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(54) Title: METHODS AND SYSTEMS USING PHARMACOKINETIC AND PHARMACODYNAMIC PROFILES IN INTERFERON-ALPHA THERAPEUTIC REGIMENS

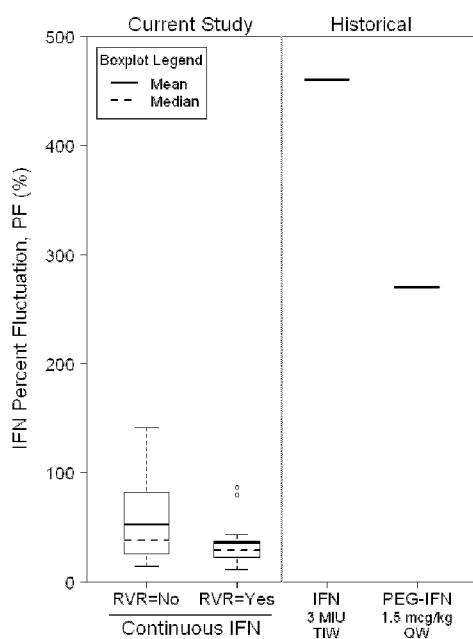


FIG.24A

(57) Abstract: Methodologies and systems relating to the delivery of interferon- α are provided. Analyses of clinical trial data show that observations of interferon- α pharmacokinetic profiles following its from delivery via a continuous infusion device can be correlated with viral responses to this therapeutic agent. Such information can be used, for example, to optimize the treatment of individuals infected with the hepatitis B and C viruses.



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**METHODS AND SYSTEMS USING PHARMACOKINETIC AND
PHARMACODYNAMIC PROFILES IN INTERFERON-ALPHA
THERAPEUTIC REGIMENS**

5 **CROSS REFERENCE TO RELATED APPLICATIONS**

This application claims priority under Section 119(e) from U.S. Provisional Application Serial No. 61/446,764 filed February 25, 2011; U.S. Provisional Application Serial No. 61/469,042, filed March 29, 2011; and U.S. Provisional Application Serial No. 61/556,058, filed November 4, 2011, the contents of each of which are incorporated
10 herein by reference.

FIELD OF THE INVENTION

This invention is in the field of therapeutic agents and their pharmacokinetics and pharmacodynamics.

15 **BACKGROUND OF THE INVENTION**

In the United States, chronic liver diseases account for about 25,000 deaths annually making it the tenth leading cause of death among adults in the United States. A significant number of these deaths result from infection with the Hepatitis B and Hepatitis C viruses. Hepatitis B virus (HBV) infection is a major public health challenge,
20 with an estimated 730,000 chronically infected adults in the United States alone. Hepatitis C virus (HCV), is an even more deadly type of hepatitis virus which is associated with chronic liver diseases such as liver cirrhosis and cancer.

Human recombinant interferon-alpha (IFN- α) is approved in many countries for the treatment of hepatitis B and C infection, either as a monotherapy or in combination
25 with additional agents such as small molecule nucleoside analogs. IFN- α is also approved in many countries for treating patients with cancer. IFN- α generally stimulates patients' immune systems and is, for example, one of the earliest cytokines released by antigen presenting cells as part of the innate immune response. IFN- α modulates NK and T cell responsiveness, which consequently drives the immune response in patients.
30 In addition, IFN- α exhibits a number of virus specific effects and,, for example, is

observed to down-regulate hepatitis B virus gene expression in vivo by tumor necrosis factor-dependent and independent pathways (Guidotti et al., J Virol. 1994 Mar;68(3):1265-70).

Continuous IFN- α pressure on viral infections may be clinically important and increasing the dose level of interferon appears to improve the success rate of viral therapy, as measured by sustained viral response, "SVR", (see, e.g., Shudo et al., J Viral Hepat 2008a;15(5):379-82). Unfortunately, IFN- α , as a recombinant human therapeutic agent, is hindered by its short half-life in vivo. This rapid decay requires multiple injections, usually three times weekly, to maintain therapeutic levels. In order to mitigate this rapid in vivo degradation, longer-acting versions of IFN- α 2b have been developed, by polyethylene glycol modification of the molecule. For example, Pegylated IFN- α 2b (PEGIntron®) is approved for the treatment of hepatitis C. Its half-life is about 40 hours and it is administered once weekly by SC injection. However, PEGIntron®, being a modified IFN- α 2b molecule, compared to unpegylated IFN- α 2b, it has reduced affinity for the IFN- α 2b receptor, distributes differently in the body and hence its safety and efficacy are not necessarily comparable to IFN- α 2b. Current interferon therapies for treatment of HBV and HCV infection appear limited by one or more of the following: 1) fluctuating blood levels of drug, which preclude continuous drug pressure on the virus; 2) limited biological potency; 3) limited systemic distribution of the drug; and/or 4) short half-lives relative to once-weekly dosing regimens (see, e.g., Caliceti et al., Digestive and Liver Disease 2004;36 (Supplement 3):S334).

Interferon therapies further carry a risk of side effects, including neutropenia, thrombocytopenia, serious depression, and systemic flu-like symptoms. Interferon therapies can also exacerbate or induce fatigue in patients with chronic viral infection and compromise quality of life. Clinical evidence suggests that the incidence and/or severity of certain AEs (adverse events) associated with conventional interferon therapies correlate with peak blood levels or with rapidly changing blood levels of interferon (see, e.g., Arimura et al., J Neurovirol 2007;13(4):364-72, Bonnem et al., J Biol Response Mod 1984;3(6):580-98 and Budd et al., Cancer Chemother Pharmacol 1984;12(1):39-42).

Near-constant blood levels combined with the maximal levels of penetration into non-hepatic and hepatic tissues achieved by nonpegylated interferons may be able to decrease the incidence and/or severity of certain AEs as well as improve therapeutic efficacy by exposing HBV and HCV to an environment that comprises continuous, physiologically effective interferon- α levels in as many tissues as possible. The continuous subcutaneous administration of a nonpegylated, fully biopotent interferon- α (e.g. INTRON A®) via an external pump infusion system (e.g. the Medtronic MiniMed Paradigm® Insulin Infusion System) results in more constant blood interferon- α levels. Furthermore, relatively stable blood interferon- α levels appear to allow patients to tolerate relatively high doses of interferon that can provide improved therapeutic efficacy (e.g. SVR rates). In such contexts, methods and systems that facilitate the optimized doses of interferon- α are desirable. As discussed below, pharmacokinetic and/or pharmacodynamic markers can be utilized in order to, for example, optimize therapeutic regimens for patients treated with IFN- α .

SUMMARY OF THE INVENTION

As disclosed herein, results from pharmacokinetic and pharmacodynamic analyses of clinical trial data demonstrate that pharmacokinetic profiles of interferon- α administered to patients via a continuous administration regimen can be correlated with aspects of disease states and consequently be used to optimize patient treatment. Embodiments of the invention disclosed herein address important needs in this technology and, for example, allow medical personnel to administer optimized interferon- α dosing regimens, including those designed to address the unique parameters of an individual patient's physiology.

The invention disclosed herein has a number of embodiments. One illustrative embodiment of the invention is a method of characterizing one or more pharmacokinetic profile(s) resulting from a therapeutic regimen that comprises administering interferon- α to a patient via a continuous infusion device. In typical embodiments, the one or more pharmacokinetic profile(s) are correlated with a viral response to the therapeutic regimen

(e.g. an early virological response (EVR), and/or a sustained virological response (SVR); and/or viral clearance). Consequently such methodologies allow artisans to obtain information that can be used to address and/or overcome problematical phenomena observed in therapeutic regimens that use interferon- α to fight viral infections (e.g. in
5 patients infected with the hepatitis B or hepatitis C virus). Typically such methods comprise the steps of obtaining one or more interferon- α serum concentration measurements from the patient following initiation of the therapeutic regimen. These measurements can then be used to determine one or more pharmacokinetic factors such as a percent fluctuation (PF%) of interferon- α concentrations in the patient, a standard
10 deviation of interferon- α concentrations in the patient, and a coefficient of variation of interferon- α concentrations in the patient, and in this way characterize a pharmacokinetic profile of interferon in a patient specific manner.

Typically, the methods include determining if the pharmacokinetic profile of interferon- α conforms to one or more parameters (e.g. exhibits relatively uniform
15 concentration levels *in vivo*) that identifies the patient as more likely to exhibit a viral response as compared to patients having pharmacokinetic profiles that do not conform to the parameter(s). In doing so, artisans can then select one or more continued therapeutic regimen(s) or course(s) of action based upon the determination(s). For example, the continued therapeutic regimen or course of action can comprise
20 maintaining the therapeutic regimen for a duration of at least 4, 5, 6, 7, 8, 12, 24, 36 or 48 weeks. The course of action can also or alternatively comprise initiating a modified therapeutic regimen for the patient that comprises an increased dose of interferon- α (e.g. so that levels of this agent are above a critical efficacy threshold), or a decreased dose of interferon- α (e.g. so that levels of this agent are below those that produce significant side
25 effects in the patient). Alternatively, the course of action can comprise discontinuing the therapeutic regimen.

Yet another embodiment of the invention is a system for administering interferon- α to a patient. In such embodiments the system comprises a continuous infusion pump having a medication reservoir comprising interferon- α , and a processor

operably connected to the continuous infusion pump and comprising a set of instructions that causes the continuous infusion pump to administer the interferon- α to the patient according to a patient-specific therapeutic regimen. Typically this patient-specific therapeutic regimen is made by administering interferon- α to the patient via a continuous infusion pump according to a test therapeutic regimen and then observing concentrations of interferon- α present in the serum of the patient that result from the test therapeutic regimen so as to obtain information on whether a pharmacokinetic profile of the interferon- α conforms to one or more parameters that identify the patient as more likely to exhibit a viral response to interferon- α as compared to patients having pharmacokinetic profiles that do not conform to the parameter(s). In this context, the processor in this system uses instructions that result from the observed profile(s) and comprises an increased dose of interferon- α ; or a decreased dose of interferon- α as compared to the test therapeutic regimen.

Other embodiments of the invention include the use of interferon- α in the manufacture of a composition adapted for a continuous infusion apparatus. In such use embodiments, the interferon- α composition is manufactured so that a continuous infusion apparatus using the composition modulates one or more pharmacokinetic profile(s) of the manufactured composition. In some embodiments, the composition is manufactured so that, when delivered via a continuous infusion device, the percent fluctuation (PF%) of interferon- α concentrations in vivo are not greater than a predetermined value, for example not greater than about 100, 150 or 200%. Optionally, the composition is manufactured to maintain mean circulating levels of interferon- α in serum of a patient above a specific steady state concentration, for example one that ranges from 30-35 IU/mL (e.g. is at least 33 IU/mL).

A related embodiment of the invention is the use of interferon- α in the manufacture of a composition for treating hepatitis C infection for use in a continuous infusion apparatus, wherein the interferon- α composition is manufactured to allow the continuous infusion apparatus to maintain mean circulating levels of interferon- α in serum of a patient above a steady state concentration that ranges from 30-35 IU/mL (e.g.

is at least 33 IU/mL) for at least 1 to at least 48 weeks when administered subcutaneously. Another related embodiment of the invention is a method of administering a therapeutic regimen comprising interferon- α delivered to a patient infected with a hepatitis C virus via a continuous infusion device, the method comprising

5 determining average serum interferon- α concentrations in the patient that are occurring on about a third day of administering interferon- α , wherein serum interferon- α concentrations of above about 30-35 IU/mL identify the patient as having a greater probability of achieving rapid virologic response (RVR) as compared to a patient having serum interferon- α concentrations below about 30-35 IU/mL. In this method, these

10 observed serum interferon- α concentrations can further be used to design a modified therapeutic regimen for the patient that comprises an increased dose of interferon- α ; or alternatively, a decreased dose of interferon- α .

