Janssen Research & Development *

Independent Flare Expert Panel (iFLEP) Charter

Protocol 73763989HPB2003; Phase 2

A Phase 2 Randomized, Open-label, Parallel-group, Multicenter Study to Assess Intrahepatic and Peripheral Changes of Immunologic and Virologic Markers in Response to Combination Regimens Containing JNJ-73763989 and Nucleos(t)ide Analog With or Without JNJ-56136379 in Patients With Chronic Hepatitis B Virus Infection

The INSIGHT Study

JNJ-73763989 and JNJ-56136379

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ALT	Alanine aminotransferase
iFLEP	Independent Flare Expert Panel
AE	adverse event
eCRF	electronic Case Report Form
SOC	standard-of-care
SRP	Study responsible physician
SRS	Study Responsible Scientist
SSG	Statistical Support Group
NA	Nucleos(t)ide Analog

1. INTRODUCTION

Clinical Protocol **73763989HPB2003** is a Phase 2 Randomized, Open-label, Parallel-group, Multicenter Study to Assess Intrahepatic and Peripheral Changes of Immunologic and Virologic Markers in Response to Combination Regimens Containing JNJ-73763989 and Nucleos(t)ide Analog With or Without JNJ-56136379 in Patients With Chronic Hepatitis B Virus Infection.

A target of 24 chronic HBV-infected male and female participants, 18-65 years (inclusive) of age will be enrolled in 2 panels, approximately 12 participants in each panel. Panel 1 will consist of participants who are HBeAg positive and not currently treated and Panel 2 will consist of participants who are HBeAg negative and virologically suppressed by entecavir (ETV), tenofovir disoproxil, or tenofovir alafenamide (TAF) treatment. The study will be conducted in 3 phases for all participants: a screening phase (4 weeks), an open label study intervention phase (48 weeks), and a follow-up phase (48 weeks).

JNJ-73763989 (JNJ-3989) is a liver-targeted antiviral therapeutic for subcutaneous injection designed to treat chronic hepatitis B virus (HBV) infection via a ribonucleic acid interference (RNAi) mechanism. Engagement of the cellular RNAi machinery by JNJ-3989 results in specific cleavage of HBV ribonucleic acid (RNA) transcripts, thereby reducing the levels of HBV proteins and the pre-genomic ribonucleic acid (pgRNA), the precursor of viral relaxed circular deoxyribonucleic acid (DNA). The RNAi triggers (JNJ-73763976 [JNJ-3976] and JNJ-73763924 [JNJ-3924]) in JNJ-3989 are designed to target all HBV RNA transcripts derived from covalently closed circular DNA (cccDNA), as well as transcripts derived from integrated viral DNA. The latter has been suggested to be a significant source of hepatitis B surface antigen (HBsAg) in hepatitis B e antigen (HBeAg)-negative patients or patients on long-term treatment with nucleos(t)ide analogs (NAs), the current standard of care.

JNJ-56136379 (JNJ-6379) is an orally administered capsid assembly modulator that is being developed for the treatment of chronic HBV infection. JNJ-6379 binds to hepatitis B core protein and interferes with the viral capsid assembly process, thereby preventing the polymerase-bound pgRNA encapsidation. This results in the formation of HBV capsids, devoid of HBV DNA or RNA (non-functional capsids), and ultimately in the inhibition of HBV replication. In addition, JNJ-6379 also acts at an early stage of the viral life cycle by inhibiting the de-novo formation of cccDNA potentially by interfering with the capsid disassembly process.

The term "study intervention" throughout the protocol, refers to JNJ-3989, JNJ-6379, and NA.

To characterize ALT flares that may occur during and after treatment, subjects who have an ALT and/or AST ≥3 x ULN and ≥3 x nadir will have specific clinical data (outlined in Attachment 2) reviewed by an independent FLare Expert Panel (iFLEP), who will serve as adjudication committee. The panel will provide an independent opinion as to whether the ALT Flare is associated to response to treatment, lack of response, drug liver injury, autoimmune hepatitis or other causes. Severity of the Flare will also be assessed. This charter will define the membership of the iFLEP, their responsibilities, and the procedures used to carry out these responsibilities. The charter has been drafted by the Sponsor and approved by the iFLEP members prior to the review of any trial data by the iFLEP. The charter may be amended by a vote of the entire iFLEP with concurrence from the Sponsor. The need for update should be evaluated in case of substantial protocol amendment.

