Double-Blind Trial to Evaluate the Efficacy, Safety and Tolerability of TMC435 versus Telaprevir, both in Combination with PegIFNα-2a and Ribavirin, in Chronic Hepatitis C Genotype-1 Infected Subjects who were Null or Partial Responders to Prior PegIFNα and Ribavirin Therapy."

The timetable you submitted on November 8, 2013, states that you will conduct this trial according to the following schedule:

Trial Completion	06/14
Final Report Submission	12/14

2105-6 Submit the final report and datasets for trial TMC435HPC2002, entitled, "An Exploratory Phase 2a, Randomized, Open-Label Trial to Investigate the Efficacy and Safety of 12 weeks or 24 weeks of TMC435 in Combination with PSI-7977 with or without Ribavirin in Chronic Hepatitis C Genotype 1 Infected Prior Null Responders to Peginterferon/Ribavirin Therapy or HCV Treatment-Naïve Subjects."

The timetable you submitted on November 15, 2013, states that you will conduct this trial according to the following schedule:

Trial Completion:	02/14
Final Report Submission:	10/14

2105-7 Submit the final report and datasets for trial TMC435-TiDP16-C212, entitled, "A Phase 3 Open-Label Study to Evaluate the Safety, Tolerability and Efficacy of TMC435 Plus PegIFNα-2a (Pegasys®) and Ribavirin (Copegus®) Triple Therapy in Chronic Hepatitis C Genotype-1 Infected Subjects who are Co-Infected with Human Immunodeficiency Virus Type 1 (HIV-1)."

The timetable you submitted on November 15, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission:	05/14

Submit clinical protocols to your IND 75391 for this product. Submit all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Victoria Tyson, Regulatory Project Manager, at (301) 796-0827.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, M.D., MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling
Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDWARD M COX
11/22/2013