Other objects, features and advantages of the present invention can become apparent to those skilled in the art from the following detailed description. It is to be

15 understood, however, that the detailed description and specific examples, while indicating some embodiments of the present invention are given by way of illustration and not limitation. Many changes and modifications within the scope of the present invention may be made without departing from the spirit thereof, and the invention includes all such modifications.

20

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates median serum IFN concentrations vs. nominal study time. IFN concentrations missing for any reason were not included in the determination of the median value. Detailed summary statistics of the serum IFN concentrations are provided

25 in Figure 7. For the PEG-IFN arm after Day 3, the serum IFN concentrations represent an upper bound for the weekly C_{min} .

Figure 2 illustrates selected IFN exposure variables through 4 and 12 weeks for the Continuous Subcutaneous IFN Delivery (CSID) arms of the COPE-HCV clinical trial. Boxes range the 25th and 75th percentile with horizontal line at the median and

solid diamonds at the mean. Whiskers range the 10th and 90th percentiles. Empty circles represent outliers. Detailed summary statistics for the complete set IFN exposure variables are provided in Figures 8 and 9.

Figure 3 illustrates stability in serum IFN concentrations resulting from CSID vs. historical controls from Day 3 through 4 (left) and 12 (right) weeks of therapy. Boxes range the 25th and 75th percentile with horizontal line at the median and solid diamonds at the mean. Whiskers range the 10th and 90th percentiles. The $PF\%$ of the PEG arm for COPE-HCV was not calculated for comparison with the CSID arms due to the infrequent sampling relative to once-weekly dosing for PEG-IFN. For PEG-IFN- α -2a and PEG-IFN- α -2b administered QW, $PF\%$ was estimated using published PK model parameters for individual subjects (see, e.g. Dahari H, et al. Pharmacodynamics of PEG-IFN- α -2a in HIV/HCV co-infected patients: Implications for treatment outcomes. Journal of Hepatology 2010;53:460-467; Talal AH, et al. Pharmacodynamics of PEG-IFN alpha differentiate HIV/HCV coinfectd sustained virological responders from nonresponders. Hepatology 2006;43:943-953). For IFN- α -2b administered TIW, $PF\%$ was estimated from mean data published for Week 4 of therapy (see, e.g. Glue P, et al. Pegylated interferon-alpha2b: pharmacokinetics, pharmacodynamics, safety, and preliminary efficacy data. Hepatitis C Intervention Therapy Group. Clin Pharmacol Ther 2000;68:556-567). P-values comparing CSID with controls were calculated using the Wilcoxon rank-sum/signed-rank test, as appropriate.

Figure 4 illustrates individual subject plasma HCV RNA levels vs. nominal study time. Lines terminating prior to 12-weeks reflect subjects who discontinued prior to 12 weeks. Results $< \text{LLOD}$ are reported as $\log_{10}(\text{LLOD}/2) = 0.95 \log_{10} (\text{IU/mL})$.

Figure 5 illustrates subject disposition through the week 12 efficacy decision. Subjects were required to have a $\geq 2\text{-log}_{10}$ decline in their plasma HCV RNA after 12 weeks in order to continue drug therapy.

Figure 6 illustrates subject disposition and early virologic response (EVR) after 12 weeks of therapy.

Figure 7 illustrates serum IFN concentration detailed summary statistics. The column headings provide the number of mITT subjects by arm (N). The number of IFN concentration measurements that are available for each study visit are also denoted (n).

Figure 8A-B illustrates IFN exposure variables, depicting week 4 interferon exposure variable descriptive statistics. (#) *AUC* summary statistics are reported to 3 significant digits. All other Interferon Exposure Variable Descriptive Statistics are reported to 1 decimal place. *AUC*, C_{avg} and C_{max} are based on the nominal time interval from Baseline through Week 4. In contrast, $PF\%$ and C_{min} are based on the nominal time interval from Day 3 through Week 4.

Figure 9A-B illustrates week 12 interferon exposure variable descriptive statistics. (#) *AUC* summary statistics are reported to 3 significant digits. All other Interferon Exposure Variable Descriptive Statistics are reported to 1 decimal place. *AUC*, C_{avg} and C_{max} are based on the nominal time interval from Baseline through Week 12. In contrast, $PF\%$ and C_{min} are based on the nominal time interval from Day 3 through Week 12.

Figure 10 illustrates detailed results from a power model analysis, depicting week 4 IFN exposure variable power model analysis results. None of the interferon exposure variables had a statistically significant ($p < 0.05$) quadratic term.

Figure 11 illustrates week 4 IFN exposure variable power model analysis results.

Figure 12 illustrates week 12 IFN exposure variable power model analysis results. None of the interferon exposure variables had a statistically significant ($p < 0.05$) quadratic term.

Figure 13 illustrates week 12 IFN exposure variable power model analysis results.

Figure 14 illustrates an analysis of PD relationships, depicting multivariate regression for week 4 C_{min} as a predictor of RVR and discontinuation. (A) Independent variables used in the multivariate regression analysis. Multivariate logistic regression models were used to assess the ability of the Week 4 IFN exposure variables to predict RVR and discontinuation before Week 12 of therapy. The independent variables listed here were provided to the backward selection algorithm. (B) Multivariate Regression

Results: Week 4 Exposure Variables & Baseline Characteristics as Predictors of RVR. Variables with p-values > 0.05 were excluded from the final form of the model by the backward selection algorithm. (C) Multivariate Regression Results: Week 4 Exposure Variables & Baseline Characteristics as Predictors of Discontinuation before Week 12.

5 **Figure 15** illustrates Receiver Operating Characteristic curves for week 4 C_{min} as a predictor of RVR and discontinuation, depicting a Receiver Operating Characteristic curve for week 4 IFN C_{min} as a predictor for RVR.

Figure 16 illustrates a Receiver Operating Characteristic curve for week 4 IFN C_{min} as a predictor for discontinuation before week 12. Only discontinuations for reasons
10 other than the Week 12 futility rule are included (<2-log10 drop HCV RNA).

Figure 17 illustrates a multivariate contingency table for week 4 C_{min} as a predictor for RVR and therapy discontinuation. Of the 78 CSID subjects in the mITT population, 60 met the prospective exclusion rules for Week 4 C_{min} . Two of the 60 subjects with Week 4 C_{min} values had missing Week 4 HCV RNA levels. Therefore, there
15 are 58 subjects in this multivariate contingency table.

Figure 18 illustrates Day 3 IFN concentration as a predictor of RVR. (A) Independent variables used in the multivariate regression analysis. Multivariate logistic regression models were used to assess the ability of a single IFN concentration measurement from the Day 3 study visit to predict RVR. The independent variables
20 listed here were provided to the backward selection algorithm. For the Day 3 study visit, the actual time on CSID had a median of 2.1 days and range of 1.6-5.2 days. (B) Multivariate Regression Results: Day 3 Serum IFN Concentration & Baseline Characteristics as Predictors of RVR.

Figure 19 illustrates a contingency table for Day 3 IFN concentration as a
25 univariate predictor for RVR and therapy discontinuation.

Figure 20 illustrates a Receiver Operating Characteristic curve for Day 3 IFN concentration as a predictor for RVR.

Figure 21 illustrates a correlation of Week 4 viral decay with Week 4 IFN exposure variables. The correlation of Week 4 viral decay with C_{avg} , $PF\%$, C_{max} , and C_{min}
30 was assessed by reporting and testing whether parametric (Pearson's coefficient) and

non-parametric (Spearman's ρ and/or Kendall's τ) measures of correlation are significantly different from 0, as presented in Figure 21 and illustrated by Figure 22. Correlation of Week 4 IFN exposure variables with viral decay. Note: C_{avg} and C_{max} are based on the nominal time interval from Baseline through Week 4. In contrast, $PF\%$ and C_{min} are based on the nominal time interval from Day 3 through Week 4.

Figure 22 illustrates scatterplots of Week 4 viral decay vs. Week 4 IFN exposure variables.

Figure 23 illustrates RVR and viral kinetics in subjects with refractory host or virus genotypes. (A) RVR by treatment arm and Hepatitis C virus subgenotype. RVR is defined as undetectable HCV RNA ($< \text{LOOD} = 18 \text{ IU/mL}$) after 4 weeks of therapy. Column headings provide the number of mITT subjects by arm. (B) RVR by treatment arm and host IL28B genotype. Column headings provide the number of mITT subjects by arm. IL28B genotype information is available for 68 /106 mITT subjects, as this was added to the protocol after the study was initiated.

Figure 24A shows the stability of serum IFN levels from continuous IFN therapy ($PF\%$ from Day 3 through Week 4) compared to historical controls. Percent fluctuation for IFN and PEG-IFN calculated from data published for week 4 of therapy (see, e.g. GLUE et al., Clin Pharmacol Ther 2000;68(5):556-67). Dosing regimens for IFN (INTRON A) and PEG-IFN (PEGINTRON) are taken from the respective package inserts. **Figure 24B** shows a detailed relationship of significant predictors of RVR or discontinuation from multivariate logistic regression analyses. The two significant continuous variables (baseline HCV RNA and MW1-IFN concentration) are plotted against each other for each combination of the two significant categorical variables - IL28B genotype and gender. The critical value found for the achievement of RVR is 32.8. Genotypes are grouped into CC, CT, TT or unknown, which are indicated by "NA" in the figure.

Figure 25 illustrates Neopterin PD response. (A) Time-averaged Neopterin response from individual baseline (E_{avg}). E_{avg} is based on the nominal time interval from Baseline through Week 4 or Week 12. (B) Time-averaged Neopterin response from individual baseline (E_{avg}).

Figure 26 illustrates (A) correlation of Neopterin response with IFN exposure. CSID arms only. (B) Scatterplots of Neopterin Eavg vs. IFN C_{avg} .

Figure 27 illustrates (A) correlation of Neopterin response with viral decay. PEG and CSID subjects. (B) Scatterplots of Viral Decay vs. Neopterin Eavg. PEG and
5 CSID subjects.

Figure 28A presents an exemplary generalized computer system 202 that can be used to implement elements of the present invention. **Figure 28B** presents one embodiment of a specific illustrative computer system embodiment that can be used with
embodiments of the invention in the treatment of Hepatitis virus infection.

10

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise defined, all terms of art, notations and other scientific terms or terminology used herein are intended to have the meanings commonly understood by those of skill in the art to which this invention pertains. In some cases, terms with
15 commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art. As appropriate, procedures involving the use of commercially available kits and reagents are generally carried out in accordance with manufacturer defined protocols
20 and/or parameters unless otherwise noted.