2. IFLEP ORGANIZATION

2.1. Independent FLEP Members

The iFLEP will comprise 3 independent medical experts (see Table **1**: Names, Affiliations and Contact Information –ALT Flare Adjudication Committee). One of these individuals will chair the committee. All members are experts in the diagnostic, clinical, and therapeutic management of Chronic Hepatitis B.

The iFLEP will review protocol management of ALT Flares and review retrospectively ALT Flares for characterization.

To ensure for an unbiased assessment, members of the panel will be blinded to treatment assignment unless they need to request unblinded information from the Sponsor. The independent review by this adjudication committee ensures that events are evaluated in a uniform manner, eliminating the variability associated with site-based event evaluation and improving the validity of the study results. iFLEP members will be independent of the JNJ-73763989 and/or JNJ-56136379 phase 2 INSIGHT study and as such cannot be participating as principal investigators or sub-investigators. Otherwise, iFLEP members will not be restricted from other contractual commitments with the Sponsor during the time that they are serving on

the iFLEP. If a member expresses inability to serve on the iFLEP and resigns, the Sponsor will appoint an appropriate replacement in consultation with the iFLEP chair.

Table **1**: Names, Affiliations and Contact Information –ALT Flare Adjudication Committee

Name	Speciality	Affiliation	Contact information
[redacted]	[redacted]	[redacted]	[redacted]

2.2. Clinical Liaison

A Clinical Liaison to the iFLEP, appointed by the Sponsor, will be responsible for communicating, and coordinating operational and logistical support (including meeting support) for the iFLEP. Additionally, the Clinical Liaison will be responsible for coordinating creation and distribution of the Data Packages for review by the iFLEP, with the support of Sponsor Data management and Statistical Support Group.

2.3. Statistical Support Group

An internal Statistical Support Group (SSG) independent of the Study Team will support the iFLEP. A SSG constitutes a statistician (SSG statistician). The SSG Statistician is a person who is capable of performing the duties as described in Section 5.2.1. The roles and responsibilities of the SSG are detailed in Section 5.2.

The names of clinical liasison and SSG statistician, roles in the project, and the contact information are included in Table 2.

Table **2**: Key supporting personnel to iFLEP

Name	Role	Affiliation	Contact information
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

3. ROLES AND RESPONSIBILITIES

3.1. Independent Flare Expert Panel

The responsibilities of the iFLEP are:

- Conduct regular review of all relevant and available individual subject blinded study data related to ALT Flares provided in the Adjudication Data Package described in attachment 2.
- Conduct ad-hoc review for urgent assessment of ALT Flare upon sponsor's request
- Determine and adjudicate for each ALT Flare whether it is:

A. **Flare associated with response to treatment**:

Characterize by favorable evolution of HBV markers with subsequent classification according to severity:

a. Tolerable Flare (study treatment continuation)
b. Severe Flare (with symptoms and/or abnormal other liver functions tests, study treatment discontinuation)

B. Flare associated to lack of response to treatment

Characterize by HBV breakthrough or relapse with subsequent classification according to severity:

a. Tolerable Flare
b. Severe Flare

C. Flare associated with drug liver tox (DILI)

D. Flare related to Autoimmune hepatitis

E. Others cause of Flare (alcohol, other viruses, concomitant medications…)

- Provide documentation of the final decision, after each member evaluated the Flare individually. Majority of 3 votes will be considered the final adjudication. In case lack of agreement, the iFLEP chair will make the final decision.

- Review the final summary report that will describe the methods, observations, conclusions and recommendations of this iFLEP convened to characterize ALT Flare

The adjudication workflow for the panel is provided in Attachment 1.