DEFINITIONS:

The term “pharmacokinetics” is used according to its art accepted meaning and refers to the study of the action of drugs in the body, for example the effect and duration
25 of drug action, the rate at they are absorbed, distributed, metabolized, and eliminated by the body etc. (e.g. the study of a concentration of interferon- α in the serum of the patient following its administration via a specific dose or therapeutic regimen). The term “pharmacodynamics” is used according to its art accepted meaning and refers to the study of the biochemical and physiological effects of drugs on the body or on
30 microorganisms such as viruses within or on the body, the mechanisms of drug action

and the relationship between drug concentration and effect etc. (e.g. the study of hepatitis virus present in a patient's plasma following one or more therapeutic regimens). The terms "pharmacodynamic models" and "pharmacodynamic parameters" as used herein include interferon and/or viral kinetic models and interferon and/or viral kinetic parameters (e.g. in vivo concentration). Various models to estimate parameters associates with Hepatitis B and C infections have been developed, and may be adapted for use with methods described herein. Examples of viral kinetic models include, but are not limited to, models disclosed in the following references: the contents of which are incorporated by reference: Perelson, et al. (2005), *Hepatology* 42(4): 749-754; Talal, et al. (2006), *Hepatology* 43(5): 943-953; Dahari et al. (2007), *J Theor Biol* 247(2): 371-81; Dahari et al. (2007), *Hepatology* 46(1): 16-21; Dixit et al. (2004), *Nature* 432(7019): 922; Neumann et al. (1998), *Science* 282(5386): 103-7; Powers, et al. (2003), *Semin Liver Dis* 23 Suppl 1: 13-18; Powers et al. (2006); *Liver Transpl* 12(2): 207-16; Bonate, P.L. (2006). *Pharmacokinetic-Pharmacodynamic Modeling and Simulation*. New York, Springer Science&Business Media; Gabrielsson, J. and D. Weiner (2000); and *Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications*. Stockholm, Swedish Pharmaceutical Press.

The terms "continuous administration" (e.g. as in a "continuous administration regimen") and "continuous infusion" (e.g. as in a "continuous infusion regimen") are used interchangeably herein, exclude administration or infusion of an agent via a bolus, and mean delivery of an agent such as interferon- α in a manner that, for example, avoids significant fluctuations in the in vivo concentrations of the agent throughout the course of a treatment period (e.g. as occur when administering an agent such as interferon- α via one or more boluses spaced over a periods of time such as 12 hours, 1 or 2 or more days). This can be accomplished by constantly or repeatedly injecting substantially identical amounts of interferon- α (typically with a continuous infusion pump device), e.g., at least every hour, 24 hours a day, seven days a week for a period such as at least 1 week to at least 48 weeks, such that a steady state serum level is achieved for the duration of treatment. Continuous interferon- α may be administered according to art accepted

methods, for example via subcutaneous, interperitoneal, or intravenous injection at appropriate intervals, e.g. at least hourly, for an appropriate period of time in an amount which will facilitate or promote *in vivo* inactivation of hepatitis B or C viruses.

The term "continuous infusion system" refers to a device for continuously
5 administering a fluid to a patient parenterally for an extended period of time or for intermittently administering a fluid to a patient parenterally over an extended period of time without having to establish a new site of administration each time the fluid is administered. The fluid typically contains a therapeutic agent or agents. The device typically has one or more reservoir(s) for storing the fluid(s) before it is infused, a pump,
10 a catheter, cannula, or other tubing for connecting the reservoir to the administration site via the pump, and control elements to regulate the pump. The device may be constructed for implantation, usually subcutaneously. In such a case, the reservoir will usually be adapted for percutaneous refilling. An exemplary "continuous infusion system" is the Medtronic MiniMed Paradigm® Insulin Infusion System.

15 The term "administer" means to introduce a therapeutic agent into the body of a patient in need thereof to treat a disease or condition. The term "treating" and/or "treatment" refers to the management and care of a patient having a pathology such as a viral infection or other condition for which administration of one or more therapeutic compounds is indicated for the purpose of combating or alleviating symptoms and
20 complications of those conditions. Treating includes administering one or more formulations of the present invention to prevent the onset of the symptoms or complications, alleviating the symptoms or complications, or eliminating the disease, condition, or disorder. As used herein, "treatment" or "therapy" refer to both therapeutic treatment and prophylactic or preventative measures. In addition, "treating"
25 or "treatment" does not require complete alleviation of signs or symptoms, does not require a cure, and specifically includes protocols which have only a marginal effect on the patient.

The term "therapeutically effective amount" refers to an amount of an agent (e.g. a cytokine such as interferon- α) effective to treat at least one sign or symptom of a

disease or disorder in a human. Amounts of an agent for administration may vary based upon the desired activity, the diseased state of the patient being treated, the dosage form, method of administration, patient factors such as the patient's sex, genotype, weight and age, the underlying causes of the condition or disease to be treated (e.g. infection with a specific virus, viral genotype etc.), the route of administration and bioavailability, the persistence of the administered agent in the body, the formulation, and the potency of the agent. It is recognized that a therapeutically effective amount is provided in a broad range of concentrations. Such range can be determined based on *in vitro* and/or *in vivo* assays.

10 The term “therapeutic regimen” is used according to its art accepted meaning and refers to, for example, a part of treatment plan for an individual suffering from a pathological condition (e.g. chronic hepatitis infection) that specifies factors such as the agent or agents to be administered to the patient, the doses of such agent(s), the schedule and duration of the treatment etc. Therapeutic regimens include, for example, the continuous administration of interferon- α according to embodiments of the invention.

15 The term “profile” is used according to its art accepted meaning and refers to the collection of results of one or more analyses or examinations of: (1) the presence of; or (2) extent to which an observed phenomenon exhibits various characteristics. Illustrative profiles typically include the results from a series of observations which, in combination, offer information on factors such as, for example, the presence and/or levels and/or characteristics of one or more agents infecting a patient (e.g. the hepatitis B or C virus), as well as the pharmacokinetic and/or pharmacodynamic characteristics of one or more therapeutic agents administered to a patient as part of a treatment regimen (e.g. interferon- α), as well as the physiological status or functional capacity of one or more organs or organ systems in a patient (e.g. the liver), as well as the genotype of one or more single nucleotide polymorphisms in a patient etc.

ILLUSTRATIVE APPLICATIONS FOR EMBODIMENTS OF THE INVENTION

As is known in the art, Hepatitis B virus (HBV), is a DNA virus that exists in at least eight genetically distinct genotypes. These genotypes are designated A through H and are further grouped into a number of subtypes that exhibit differing responses to therapeutic regimens. As is also known in the art, Hepatitis C virus (HCV) is a positively stranded RNA virus that exists in at least six genetically distinct genotypes that also exhibit differing responses to therapeutic regimens. These genotypes are designated Type 1, 2, 3, 4, 5 and 6, and their full length genomes have been reported (see, e.g. Genbank/EMBL accession numbers Type 1a: M62321, AF009606, AF011753, Type 1b: AF054250, D13558, L38318, U45476, D85516; Type 2b: D10988; Type 2c: D50409; Type 3a: AF046866; Type 3b: D49374; Type 4: WC-G6, WC-G11, WG29 (Li-Zhe Xu et al, J. Gen. Virol. 1994, 75: 2393-98), EG-21, EG-29, EG-33 (Simmonds et al, J. Gen. Virol. 1994, 74: 661-668), the contents of which are incorporated by reference.

Human recombinant interferon-alpha (IFN- α) is approved in many countries for the treatment of hepatitis B and C infection. PEG-IFN α is known to facilitate HBsAg clearance or seroconversion in HBV infected patients. For example, studies have shown that PEG-IFN α -based therapy is more effective than LAM monotherapy in achieving HBsAg clearance or seroconversion for both HBeAg-positive and HBeAg-negative CHB patients (Li et al., BMC Infect Dis. 2011 Jun 9;11:165. doi: 10.1186/1471-2334-11-165. Moreover, specific viral response such as rapid decline in HBsAg concentration during interferon therapy has been associated with a higher chance for sustained virological response. By contrast, a much slower decline often occurs during nucleoside analog therapy and limits the ability of conventional tests to provide useful prognostic indicators during the first year or two of treatment (Perrillo, Am J Gastroenterol. 2011 Oct;106(10):1774-6). The invention disclosed herein addresses certain limitations in conventional technologies.

As is known in the art, individual patients do not have identical physiological characteristics, and for example, commonly exhibit differing responses to the same therapeutic agent (e.g. interferon- α). Such differing physiological characteristics include therapeutic agent efficacy, tolerance as well as the clearance rate at which a therapeutic

agent is removed from the body. Consequently, the optimal dosing of a therapeutic agent can be very difficult to predict, particularly in situations where high levels of the drug are concurrently associated with high efficacy as well as unpleasant side effects (e.g. interferon- α). As disclosed herein, if the dosing of interferon- α (e.g. non-pegylated
5 interferon) is modulated in a manner that results in both stable as well as sustained levels of this cytokine in the patient (e.g. via a continuous infusion pump), this therapeutic agent can play an enhanced role preventing immune exhaustion and enhancing the adaptive immune response that is directed towards the hepatitis B and C viruses, thereby leading to greater rates of desirable phenomena such as clearance and/or seroconversion.

10 Aspects of the invention disclosed herein relate to and are part of a clinical trial designed to compare the safety and efficacy of the continuous infusion of interferon with the current standard of care for chronic hepatitis C infection. This study is termed the "COPE-HCV" clinical trial, see, e.g. ClinicalTrials.gov: Identifier: NCT00919633. Briefly, this study includes patients who are diagnosed with chronic hepatitis C genotype
15 1 infection and who have received no previous interferon or other anti-HCV treatment. The safety objective in this study is to determine the tolerability and safety of continuous interferon infusion versus the standard of care, at the standard-of-care dose regimen when given with oral weight-based ribavirin. The efficacy objective in this study is to determine the virologic response to continuous interferon infusion in subjects with
20 hepatitis C genotype 1 infection, and to test a selected continuous interferon dose against standard treatment. The COPE-HCV study has 4 treatment arms, as follows: Group 1 (n = 31): continuous Intron A 80,000 IU/kg/day for 48 weeks (up to 12 subjects will participate in the PK/PD substudy); Group 2 (n = 31): continuous Intron A 120,000 IU/kg/day for 48 weeks (up to 12 subjects will participate in the PK/PD substudy);
25 Group 3 (n = 31): continuous Intron A 160,000 IU/kg/day for 48 weeks (up to 12 subjects will participate in the PK/PD substudy); and Group 4 (n = 31): PegIntron 1.5 μ g/kg SC weekly for 48 weeks (reference agent, active-control arm; up to 12 subjects will participate in the PK/PD substudy). All subjects will also receive oral ribavirin (1000 mg/day if weight <75 kg; 1200 mg/day if weight >75 kg). Intron A® (interferon alfa-

2b, recombinant) is used as the non-pegylated interferon- α , while PegIntron® (peginterferon alfa-2b) is used as the pegylated interferon- α . The interferon- α is continuously administered via the MiniMed Paradigm® Insulin Infusion System, Medtronic, Inc.

5 As disclosed herein, results from pharmacokinetic and pharmacodynamic analyses of clinical trial data demonstrate that pharmacokinetic and pharmacodynamic profile data of interferon- α administered to patients via a continuous administration regimen can be correlated with viral responses and consequently used to optimize patient treatment. Typically, the viral response is the response of a hepatitis B or hepatitis C
10 virus that infects the patient to a specific therapeutic regimen and comprises an early virological response (EVR) and/or a sustained virological response (SVR). In some embodiments, the viral response comprises a 1, 2 or 3 log drop in viral particles observed in serum of the patient, typically within a certain time period following initiation of the therapeutic regimen, for example within 1, 2, 3 or 4 weeks. In some embodiments, the
15 viral response comprises viral clearance at the end of the therapeutic regimen. As used herein, viral clearance means undetectable HCV RNA in persons infected with HCV. Similarly, as used herein viral clearance means undetectable non-integrated HBV DNA (e.g. undetectable HBV virion DNA circulating in the blood) in persons infected with HBV.

20 In embodiments of the invention, viral load can be measured by a variety of procedures known in the art, for example, by measuring the titer or level of virus in serum. These methods include, but are not limited to, a quantitative polymerase chain reaction (PCR) and/or a branched DNA (bDNA) test. Many such assays are available commercially, including a quantitative reverse transcription PCR (RT-PCR). While viral
25 titers are the most important indicators of effectiveness of a dosing regimen, other parameters can also be measured as secondary indications of effectiveness. Secondary parameters include reduction of liver fibrosis; and reduction in serum levels of particular proteins. HBsAg clearance and seroconversion, characterized by the loss of serum HBsAg with or without anti-HBs antibody development, are the main markers of a
30 successful immunological response to HBV infection and the closest outcome to clinical

cure. HBsAg clearance is defined as the disappearance of HBsAg from the serum. A decline in hepatitis B virus surface antigen (HBsAg) predicts clearance, but does not correlate with quantitative HBeAg or HBV DNA levels (Wiegand et al., Antivir Ther. 2008;13(4):547-54). HBsAg seroconversion is defined as HBsAg disappearance and anti-HBs antibody appearance.

In illustrative embodiments of the invention, HCV RNA levels were used to calculate the viral decay as function of time for all COPE-HCV study subjects. Viral decay can be defined by the Equation:

$$VD_t = \log_{10}(V_0) - \log_{10}(V_t)$$

Here V_t is the viral load (IU_{HCV}/mL) at time t , V_0 is the viral load (IU_{HCV}/mL) at pre-dose Baseline, and VD_t is the viral decay (dimensionless). Rapid virologic response (RVR) is defined as undetectable HCV RNA level (< LLOD = 18 IU/mL) at Study Week 4.

Embodiment of the invention include methods of characterizing a pharmacokinetic profile resulting from a therapeutic regimen that comprises administering non-pegylated interferon- α to a patient via a continuous infusion device. Typically such embodiments, the pharmacokinetic profile correlates with a viral response to the therapeutic regimen and can be used to address and/or overcome problematical phenomena observed in therapeutic regimens that use interferon- α to fight viral infections (e.g. in patients infected with the hepatitis B or hepatitis C virus).

Statistics of the IFN exposure variables and viral kinetics are listed in Table D in order to illustrate the power of embodiments of the invention. Out of the 32 subjects for whom Week 4 HCV RNA data was available, 13 attained RVR. The mean (46%) and maximum (140%) PF% for continuous IFN are far below the values estimated from average data published for week 4 of therapy with IFN α -2b (460%) or PEG-IFN α -2b (270%) administered according to their respective package inserts. This comparison is further illustrated by Figure 24A, where it is also illustrated that subjects who achieved

RVR tended to have more stable IFN concentrations (lower PF%) than those who did not reach RVR. These results provide evidence that continuously infused IFN results in relatively stable blood levels, and that relatively stable blood levels results in enhanced viral kinetics.

5 Typically, the methods of the invention comprise the steps of obtaining a plurality of interferon- α serum concentration measurements from the patient following initiation of the therapeutic regimen, obtaining at least 1, 2, 3, 4, 5, 6 or more samples from the patient over the period of time (e.g. samples taken from serum, plasma or whole blood over a period of 1, 2, 3, 4, 5, 6, or 7 days). Then, the plurality of interferon-
10 α concentration measurements is used to observe one or more characteristics of the interferon- α concentrations in the patient that result from this therapeutic regimen so that one or more aspects of its pharmacokinetic profile can be characterized. In some embodiments of the invention, the one or more characteristics of the interferon- α concentrations that are observed include the percent fluctuation (PF%) of interferon- α
15 concentrations in the patient. In some embodiments of the invention, the one or more characteristics of the interferon- α concentrations that are observed include a standard deviation of interferon- α concentrations in the patient. In some embodiments of the invention, the one or more characteristics of the interferon- α concentrations that are observed include determining a coefficient of variation of interferon- α concentrations in
20 the patient. In some embodiments of the invention, the one or more characteristics of the interferon- α concentrations that are observed include determining the Cmin of this therapeutic agent in the patient. In some embodiments of the invention, the one or more characteristics of the interferon- α concentrations that are observed include determining the Cmax of this therapeutic agent in the patient. In some embodiments of
25 the invention, the one or more characteristics of the interferon- α concentrations that are observed include determining the Cavg of this therapeutic agent in the patient.

Optionally the methods of the invention further comprises determining if the pharmacokinetic profile conforms to a parameter that identifies the patient as more likely

to exhibit a viral response as compared to patients having pharmacokinetic profiles that do not conform to the parameter; and then selecting a continued therapeutic regimen or course of action based upon said determination. In this context, the terms “conforms to a parameter” are used according to their art accepted meaning and refer to, for example a data point that is above (or below) a boundary value or inside of a range of values. In illustrative embodiments of the invention, the parameter comprises a maximum PF% of interferon- α concentrations not greater than about 50%, 100%, 125%, 150%, 175%, 200%, 225% or 250%. In some embodiments of the invention, the parameter can comprise a standard deviation of interferon- α concentrations not greater than 5 IU/ML, 10 IU/ML, 15 IU/ML, 20 IU/ML or 25 IU/ML. In embodiments of the invention, the parameter can also comprise a coefficient of variation of interferon- α concentrations not greater than 10%, 20 %, 30% or 40%. Cmax and Cavg parameters that are associated with viral responses are discussed in the sections below and in the Examples and in the associated Figures and Tables (see, e.g., Figures 14-17 and 21 and Table 4).

In some embodiments, the continued therapeutic regimen or course of action comprises maintaining the therapeutic regimen for a duration of at least 4, 5, 6, 7, 8, 12, 24, 36 or 48 weeks. Alternatively in such methods, the continued therapeutic regimen or course of action comprises initiating a modified therapeutic regimen for the patient that comprises an increased dose of interferon- α (e.g. so that levels of this agent are above a concentration threshold such as about 25-40 IU/mL, and typically about 30-35 IU/mL), or a decreased dose of interferon- α (e.g. so that levels of this agent are below those that produce significant side effects in that specific patient, e.g. below about 60, 70, 80 or 90 IU/mL). Alternatively, the course of action can comprise discontinuing the therapeutic regimen (e.g. in situations where pharmacokinetic profiling data provides evidence that a patient is unlikely to benefit from a therapeutic regimen that has been initiated).

Embodiments of the invention involve the continuous subcutaneous administration of interferon- α in order to maintain in vivo concentrations of this therapeutic agent above a critical efficacy threshold in vivo for a sustained period of time. As noted in Examples 1 and 2, a serum IFN concentration of approximately 33 IU/mL

from a single blood sample a few (1.6 – 5.2) days after initiating CSID is identified as an early predictor of both RVR and discontinuation before 12 weeks. Illustrative embodiments of the invention involve the continuous subcutaneous administration of interferon- α in order to maintain in vivo concentrations of this therapeutic agent above a certain IU/mL, or a certain pg/mL, for example at least 100-700 pg/mL (e.g. 300 pg/mL) for at least 1 to at least 48 weeks (a 48-week course of therapy is conventionally recommended for patients infected with HCV genotype 1). By the term “at least 100-700 pg/mL” of interferon- α it is understood that values such as at least 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, 425, 450, 475, 500, 525, 550, 575, 600, 625, 650, 675 or 700.

Certain embodiments of the invention further comprise using an observation of a genomic sequence in the patient for selecting a continuing or modified therapeutic regimen or course of action. In one illustrative embodiment, the patient is infected with a hepatitis B virus and the genomic sequence comprises a single nucleotide polymorphism (SNP) designated rs2856718, rs7453920, rs3077, rs9277535, rs2284553, rs9808753 or rs17401966. Alternatively, the patient is infected with a hepatitis C virus and the genomic sequence comprises a single nucleotide polymorphism (SNP) designated rs12979860, rs12980275, rs8099917, rs12972991, rs8109886, rs4803223, rs8103142, rs28416813, rs4803219, rs4803217, rs581930, rs8105790, rs11881222, rs7248668 or rs12980602.

Yet another embodiment of the invention is a system for administering interferon- α to a patient. In such embodiments the system comprises a continuous infusion pump having a medication reservoir comprising interferon- α (e.g. interferon- α is not conjugated to a polyol), and a processor operably connected to the continuous infusion pump and comprising a set of instructions that causes the continuous infusion pump to administer the interferon- α to the patient according to a patient-specific therapeutic regimen. Typically this patient-specific therapeutic regimen is made by first administering interferon- α to the patient via a continuous infusion pump according to a test therapeutic regimen and then observing concentrations of interferon- α present in the

serum of the patient that result from the test therapeutic regimen so as to obtain information on whether a pharmacokinetic profile of the interferon- α conforms to a parameter that identifies the patient as more likely to exhibit a viral response to interferon- α as compared to patients having pharmacokinetic profiles that do not conform to the parameter. In this context, the processor in this system uses instructions that result from the observed profile and comprises an increased dose of interferon- α ; or a decreased dose of interferon- α as compared to the test therapeutic regimen. Optionally in such systems, the continuous infusion pump has dimensions smaller than 15 x 15 x 15 centimeters; and/or is operably coupled to an interface that facilitates the patient's movements while using the continuous infusion pump, wherein the interface comprises a clip, a strap, a clamp or tape.

Yet another embodiment of the invention is the use of interferon- α in the manufacture of a composition for treating hepatitis C infection for use in a continuous infusion apparatus, wherein the interferon- α composition is manufactured to allow the continuous infusion apparatus to maintain mean circulating levels of interferon- α in serum of a patient above a steady state concentration of at least about 25, 30, 35 or 40 IU/mL (e.g. about 33 IU/mL) for at least 1 to at least 48 weeks when administered subcutaneously.

As noted in the Examples below, analyses of study data from the COPE-HCV clinical trial show that continual serum levels above a critical value and in a stable manner during the first 4 weeks of therapy predict increased likelihood of rapid virologic response (RVR), defined as undetectable HCV RNA at week 4. As noted above, typical embodiments of the invention include obtaining at least 1, 2, 3, 4, 5, or 6 or more different serum samples from a patient. In addition, these studies show that a single, early measurement of serum IFN can predict therapy efficacy and discontinuation. Consequently, in one illustrative embodiment, only a single serum interferon measurement is obtained. As disclosed in Example 2, even a single serum measurement can be used to predict viral responses such as RVR as well as therapy discontinuation. As noted in Examples 1 and 2, a serum IFN concentration of approximately 33 IU/mL

from a single blood sample a few (1.6 – 5.2) days after initiating CSID is identified as an early predictor of both RVR and discontinuation before 12 weeks. This disclosure provides clinicians with the ability to more effectively tailor CSID therapy for improved efficacy and tolerability.

5 Another embodiment of the invention is a method of administering a therapeutic regimen comprising interferon- α delivered to a patient infected with a hepatitis C virus via a continuous infusion device, the method comprising determining average serum interferon- α concentrations in the patient that are occurring on about a third day of administering interferon- α (e.g. by obtaining at least 1, 2, 3, 4, 5, or 6 or
10 more different serum samples from the patient over a period of time such as 1, 2, 3 or more days), wherein serum interferon- α concentrations of above about 30-35 IU/mL (e.g. above about 33 IU/mL) identify the patient as having a greater probability of achieving rapid virologic response (RVR) as compared to a patient having serum interferon- α concentrations below about 30-35 IU/mL. In this method these observed
15 serum interferon- α concentrations are then used to design a modified therapeutic regimen for the patient that comprises an increased dose of interferon- α ; or a decreased dose of interferon- α , for example, one designed to produce serum interferon- α concentrations in the patient above about 15, 20, 25, 30, 35 or 40 IU/mL and below about 50, 60, 70, 80 or 90 IU/mL (depending upon, for example each patient's individual
20 IFN response and/or tolerance levels).