3.2. Clinical Liaison

The Clinical Liaison has the following responsibilities:

- Be the primary Sponsor contact with iFLEP
- Coordinate with the iFLEP to set up a kick-off meeting (to review the protocols, review and approve the charter) and if needed, ad-hoc meetings
- Work with the other clinical study team members to prepare the content of the adjudication data package (Attachment 2) that will be reviewed by iFLEP members
- Supplement data package with additional information obtained from the site, if asked by the iFLEP Chair

3.3. Statistical Supporting Group

The SSG Statistician has the following major responsibilities:

- Work with data management to ensure updated clinical data relevant to flares are correctly transferred to programming for analysis

- Provide the data package including the subject's profiles (for the initial adjudication and in case an ALT Flare needs to be re-adjudicated) and other relevant clinical data

- Act as an independent statistician who is not related to the study conduct and serves as statistical support to ensure the correctness of the subject's profiles and provide logistic support to the iFLEP including the minutes of each iFLEP meeting

- Provide meeting minutes to be communicated to the study team

4. FLEP DATA PACKAGE

The laboratory tests and subject profile will be the primary data source provided to the iFLEP for characterization of ALT Flares and will include the following individual subject data. Details are in the attachment 2.

a. Demographic information
b. Medical history
c. Liver tests, INR, direct bilirubin, albumin, hematology, chemistry
d. Other tests to exclude other causes of ALT elevation
e. HBV DNA, HBeAg, antiHBe, sAg level
f. Concomitant medications
g. Medical interventions
h. Any reported AEs

The specification of data package is provided in (Attachment 2).

If additional data is required to aid the adjudication process, then this can be requested by the iFLEP Chair (Attachment 1).

5. FLEP REVIEW PROCESSES AND COMMUNICATION FLOW

The iFLEP together with the Clinical Liaison will set up the following review procedures:

- Finalize the iFLEP charter and content specifications of the Adjudication Data Package
- Establish review timeline
- Review and document ALT Flares event within 2 weeks of receiving the adjudication data package
- Ad-hoc review might be set up as needed. In case of SAE, iFLEP might be asked to adjudicate in real time by the study team

The details of the process flow to the Adjudication committee, procedures for evaluation of the data, and communication of the iFLEP conclusions are described below.

The data management team in conjunction of the SRP/SRS will identify the set of ALT Flares ready for adjudication as defined in the adjudication package (attachment 2) at the time of each adjudication period. An Adjudication Data Package for each ALT Flare will be prepared and made available for review to each iFLEP member prior to each adjudication period by SSG. Each iFLEP member will review the Adjudication Data Package individually.

For each Flare characterized, the iFLEP must further agree by a majority vote on the Flare adjudication. In case no majority is reached for a specific Flare, the iFLEP chair will make the final decision (Attachment 1). For that purpose, the iFLEP chair can request additional information to the Clinical Liaison. Depending on the availability of the requested additional information, final adjudication of flares will occur during the review cycle or as soon as possible during subsequent review cycles.

The result of the votes and the review history for each flare will be documented. The Clinical Liaison will communicate adjudication results and meeting minutes to the study team (SRP/SRS) after each review period.

6. IFLEP REVIEW AND ADJUDICATION PERIODS

[redacted]

Given the small sample size of the study, the adjudication periods may depend on the cases of emerging flares. Generally, iFLEP will review the flares whenever the new cases of flares are identified during treatment period.

The Sponsor may request ad-hoc reviews and meetings where necessary. Meetings will be F2F during the main Hepatology congresses (EASL, AASLD) or virtual meetings using teleconference and/or web technologies. The minutes of all meetings will be fully documented, including attendees and major decisions.

7. CONFIDENTIALITY

All information, documentation, reports, meeting minutes etc., provided to, or received from JNJ-73763989 and/or JNJ-56136379 phase 2 study by the iFLEP will be treated as confidential. Discussions of the JNJ-73763989 and/or JNJ-56136379 phase 2 study shall be treated as confidential and not disclosed outside the iFLEP or Sponsor without the written approval of the appropriate Sponsor representative. At the end of the study, all information related to the iFLEP will be archived as per the Sponsor's documentation guidelines.