Other typical embodiments include the use of interferon- α in the manufacture of a composition adapted for a continuous infusion apparatus. In such embodiments, the interferon- α composition is manufactured so that a continuous infusion apparatus using the composition modulates a pharmacokinetic profile the manufactured composition. In
25 some embodiments, the composition is manufactured so that the percent fluctuation (PF%) of interferon- α concentrations in vivo are not greater than 50, 100, 150, 200 or 250%. Optionally, the composition is manufactured to maintain mean circulating levels of interferon- α in serum of a patient above a specific steady state concentration, for

example one that is at least about 25-40 IU/mL, and typically about 30-35 IU/mL (e.g. at least about 33 IU/mL).

In certain embodiments of the invention, the concentrations of exogenous interferon- α present in the serum of the patient that result from administering exogenous interferon- α to the patient are sampled for a specific period of time ("window") comprising at least (or alternatively not more than) 24 or 36, 48 or 72 hours or 4, 5, 6 or 7 days. In one embodiment of the invention, the concentrations of exogenous interferon- α present in the serum of the patient that result from administering exogenous interferon- α to the patient are sampled for a period of time equal to a number of biological $\frac{1}{2}$ lives of the interferon- α species administered to the patient (e.g. pegylated or non-pegylated interferon- α), for example for a period of time equal to between 3-20 e.g. 5, 10, 15, or 20) $\frac{1}{2}$ lives of the interferon- α species administered to the patient. In an illustrative embodiment of the invention, one starts a patient on an initial dose of continuous interferon- α , wait for the subject to approach steady-state, and then obtain a plurality of serum interferon measurements in order to calculate the AUC or C_{avg} (time-averaged interferon concentration) over a specific period of time. Based on this AUC value, one can then calculate the clearance $[CL = Q \cdot (t_2 - t_1) / [AUC]_{t_1}^{t_2}]$ and then use this clearance parameter to determine and/or set the new interferon- α infusion rate $[Q]$.

In some embodiments of the invention, the concentrations of exogenous interferon- α in the serum of a patient that result from administering exogenous interferon- α to the patient via a continuous administration regimen are estimated by employing a compartmental pharmacokinetic model for subcutaneous interferon- α administration. In addition to such compartmental models, other models or analysis methods can be used in embodiments of the invention in order to, for example, obtain estimates on the clearance of an interferon- α species in a patient. In particular, a variety of "Compartmental Models" and "non-compartmental analysis" techniques (e.g. non-compartmental analysis involves using the trapezoidal rule or similar numerical methods etc.) are known to those skilled in the art of pharmacokinetic analysis which can be adapted for use with embodiments of the invention. In this context, a number of different illustrative models that can be adapted for use with embodiments of the

invention are described in PHARMACOKINETIC & PHARMACODYNAMIC DATA ANALYSIS: CONCEPTS & APPLICATIONS. 4th edition. Authors: Johan Garbielsson & Dan Weiner (2000); Swedish Pharmaceutical Press: Stockholm (see, e.g. pages 161-177 for discussions of non-compartmental analysis), the contents of which are
 5 incorporated by reference.

Optionally, the compartmental pharmacokinetic model for subcutaneous interferon- α administration includes analyses using the following equations:

$$\begin{aligned} \frac{dD}{dt} &= Q - k_a D \\ V_d \frac{dC}{dt} &= k_a D - CL \times C \end{aligned}$$

10

wherein D is the total interferon- α content at the injection site in IU; C is the interferon- α concentration in serum in IU/mL; V_d is the apparent volume of distribution of interferon- α in mL; Q is the subcutaneous infusion rate of interferon- α in IU/hour; an
 15 CL is the clearance in mL/hr; and k_a is the rate constant for interferon- α absorption per hour.

Embodiments of the invention can further use the observations of pharmacokinetic profiles of concentrations of exogenous interferon- α in the serum of a
 20 patient that result from administering exogenous interferon- α to the patient via the continuous administration regimen to design (and optionally administer) a patient-specific continuous administration regimen for the patient, for example one that is sufficient to maintain circulating levels of the interferon- α in the patient above a mean steady state concentration of at least 100, 200, 300, 400, 500, 600 or 700 pg/mL. In this
 25 context, the units "pg/mL" are used as merely one example and alternatives ways to characterize these levels such as IU/mL are considered. For example, as is known in the art, different preparations of therapeutic molecules such as the interferons do not exhibit identical activities and such activities are therefore published by the manufacturer. Those of skill in the art understand that, information on the specific activity of an interferon- α

(e.g. 2.6×10^8 IU/mg for INTRON® A), readily allows one to characterize an interferon- α in terms of both picograms and IU per volume (e.g. mL).

Embodiments of the invention include methods of using a patient-specific regimen responsiveness profile obtained from a patient infected with hepatitis B or C virus to design a patient-specific therapeutic regimen. As used herein, a “patient-specific regimen responsiveness profile” simply means an individual’s unique response to a specific therapeutic regimen (e.g. a specific dose of interferon- α) and a “patient-specific therapeutic regimen” simply means a therapeutic regimen designed in accordance with a patient’s unique physiological characteristics (e.g. how quickly their body is able to clear a specific dose of interferon- α). In illustrative embodiments of the invention, the method comprises administering at least one therapeutic agent to the patient following a first or test therapeutic regimen and then obtaining pharmacokinetic or pharmacodynamic parameters from the patient in order to observe a patient-specific response to the first therapeutic regimen. Typically, pharmacokinetic or pharmacodynamic parameters observed comprise a concentration of the therapeutic agent in the blood of the patient that results from the first therapeutic regimen (and/or how this concentration fluctuates over time). In this embodiment of the invention, practitioners can then use the pharmacokinetic or pharmacodynamic parameters observed in the patient in response to the first therapeutic regimen to obtain a patient-specific regimen responsiveness profile. This patient-specific regimen responsiveness profile is based upon an HBV or HCV infected patient’s individualized physiology and necessarily takes into account patient specific factors that can influence a patients’ response to treatment such as the patient’s genetic profile (e.g. the presence or absence of a SNP disclosed herein), the HBV or HCV genotype(s) infecting the patient, and/or a patient’s weight, treatment history, health status (e.g. if they suffer from diabetes), individual rate of exogenous interferon- α clearance, and the like. This patient-specific regimen responsiveness profile is then used to design a patient-specific therapeutic regimen. Embodiments of the invention include the steps of observing a variety of patient-specific factors such as a patient’s prior medical treatment history, a presence or degree of a side effect that results from

administering exogenous interferon- α to the patient, or a polynucleotide sequence of the patient. Embodiments of the invention can also include the further step of observing a type or subtype of a hepatitis virus infecting the patient.

Illustrative non-pegylated and pegylated interferons for use in embodiments of the invention include interferon α -2b (e.g. Intron A) (which is not pegylated) and pegylated interferon α -2b (e.g. PegIntron). Embodiments of the invention can include bolus doses of a nonpegylated interferon- α such as Intron A, for example those that range from about 1-15 million IU (e.g. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 million IU). Embodiments of the invention can include weight based bolus doses of a nonpegylated interferon- α such as Intron A, for example those that range from about 50,000 IU/kg - 200,000 IU/kg (e.g. 80,000 IU/kg, 120,000 IU/kg or 160,000 IU/kg). Continuous SC delivery of a nonpegylated interferon- α such as Intron A can be achieved via the Medtronic MiniMed Paradigm infusion system for 24, 26, 48 60, 72 etc. weeks of HCV therapy. Doses of interferon- α used in such continuous delivery schemes can be weight based, for example the continuous delivery of 80,000 IU/kg/day, 120,000 IU/kg/day, 160,000 IU/kg/day etc. of Intron A. Alternatively patients can receive a defined amount, for example 3, 6, 9, or 12 million IU/day.

In typical embodiments of the invention, the serum interferon- α concentrations (e.g. 100-700 pg/mL) refer to non-pegylated embodiments of interferon- α 2a or interferon- α 2b (e.g. INTRON®A made by Merck). Alternatively, the interferon- α can be pegylated. For embodiments of the invention that comprise pegylated interferon- α , equivalent concentrations can be calculated using art accepted methodologies, for example by calculating the ratio of specific activities and/or molecular weights of: 1) non-pegylated interferon- α such as INTRON®A and 2) pegylated interferon- α such as PegIntron® and then using correlations from such analysis to determine appropriate concentrations of, for example, a pegylated interferon- α .

Embodiments of the therapeutic regimens disclosed herein include the administration of interferon in combination small molecule therapeutics for patients infected with HBV or HCV, for example ribavirin. In addition to ribavirin, there are a

number of other HCV therapeutic agents known in the art in addition to interferon- α . Such anti-viral agents include for example, but are not limited to, immunomodulatory agents, such as thymosin; VX-950, CYP inhibitors, amantadine, and telbivudine; Medivir's TMC435350, GSK 625433, R1626, ITMN 191, other inhibitors of hepatitis C proteases (NS2-NS3 inhibitors and NS3/NS4A inhibitors); inhibitors of other targets in the HCV life cycle, including helicase, polymerase, and metalloprotease inhibitors; inhibitors of internal ribosome entry; broad-spectrum viral inhibitors, such as IMPDH inhibitors (see, e.g., compounds of U.S. Pat. Nos. 5,807,876, 6,498,178, 6,344,465, 6,054,472, WO 97/40028, WO 98/40381, WO 00/56331 the contents of which are incorporated by reference, and mycophenolic acid and derivatives thereof, and including, but not limited to VX-497, VX-148, and/or VX-944); or combinations of any of the above. Embodiments of the methods disclosed herein also include the administration of interferon in combination with small molecule therapeutics for patients infected with HBV. For example, medical practitioners can use interferon- α 2a in combination with a nucleoside analog such as lamivudine, adefovir dipivoxil, entecavir, telbivudine or tenofovir disoproxil in therapeutic regimens designed to treat HBV infection.

In certain embodiments of the invention, and HBV or HCV infected individual is administered a therapeutic agent such as interferon- α and/or a small molecule inhibitor and the response to such agents is then observed by monitoring changes in the levels of HBV or HCV nucleotides, and/or viral particles (e.g. viral coat proteins), and/or antibodies to viral antigens, that are detectable in vivo. In this context, an appropriate therapeutic response is associated with decreasing levels of HBV or HCV nucleotides that are detectable in the blood of an infected individual. Ideally, a therapeutic regimen will reduce this number so that there is no longer any detectable HBV or HCV nucleotides.

In addition to factors such as the serum concentration of interferon- α that results from a dose of interferon- α administered in a therapeutic regimen, embodiments of the invention consider additional factors such as a patient's genetic profile and/or physiology (e.g. Body Mass Index). Illustrating this, a number of genetic polymorphisms are observed to provide information on HBV and HCV infected individuals' response to

therapeutic regimens comprising interferon- α and ribavirin. Tables A and B show illustrative single nucleotide polymorphisms associated with HBV and HCV response. In certain embodiments of the invention, information on the SNP genotype is used in methods of determining the dose of interferon- α to be administered to the patient. In
5 other embodiments of the invention, information on the SNP genotype is used in methods of determining a target steady state concentration of interferon- α to be maintained in a patient's serum. Optionally, the methods are performed on a plurality of patients infected with hepatitis virus; and the genotype information obtained from the patients is used to stratify patients into different treatment groups (e.g. groups having
10 different IFN dose or regimen duration parameters). A variety of well known methods for the detection of known SNPs are known in the art. Common SNP analysis methods include hybridization-based approaches (see, e.g., J. G. Hacia, *Nature Genet.*, 1999, 21: 42-47), allele-specific polymerase chain reaction (R. K. Saiki et al., *Proc. Natl. Acad. Sci. USA*, 1989, 86: 6230-6234; W. M. Howell et al., *Nature Biotechnol.*, 1999, 17: 87-88),
15 primer extension (see, e.g., A. C. Syvanen et al., *Genomics*, 1990, 8: 684-692), oligonucleotide ligation (see, e.g., U. Landegren et al., *Science*, 1988, 24: 1077-1080) and enzyme-based methods such as restriction fragment length polymorphism and flap endonuclease digestion (see, e.g., V. Lyamichev et al., *Nature Biotechnol.*, 1999, 17: 292-296).

20 Embodiments of the invention disclosed herein can be performed for example, using one of the many computer systems known in the art (e.g. those associated with medication infusion pumps). FIG. 28A illustrates an exemplary generalized computer system 202 that can be used to implement elements the present invention, including the user computer 102, servers 112, 122, and 142 and the databases 114, 124, and 144. The
25 computer 202 typically comprises a general purpose hardware processor 204A and/or a special purpose hardware processor 204B (hereinafter alternatively collectively referred to as processor 204) and a memory 206, such as random access memory (RAM). The computer 202 may be coupled to other devices, including input/output (I/O) devices such as a keyboard 214, a mouse device 216 and a printer 228.

In one embodiment, the computer 202 operates by the general purpose processor 204A performing instructions defined by the computer program 210 under control of an operating system 208. The computer program 210 and/or the operating system 208 may be stored in the memory 206 and may interface with the user 132 and/or other devices to accept input and commands and, based on such input and commands and the instructions defined by the computer program 210 and operating system 208 to provide output and results. Output/results may be presented on the display 222 or provided to another device for presentation or further processing or action. In one embodiment, the display 222 comprises a liquid crystal display (LCD) having a plurality of separately addressable liquid crystals. Each liquid crystal of the display 222 changes to an opaque or translucent state to form a part of the image on the display in response to the data or information generated by the processor 204 from the application of the instructions of the computer program 210 and/or operating system 208 to the input and commands. The image may be provided through a graphical user interface (GUI) module 218A. Although the GUI module 218A is depicted as a separate module, the instructions performing the GUI functions can be resident or distributed in the operating system 208, the computer program 210, or implemented with special purpose memory and processors.

Some or all of the operations performed by the computer 202 according to the computer program 110 instructions may be implemented in a special purpose processor 204B. In this embodiment, the some or all of the computer program 210 instructions may be implemented via firmware instructions stored in a read only memory (ROM), a programmable read only memory (PROM) or flash memory in within the special purpose processor 204B or in memory 206. The special purpose processor 204B may also be hardwired through circuit design to perform some or all of the operations to implement the present invention. Further, the special purpose processor 204B may be a hybrid processor, which includes dedicated circuitry for performing a subset of functions, and other circuits for performing more general functions such as responding to computer program instructions. In one embodiment, the special purpose processor is an application specific integrated circuit (ASIC).

The computer 202 may also implement a compiler 212 which allows an application program 210 written in a programming language such as COBOL, C++, FORTRAN, or other language to be translated into processor 204 readable code. After completion, the application or computer program 210 accesses and manipulates data accepted from I/O devices and stored in the memory 206 of the computer 202 using the relationships and logic that was generated using the compiler 212. The computer 202 also optionally comprises an external communication device such as a modem, satellite link, Ethernet card, or other device for accepting input from and providing output to other computers.

In one embodiment, instructions implementing the operating system 208, the computer program 210, and the compiler 212 are tangibly embodied in a computer-readable medium, e.g., data storage device 220, which could include one or more fixed or removable data storage devices, such as a zip drive, floppy disc drive 224, hard drive, CD-ROM drive, tape drive, etc. Further, the operating system 208 and the computer program 210 are comprised of computer program instructions which, when accessed, read and executed by the computer 202, causes the computer 202 to perform the steps necessary to implement and/or use the present invention or to load the program of instructions into a memory, thus creating a special purpose data structure causing the computer to operate as a specially programmed computer executing the method steps described herein. Computer program 210 and/or operating instructions may also be tangibly embodied in memory 206 and/or data communications devices 230, thereby making a computer program product or article of manufacture according to the invention. As such, the terms "article of manufacture," "program storage device" and "computer program product" as used herein are intended to encompass a computer program accessible from any computer readable device or media.

Of course, those skilled in the art will recognize that any combination of the above components, or any number of different components, peripherals, and other devices, may be used with the computer 202. Although the term "user computer" is referred to herein, it is understood that a user computer 102 may include portable devices such as medication infusion pumps, analyte sensing apparatuses, cellphones, notebook

computers, pocket computers, or any other device with suitable processing, communication, and input/output capability.

Fig. 28B presents a specific illustrative embodiment system 10 for performing methods disclosed herein. The interferon- α may be administered at a dosing rate $Q(t)$ 12 from an infusion device 11 including, but not limited to, a pump, a depot, an infusion bag, or the like. Once the therapy is commenced, the interferon- α serum concentration 14, represented as $C(t)$, may be determined by sampling a patient's blood by assay or sensor 16, and communicated to a controller 18, as represented by a concentration feedback loop 20. In addition to or instead of loop 20, the system 10 may also include a viral load feedback loop 22. According to the loop 22, patient's viral load 24, represented as $V(t)$, may be determined by sampling patient's blood by assay or sensor 26 and may be communicated to the controller 18. Based on $C(t)$, $V(t)$ or both, controller 18 may calculate the dosing rate 12, which may then be adjusted if necessary either automatically by the controller or manually by an individual administering the therapy. In addition, patient-specific pK parameters 13 and pD parameters 15 may be determined from this data. Although the controller 18 may be a conventional process controller such as a PID controller, one can also utilize an adaptive model predictive process controller or model reference adaptive control. In general, a model predictive controller may be programmed with mathematical models of a "process" to predict "process" response to proposed changes in the inputs. These predictions are then used to calculate appropriate control actions. In response to control actions, the model predictions are continuously updated with measured information from the "process" to provide a feedback mechanism for the controller. In addition, the mathematical models may be continuously optimized to match the performance of the "process."

In the system shown in Fig. 28B, the controller 18 may be programmed with patient-specific pK or pD parameters, population or subpopulation averages, or a combination thereof together with pharmacokinetic and pharmacodynamic models to calculate the dosing rate necessary to achieve desired clinical outcome. During the therapy, the controller continuously processes the data received from the feedback loops to optimize the dosing rate based on a patient's response to the therapy. In some

embodiments, the controller 18 may also manipulate the pharmacokinetic and pharmacodynamic parameters, as well as the mathematical models based on concentration and viral load data to adopt or customize the models for individual patients and specific conditions.

5 In Fig. 28B, the controller 18 may use patient-specific pharmacokinetic or pharmacodynamic parameters, population or subpopulation averages, or combination thereof together with pharmacokinetic, pharmacodynamic, or viral kinetic models to calculate the dosing rate for desired efficacy based on $C(t)$, $V(t)$ or both. In Fig. 28B, pK refers to the physical pharmacokinetic system of a real patient. On the other hand, the
10 parameter pK' 19 refers to the pharmacokinetic model and parameter values used by the controller to describe pK, and which may be drawn from the real patient, population, or subpopulation averages. Similar notation is used for pD, C, V and Q.

In an embodiment of a system 10 having the loop 22 only, a given patient is assumed to have a set of individual pharmacokinetic parameters, represented as pK, and
15 thus actual efficacy may be represented as a function of concentration, which is a function of the dosing rate $Q(t)$. The controller 18 may use pharmacokinetic and pharmacodynamic models to calculate the suitable dosing rate for desired efficacy based on the concentration or other physiological characteristic data. Such models are known and are disclosed in, for example, Bonate, P.L. (2006). Pharmacokinetic-
20 Pharmacodynamic Modeling and Simulation. New York, Springer Science&Business Media; Andrew H Talal, et al. (2006). "Pharmacodynamics of PEG-IFN α Differentiate HIV/HCV Coinfected Sustained Virological Responders from Nonresponders." Hepatology 43(5): 943-953' Gabrielsson, J. and D. Weiner (2000). Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications. Stockholm, Swedish
25 Pharmaceutical Press.

MARKER MEASUREMENTS

Artisans have a variety of methodologies for measuring a variety of physiological phenomena or "markers" in embodiments of the invention. Methods and materials used
30 in the measurement of neopterin are described for example in Fernandez et al., J Clin

Gastroenterol. 2000 30(2):181-6). Methods and materials used in the measurement of 2',5' oligo-adenylate synthetase are described for example in Podevin et al., J Hepatol. 1997 (2):265-71). Methods and materials used in the measurement of beta-2-microglobulin are described for example in Malaquarnera Eur J Gastroenterol Hepatol. 5 2000 Aug;12(8):937-9. Methods and materials used in the measurement of neutropenia and thrombocytopenia are described for example in Koskinas et al., Med Virol. 2009 Mar 24;81(5):848-852. Methods and materials used in the measurement of alanine transaminase and/or aspartate transaminase are described for example in Sterling et al., Dig Dis Sci. 2008 May;53(5):1375-82 Epub 2007. For example, embodiments of the 10 invention can also examine, a level of alanine transaminase or aspartate transaminase in plasma of the patient; a genotype or quasispecies of the hepatitis virus; a patient's prior medical treatment history; and/or a presence or degree of a side effect that results from the first therapeutic regimen. In an illustrative embodiment where the therapeutic agent comprises interferon- α , one can also observe a presence or degree of a depression, a 15 neutropenia, a thrombocytopenia, as well as one or more systemic flu-like symptoms that results from its administration.

A number of illustrative methods for examining various PK/PD markers are discussed below.

20 INTERFERON- α

In vivo samples (e.g. blood, serum, plasma, tissue etc.) can be assayed for interferon- α concentrations using a variety of different methods known in the art. One suitable example is an electrochemiluminescence-based assay and an ORIGEN analyzer (IGEN International, Inc. Gaithersburg, MD) as disclosed for example in Obenauer- 25 Kutner et al., Journal of Immunological Methods, Volume 206, Issues 1-2, 7 August 1997, Pages 25-33. Other methods used in the art include those disclosed for example in Niewold et al., Genes Immun. 2007; 8:492-502; Pirisi et al., Digestive Diseases and Sciences, 42(4): 767-7771 (1997); Christeff et al., European Journal of Clinical Investigation. 32(1):43-50, January 2002; Sibbitt et al., Arthritis & Rheumatism, Volume

- 28 Issue 6, Pages 624 – 629, 2005; and Lam et al., Digestive Diseases and Sciences, 42(1):178-85 (1997). In addition, ELISA kits designed to provide quantitative assays of interferon- α concentrations in serum (e.g. 100-700 pg/mL) are commercially available from vendors, including for example the Human IFN-alpha Platinum ELISA CE
- 5 available from Bender MedSystems (e.g. Product # BMS216CE) and The Human IFN alpha colorimetric ELISA Kit (Serum Samples) available from Thermo Scientific Life Science Research Products (e.g. Product # 411101). Those of skill in the art understand that, information on the specific activity of an interferon- α (e.g. 2.6×10^8 IU/mg for INTRON® A), readily allows one to characterize an interferon- α in terms of both
- 10 picograms and IU. In some embodiments of the invention, interferon- α concentrations in human serum samples can be quantified using a ligand-binding assay that can be developed and validated for the COPE-HCV Study using current regulatory standards for quantitative bioanalysis of proteins (see, e.g., Desil et al., Pharm Res 2003;20(11):1885-900).
- 15 The Phoenix™ NCA object can be used to characterize the IFN levels that are observed during the 2 weeks following the initiation of continuous INTRON A therapy. This analysis will calculate the values of several parameters.

Area Under the Curve

The serum interferon AUC for each subject can be calculated over 0 hour -14 day nominal study time interval. The Linear Trapezoidal Linear Interpolation method can be used to calculate these AUC parameters. IFN concentration vs. nominal study time data can be used to calculate AUC without interpolation. The AUC value will reported as “missing” for a given subject and time interval if either of the following criteria are met: 1) one or both of the integration time interval concentration measurements are missing, or 2) there are less than 3 measured concentrations within the integration time interval (including end-points).