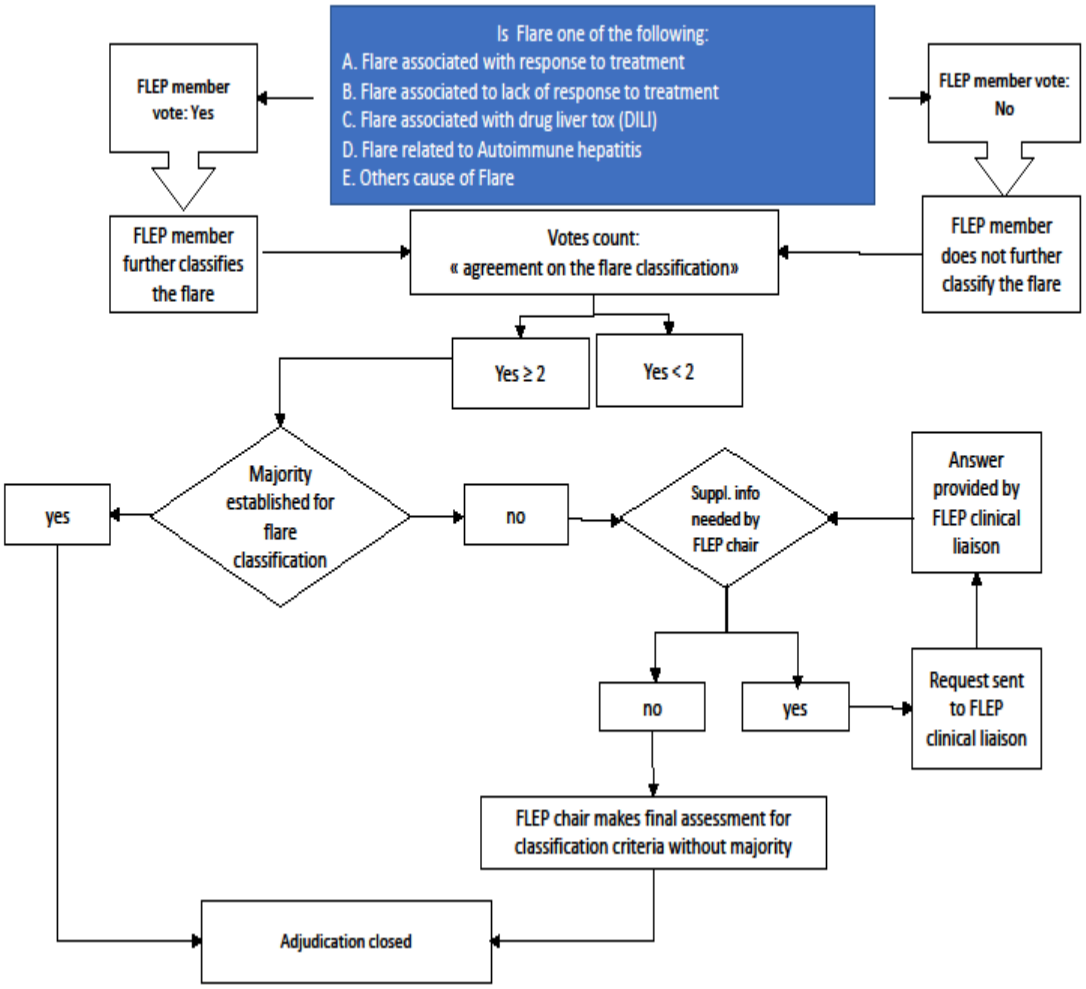
APPROVALS

IFLEP Chairperson	Signature	Date
[redacted]		

IFLEP Member	Signature	Date
[redacted]		

IFLEP Member	Signature	Date
[redacted]		