Average Observed Concentration

The average observed concentration over a time interval $\left(\left[\bar{C}_{cont}^{obs}\right]_{t_1}^{t_2}\right)$ can be calculated using the following Equation.

$$\left[\bar{C}_{cont}^{obs}\right]_{t_1}^{t_2} = \frac{\left[AUC_{cont}^{obs}\right]_{t_1}^{t_2}}{(t_2 - t_1)}$$

Here t_1 and t_2 are the beginning and the end of the integration time interval, respectively [hr]. illustrative time intervals and AUC calculation methods that can be employed for this analysis are described herein.

Maximum Observed Concentration

The maximum observed concentration over a time interval $\left([C_{max}]_{t_1}^{t_2}\right)$ can be determined using the NCA operational object. Illustrative time intervals that can be employed for this analysis are described herein.

Percent Fluctuation

The percent fluctuation ($PF_{t_1}^{t_2}$), as defined by the following Equation, can be calculated for the 24 hour-14 day *nominal* study time interval.

$$PF_{t_1}^{t_2} = \left(\frac{[C_{max}^{obs}]_{t_1}^{t_2} - [C_{min}^{obs}]_{t_1}^{t_2}}{[\bar{C}_{cont}^{obs}]_{t_1}^{t_2}} \right) \times 100\%$$

Here $[C_{max}^{obs}]_{t_1}^{t_2}$ and $[C_{min}^{obs}]_{t_1}^{t_2}$ are the maximum and minimum observed IFN concentrations over the time interval from t_1 to t_2 . Methods that can be used for calculating the $[\bar{C}_{cont}^{obs}]_{t_1}^{t_2}$ parameter values are described herein. IFN concentration vs. *nominal* study time data can be used to calculate PF_{24h}^{14d} (and $[\bar{C}_{cont}^{obs}]_{24h}^{14d}$), without interpolation.

Minimum Observed Concentration

The minimum observed concentration over a time interval $([C_{min}]_{t_1}^{t_2})$ can be determined using the NCA operational object.

2', 5'- OLIGOADENYLATE SYNTHETASE

2', 5'- oligoadenylate synthetase ("OAS") is a transcription product of an interferon-stimulated gene (see, e.g., Feld et al., Nature 2005;436(7053):967-72) and, in embodiments of the invention, its levels can be measured in serum samples as a pharmacodynamic (PD) marker. OAS expression levels can be measured, for example, using a radioimmunoassay (RIA) kit commercially available from the Eiken Chemical Company (Japan).

NEOPTERIN

Neopterin is a biosynthetic precursor of a factor secreted by stimulated macrophages (see, e.g., Quiroga et al., Dig Dis Sci 1994;39(11):2485-96) and, in
 5 embodiments of the invention, its levels can be measured in serum samples as a PD marker. Neopterin levels can be measured using an EIA (enzyme immunoassay) kit available from B.R.A.H.M.S. (Germany) and distributed in the U.S. by ALPCO.

As is known in the art, neopterin is a marker of immune system activation (see, e.g. Hoffman et al., Inflamm. res. 52 (2003) 313–321; and Murr et al., Current Drug
 10 Metabolism, 2002, 3, 175-187). In a 12 week analysis from the COPE HCV clinical trial, there was increased neopterin production in all three CSID arms compared to the control PEG arm at both 4 and 12 weeks. Increased neopterin in CSID versus PEG provides further evidence for using CSID for HBV therapy. In this analysis, samples were drawn at Baseline, Day 3 and Week 1, 2, 4, 8 and 12. Neopterin concentrations
 15 were measured by ELISA and IL28B genotypes were determined by RT-PCR. Time-averaged neopterin response from individual baseline (E_{avg}) through 4 and 12 weeks was calculated using non-compartmental methods. E_{avg} through 4 and 12 weeks was significantly ($p < 0.01$, Kruskal-Wallis) greater for each of the 3 CSID arms vs. the PEG arm (Fig. 25). CSID dose did not have a significant effect on E_{avg} ($p > 0.05$). Among
 20 CSID arms, E_{avg} did not significantly change through 12 versus 4 weeks (paired t-test). Baseline neopterin did not vary significantly with treatment arm or IL28B. IL28B was not found to have a significant effect on E_{avg} through 4 and 12 weeks. Compared to PEG-IFN-2b, CSID achieved an enhanced neopterin response in hepatitis C subjects that was sustained through 12 weeks of therapy. This finding provides evidence that
 25 CSID is potent activator of cellular immunity and has utility in treating both chronic hepatitis B & C infections.

KITS

Embodiments of the invention also provide articles of manufacture and kits
 30 including for example pump elements (e.g. one or more disposable pump elements),

and/or pump apparatuses (e.g. a disposable pump apparatus), in combination with reagents useful for performing methods of the invention. For example, embodiments of the invention include kits comprising an infusion pump apparatus (e.g. a disposable infusion pump) that allows medical personnel to deliver interferon- α to a subject, in
5 combination with reagents that allow the personnel to obtain interferon- α serum concentration measurements from the subject following initiation of the therapeutic regimen (e.g. anti- interferon- α antibodies, interferon- α standards and the like). In this way, such kits provide a combination of elements useful to characterize a pharmacokinetic profile of interferon- α in a subject.

10 Typical kits of the invention comprise a single use and/or disposable infusion apparatus designed to deliver interferon- α to a patient for a limited period of time, for example not more than 7, 5, 4, 3, 2 or 1 days. In such kits, pump elements and/or the complete pump apparatus are disposed of after this period of use. In certain embodiments, the infusion apparatus comprises a micropump and/or a tubing-free
15 system such as the Medingo® tube-free, detachable micropump. Optionally, the disposable infusion apparatus is a patch pump type apparatus including an adhesive portion that is used to affix the pump to the skin of a subject (see, e.g., U.S. patent application No. 20090259176, the contents of which are incorporated by reference). In some embodiments of the invention, the disposable infusion apparatus is a infusion
20 device with linear peristaltic pump, for example one comprising: a base that contacts a patient's skin; a reservoir arranged to contain interferon- α to be delivered beneath a patient's skin, the reservoir having an outlet through which the interferon- α flows; a flexible conduit communicating with the outlet of the reservoir; and a pump that causes the interferon- α to flow down the conduit at to the patient (see, e.g., U.S. Patent
25 Application No. 20080097324, the contents of which are incorporated by reference). In some embodiments of the invention, the disposable infusion apparatus does not include one or more components typically found on reusable infusion pumps, for example a display showing infusion data, a processor, a program code storage unit, or a replaceable battery. In embodiments of the invention, the kits further comprise reagents used in

interferon- α plasma or serum concentration measurements such as anti-interferon- α antibodies, interferon- α standards and the like. Such kits can include for example, ELISA plates and/or reagents designed to provide quantitative assays of interferon- α concentrations in serum (e.g. 100-700 pg/mL, 10-70 IU/mL etc.). Optionally such kits
5 further comprise reagents adapted to measure amounts of hepatitis B or Hepatitis C in vivo, for example, one or more anti-hepatitis B antibodies or primers specific for the Hepatitis B genome, one or more anti-hepatitis C antibodies or primers specific for the Hepatitis C genome and the like.

10 This application is related to International Application Numbers PCT/US2010/54755 (International Publication No. WO 2011/059824); PCT/US2010/44146 (International Publication No. WO 2011/014882); PCT/US2009/038617 (International Publication No. WO 2009/120991); PCT/US2009/060121 (International Publication No. WO 2010/047974); and
15 PCT/US2008/078843 (International Publication No. WO 2009/046369), and U.S. Provisional Patent Application Serial Number 61/551,798 filed on October 26, 2011, the contents of each of which are incorporated by reference. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. Publications cited herein
20 are cited for their disclosure prior to the filing date of the present application. Nothing here is to be construed as an admission that the inventors are not entitled to antedate the publications by virtue of an earlier priority date or prior date of invention. Further the actual publication dates may be different from those shown and require independent verification. All numbers recited in the specification and associated claims that refer to
25 values that can be numerically characterized can be modified by the term "about".

EXAMPLES

EXAMPLE 1: – SERUM INTERFERON MEASUREMENTS DURING THE
30 **FIRST WEEK OF CONTINUOUS INTERFERON ALPHA-2B WITH ORAL**

RIBAVIRIN PREDICTS RVR AND THERAPY DISCONTINUATION IN PATIENTS WITH CHRONIC HCV-1

The pharmacokinetics (PK) and pharmacodynamics (PD) of standard-of-care
5 pegylated-interferons (PEG-IFNs) for chronic hepatitis C appear limited by one or more
of the following: 1) fluctuating blood levels that preclude continuous pressure on the
virus, 2) short half-lives relative to once-weekly dosing regimens, 3) limited potency,
and/or 4) limited systemic distribution (see, e.g. Caliceti P, Digestive and Liver Disease
2004;36:S334). The suboptimal PK and PD of PEG-IFNs have been implicated in
10 therapy failures as well as in the selection of HCV (hepatitis C virus) mutants resistant to
the two direct-acting antivirals (DAAs) recently approved (see, e.g. McHutchison JG, et
al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. N
Engl J Med 2009;360:1827-1838; Poordad F, et al. Boceprevir for Untreated Chronic
HCV Genotype 1 Infection. New England Journal of Medicine 2011;364:1195-1206) for
15 use with PEG-IFN and ribavirin (RBV).

It is hypothesized that the PK/PD profile of interferon (IFN) therapy for HCV
infection can be improved through the continuous subcutaneous infusion of non-
pegylated IFN. The premise is that continuous delivery of non-pegylated IFN- α -2b will
result in more constant circulating IFN levels. Relatively constant blood levels of fully
20 biopotent IFN, combined with maximal penetration into hepatic and non-hepatic tissues,
could improve efficacy by exposing the HCV to continuous and physiologically effective
IFN levels in as many tissues as feasible.

The focus of this Example is the 12 Week PK/PD Analysis from the COPE-
HCV study, which provides evidence that Continuous, Subcutaneous Interferon Delivery
25 (CSID) enhances the pharmacokinetics of IFN without an associated reduction in
biopotency, and that pharmacokinetic control is critical in the determination of
therapeutic outcomes. COPE-HCV is an ongoing Phase II clinical study investigating
three doses (80, 120, 160 kIU/kg/day, corresponding to 6, 9, 12 MIU/day for a 75-kg
patient) of CSID with oral RBV versus a PEG-IFN- α -2b control (1.5 μ g/kg/week with
30 RBV) in therapy-naïve subjects chronically infected with HCV genotype 1. Eligible

subjects were randomized in a 1:1:1:1 ratio to receive weekly PEG-IFN- α -2b (PegIntron®
®, Merck, Whitehouse Station, NJ) injections or 1 of 3 weight-based doses (80, 120,
160 kIU/kg/day) of non-pegylated IFN- α -2b (Intron A®, Merck) as a continuous
subcutaneous IFN- α -2b delivery therapy (CSID) delivered by an external, wearable pump
5 (Paradigm® 722, Medtronic, Minneapolis, MN) for a planned 48 weeks; all study arms
included oral weight-based RBV (Rebetol®, Merck). Using data from this study we
show how single, early measurement of serum IFN can predict therapy efficacy and
discontinuation.