ATTACHMENT 1: ADJUDICATION WORKFLOW



ATTACHMENT 2: DATA PACKAGE SPECIFICATION

Planned Data Package including presentation format	Data will be presented descriptively blinded. Subject data listings of Flares reporting: for subjects who have an ALT and/or AST ≥3 x ULN and ≥3 x nadir, the following information will be listed by subject Serious adverse events Fatal adverse events Grade 3 or 4 adverse events Adverse events leading to permanent drug discontinuation Toxicities of at least Grade 3 in the following lab parameters: ALT, AST Subject profile (including baseline characteristics, medical history, disposition, study drug exposure, adverse events, HBV DNA, HBsAg levels, lab parameters including ALT, AST, indirect bilirubin, direct bilirubin, total bilirubin, INR, albumin, ALP) Subject graphic profile: Graphic display of individual subject with Flares over time on treatment period. See an example below. Summary of Flares over time: Tabulation of Flares over time on treatment period. Supporting Tabulations (Selected from IDMC analysis): Demographic data and baseline disease characteristics Study and trial completion/discontinuation Adverse events summary tabulation All adverse events by system organ class and preferred term All lab parameters including worst treatment emergent laboratory abnormalities

An example of subject graphic profile

PSF01A_FLEP: Individual patient profiles; Intent-to-treat (Study xxx)

[redacted]

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Adverse Events

- Grade 1
- Grade 2
- Grade 3
- Grade 4
- Grade Unknown

Chemistry Lab Parameters

- Grade 0
- Grade 1
- Grade 2
- Grade 3
- Grade 4
- Below
- Within
- Above

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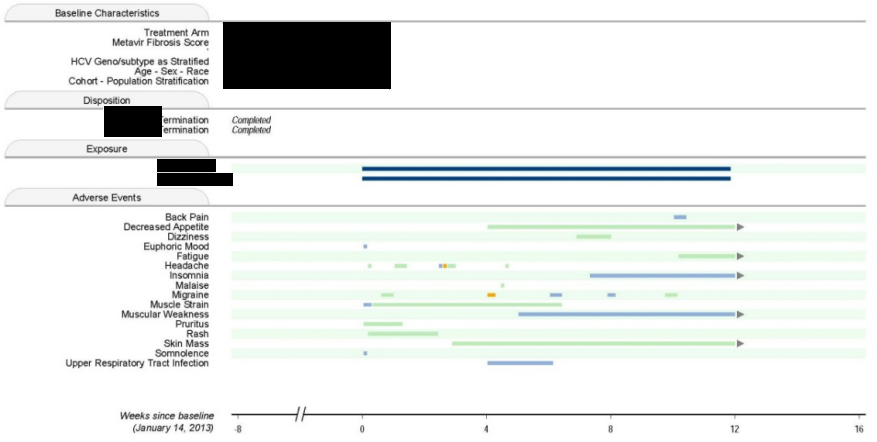

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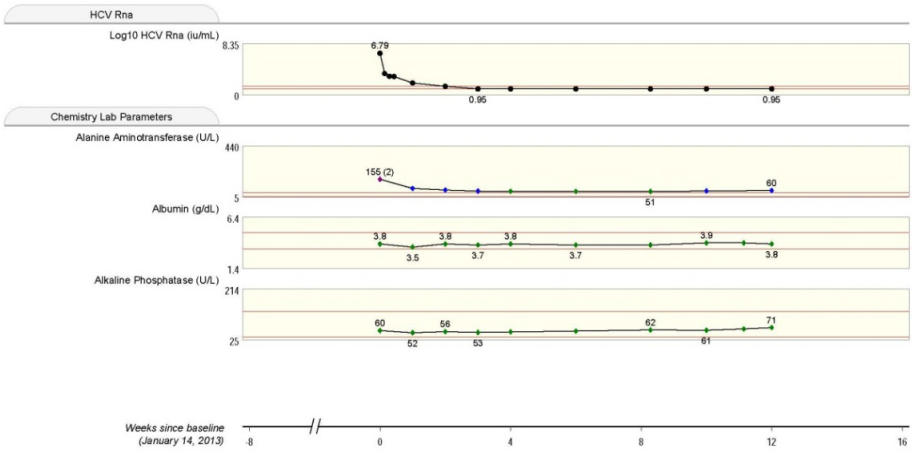

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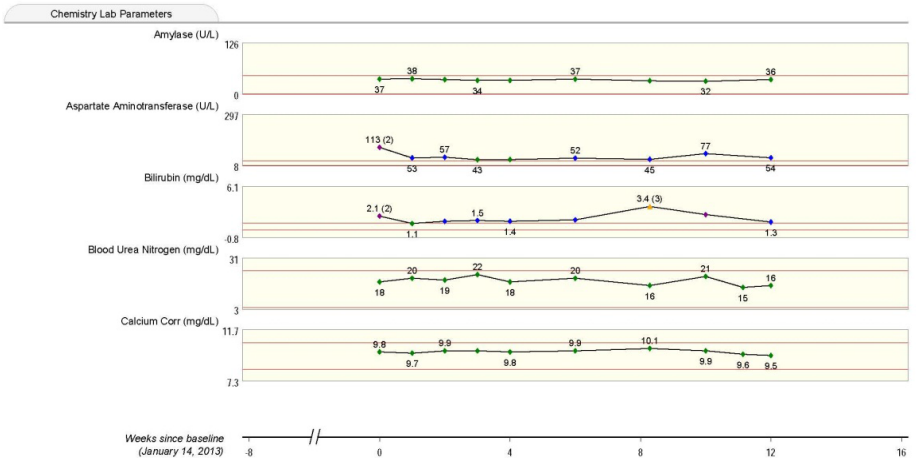

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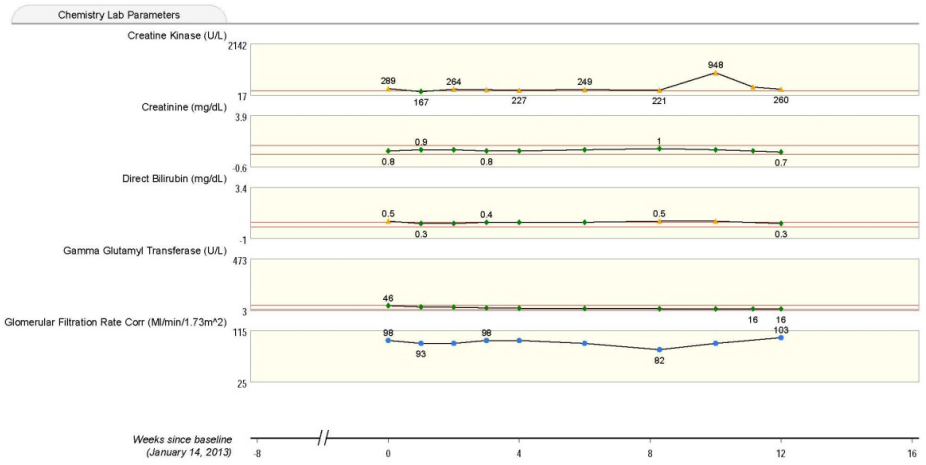

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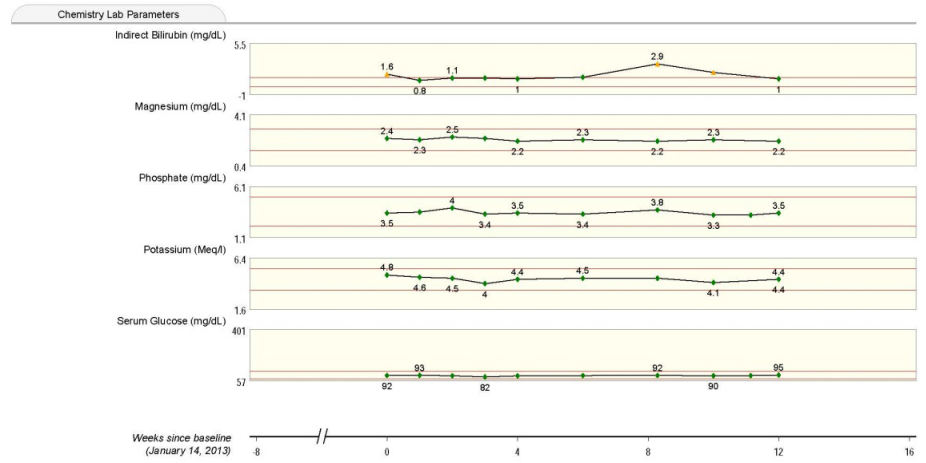

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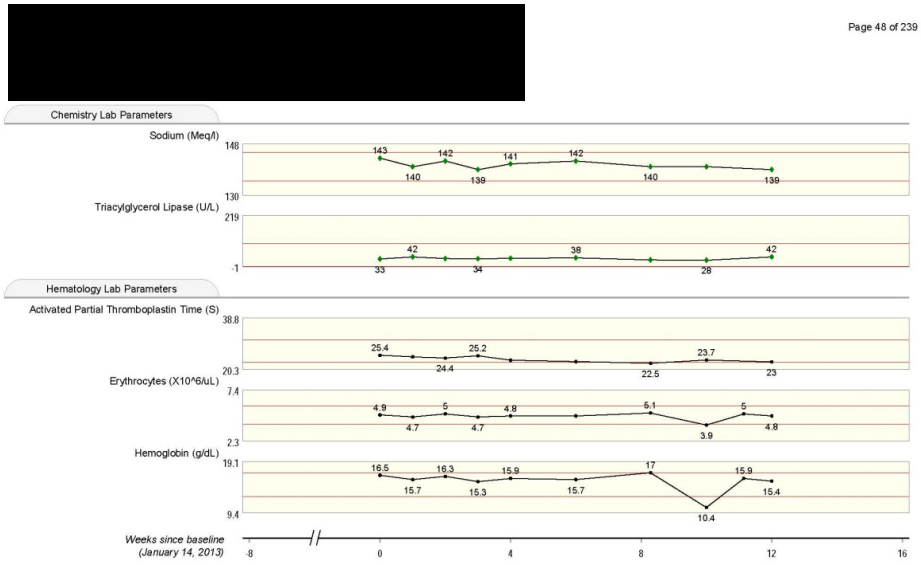

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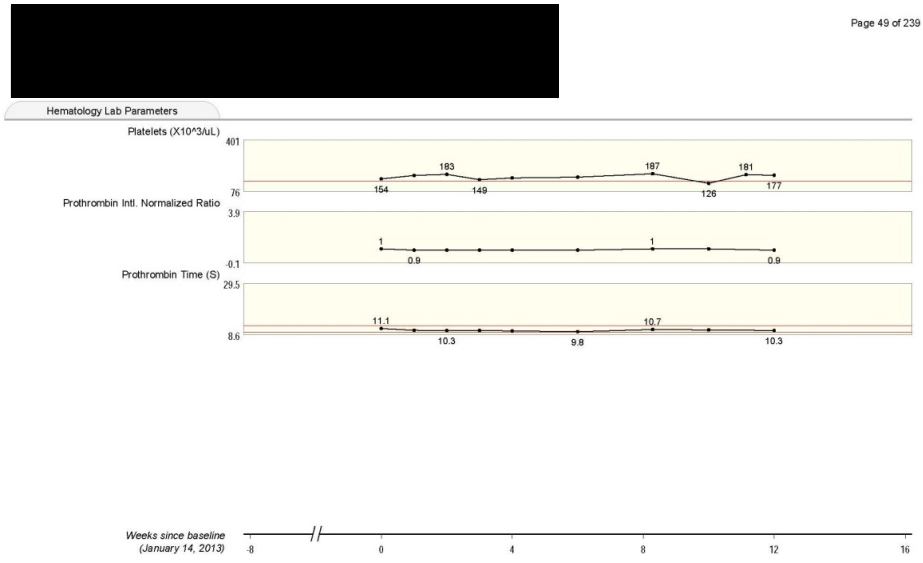

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Note: Internal Safety Review analysis, date of database snapshot= ddMMMyyyy
Data are being obtained on an ongoing basis and therefore hold no warranty towards completeness or correctness.