10 Overview

Blood samples were collected from subjects during the first week of CSID
therapy (MW1-IFN: mid-week 1 IFN concentration; time on CSID: median = 2.1, range
= 1.6 – 5.2 days). Serum interferon concentrations and plasma HCV RNA levels were
measured by ELISA (LLOQ = 5 IU/mL) or RT-PCR (LLOD = 18 IU/mL),
15 respectively. Discontinuation was defined as study discontinuation within the first 12
weeks for any reason other than failing efficacy continuation criteria. Multivariate logistic
regression (backward selection, exit p-value = 0.05) on RVR and discontinuation
included baseline characteristics. Critical values for predictive cutoff levels for MW1-
IFN were determined by recursive partitioning. Fisher's exact test was used to calculate
20 statistical significance of contingency tables.

PK and PD Blood Measurements

Blood samples were collected at pre-dose Baseline and the following scheduled
study visits while on therapy: Day 3 and Week 1, 2, 4, 8 and 12.

25 Serum IFN concentrations were quantified using ligand-binding assays
specifically developed and validated for IFN- α -2b and PEG-IFN- α -2b using current
regulatory standards (see, e.g. DeSilva B, et al. Recommendations for the bioanalytical
method validation of ligand-binding assays to support pharmacokinetic assessments of
macromolecules. Pharm Res 2003;20:1885-1900). The validated lower limit of

quantification (LLOQ) for IFN- α -2b and PEG-IFN- α -2b are 5.0 and 10 IU/mL, respectively. For IFN concentrations <LLOQ in samples drawn at Baseline and after initiation of therapy, substitution values of 0 and LLOQ/2 were used, respectively.

Plasma HCV RNA levels were measured by RT-PCR (COBAS®
 5 AmpliPrep/COBAS® TaqMan® HCV Test, version 1.0, or equivalent, Roche). The assay has a validated LLOQ of 43 IU/mL and lower limit of detection (LLOD) of 18 IU/mL. For results < LLOQ and > LLOD, a substitution value of (LLOD+LLOQ)/2 was used. For results <LLOD (“undetectable”), a substitution value of LLOD/2 was used. In the reporting of mITT counts and proportions, missing HCV RNA results were
 10 imputed for a nominal time point only if the preceding and succeeding values were both < LLOD.

The levels of two secondary PD markers were quantified in serum: neopterin and 2',5'-oligoadenylate synthetase (OAS). Neopterin was quantified using an enzyme immunoassay (B.R.A.H.M.S., Germany) with a validated LLOQ and ULOQ of 2 and 250
 15 nmol/L, respectively. OAS was quantified via a radioimmunoassay (Eiken Chemical Company, Japan) with a validated LLOQ and ULOQ of 10 and 810 pmol/dL, respectively.

IFN Exposure Variables

20 The following IFN exposure variables for individual subjects in the 3 CSID arms were calculated using non-compartmental analysis (Phoenix WinNonlin Version 6.1, Pharsight, Inc., Cary, NC): area-under-the-curve (AUC), time-averaged concentration (C_{avg}), maximum observed concentration (C_{max}), percent fluctuation ($PF\%$), and minimum concentration (C_{min}). IFN concentration vs. time data was not corrected for individual
 25 baseline values.

AUC , C_{avg} , and C_{max} were calculated over nominal study time intervals of Baseline-Week 4 and Baseline-Week 12. The following Equation describes how C_{avg} was calculated over a given time interval from t_1 to t_2 .

$$C_{avg} = C_{avg} \Big|_{t_1}^{t_2} = \frac{AUC \Big|_{t_1}^{t_2}}{(t_2 - t_1)}$$

5 $PF\%$ and C_{min} were calculated over nominal study time intervals from Day 3-Week 4 and Day 3-Week 12. The pre-dose Baseline time-point was not included to limit the characterization of the stability of serum IFN levels to a time period concomitant with IFN therapy. The following Equation describes how $PF\%$ was calculated over a given time interval from t_1 to t_2 .

$$PF\% = PF\% \Big|_{t_1}^{t_2} = \frac{\left(C_{max} \Big|_{t_1}^{t_2} - C_{min} \Big|_{t_1}^{t_2} \right)}{C_{avg} \Big|_{t_1}^{t_2}} \times 100\%$$

10 IFN exposure variables were not calculated for PEG-IFN subjects because of the infrequent sampling schedule relative to the once-weekly dosing period and the known temporal fluctuation of IFN levels resulting from once-weekly bolus administration of PEG-IFN- α -2b (see, e.g. Glue P, et al. Pegylated interferon-alpha2b: pharmacokinetics, pharmacodynamics, safety, and preliminary efficacy data. Hepatitis C Intervention Therapy Group. Clin Pharmacol Ther 2000;68:556-567).

15 **PD Response Variables**

The following types of response variables were included in the PD analysis: 1) virologic response (HCV RNA < LLOD, or “undetectable”), 2) viral decay (decline in $\log_{10}$ HCV RNA from individual baseline), 3) time-averaged changes from individual baseline (E_{avg}) in neopterin and OAS levels in serum, and 4) discontinuation of therapy
 20 for any reason other than treatment futility (as a measure of tolerability).

Rapid virologic response (RVR) and complete early virologic response (cEVR) were defined as having a virologic response after 4 and 12 weeks of therapy, respectively. E_{avg} for neopterin and OAS was calculated through 4 and 12 weeks, using non-compartmental analysis methods analogous to the calculation of C_{avg} for IFN.
 25 Discontinuation before 12 weeks for any reason other than lack of efficacy (< 2- $\log_{10}$

drop HCV RNA) was included as catch-all general measure of reduced safety and tolerability.

Statistics

5 All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC) unless otherwise noted. A critical alpha value of 0.05 was used to determine statistical significance.

Dose dependence and proportionality of selected IFN exposure variables on weight-based dose was assessed by a power model, fit to the exposure variable data via
10 linear regression (see, e.g. Gough K, et al. Assessment of Dose Proportionality: Report from the Statisticians in the Pharmaceutical Industry/Pharmacokinetics UK Joint Working Party. Drug Information Journal 1995;29:1039-1048). A 95% CI was calculated for the model parameter β . Each 95% CI for β was inspected for the inclusion of 1, as evidence of dose-proportionality, and 0, as evidence of dose-independence. Linearity of
15 the regressions was further evaluated through the significance of a quadratic term in the regression model.

The proportions of subjects with selected categorical PD responses were calculated for each treatment arm using the number of mITT subjects as the denominator. Differences in categorical efficacy rates between the PEG-IFN arm and
20 each CSID arm were explored by calculating 95% CI's of the difference between two proportions, and p-values were calculated using the normal approximation to the binomial distribution.

A multivariate logistic regression analysis, via backward selection, was performed with an exit p-value of 0.05 to assess the ability of: 1) selected Week 4 IFN exposure
25 variables to predict RVR, 2) selected Week 12 exposure variables to predict cEVR, and 3) selected Week 4 exposure variables to predict discontinuation before Week 12. Only the CSID arms were included. Since a Week 4 serum IFN measurement was required by the prospective data exclusion rule to calculate the Week 4 exposure variables, the analysis of

discontinuation vs. IFN exposure variables effectively considered discontinuations between Weeks 4 and 12.

The following baseline characteristics were included as covariates in the multivariate logistic regression: age, gender, baseline HCV RNA level, fibrosis category (no/minimal fibrosis, portal fibrosis, bridging fibrosis, cirrhosis), IL28B group (CC, CT, TT, missing genotype), race (black/hispanic vs. not black/hispanic), and HCV genotype with all selected Week 4 or Week 12 IFN exposure variables.

Recursive partitioning (rpart, “R”, version 2.12.0, The R Project for Statistical Computing, <http://www.r-project.org>), was performed univariately to determine the optimal split, or critical value, for measures of IFN exposure that were found to be robust predictors of RVR or discontinuation. Fisher’s exact test was used to confirm the statistical significance of the critical values.

The effect of treatment arm on neopterin and OAS E_{avg} through 4 and 12 weeks was assessed non-parametrically using an omnibus Kruskal-Wallis test, followed by pairwise Wilcoxon Rank-Sum tests between each CSID arm and the PEG-IFN control, if appropriate. The dose dependence of E_{avg} was assessed in a similar fashion, starting with an omnibus test of the 3 CSID arms, followed by pair-wise comparisons, if appropriate.

In multivariate logistic regression, MW1-IFN concentration remained a statistically significant predictor of RVR (with baseline viral load and IL28B status) and discontinuation (with gender). Subjects with MW1-IFN concentrations ≥ 32.8 IU/mL had a 39% probability of attaining RVR, while subjects below this value had a 5% chance of attaining RVR. Subjects with MW1-IFN concentrations ≥ 33.2 IU/mL had a 42% probability of discontinuation, while subjects below this value had a 9% chance of discontinuation (Table 1).

MWI-1FN			
RVR	(Critical Value = 32.8 IU/mL)		
	< Critical		$\geq$ Critical
No	21		30
Yes	1		19

P-value		0.003	
Odds Ratio		12.95	
Negative Predictive Value	21/22 (95%)		
Positive Predicted Value	19/49 (39%)		
	MWI-IFN		
Discontinuation Before Week 12	(Critical Value = 33.2 IU/mL)		
	< Critical		≥ Critical
No	21		28
Yes	2		20
P-value		0.006	
Odds Ratio		7.32	
Negative Predictive Value	21/23 (91%)		
Positive Predicted Value	20/48 (42%)		

MW1-IFN, Mid-Week 1
IFN concentration

Table 1. Contingency Tables

Baseline Characteristics

- 5 Selected Baseline characteristics of subjects in the mITT population are summarized in **Table 2**. The column headings provide the number of mITT subjects by arm. IL28B genotype information is available for 68 /106 mITT subjects, as this was added to the protocol after the study was initiated.

	PEG-IFN 1.5 mcg/kg/wk (N=28)	CSID (kIU/kg/day)			Total (N=106)
		80 (N=25)	120 (N=27)	160 (N=26)	
Sex					
Male	20/28 (71.4%)	13/25 (52.0%)	16/27 (59.3%)	14/26 (53.8%)	63/106 (59.4%)
Age (years)					

Median (Q1, Q3)	51.2 (48.5, 53.8)	51.5 (47.0, 56.1)	51.3 (46.7, 55.5)	49.1 (44.6, 53.2)	50.8 (46.7, 55.4)
Race					
Caucasian	21/28 (75.0%)	23/25 (92.0%)	22/27 (81.5%)	21/26 (80.8%)	87/106 (82.1%)
Black	5/28 (17.9%)	2/25 (8.0%)	4/27 (14.8%)	3/26 (11.5%)	14/106 (13.2%)
Other	2/28 (7.1%)	0/25 (0.0%)	1/27 (3.7%)	2/26 (7.7%)	5/106 (4.7%)
Ethnicity					
Hispanic	2/28 (7.1%)	3/25 (12.0%)	3/27 (11.1%)	4/26 (15.4%)	12/106 (11.3%)
BMI (kg/m²)					
Mean (SD)	28.2 (4.6)	31.1 (5.4)	29.1 (5.2)	28.2 (5.3)	29.1 (5.2)
Baseline HCV RNA					
Log₁₀ (IU/mL)					
Median (Q1, Q3)	6.4 (5.9, 6.7)	6.1 (5.9, 6.5)	6.2 (5.5, 6.7)	5.8 (5.3, 6.4)	6.2 (5.7, 6.6)
Hepatitis C					
Genotype					
1a	24/28 (85.7%)	19/25 (76.0%)	23/27 (85.2%)	19/26 (73.1%)	85/106 (80.2%)
1b	4/28 (14.3%)	6/25 (24.0%)	4/27 (14.8%)	7/26 (26.9%)	21/106 (19.8%)
IL28B Genotype					
Available	16/28 (57%)	18/28 (64%)	16/27 (59%)	18/26 (69%)	68/106 (64%)
CC	5/16 (31%)	8/18 (44%)	6/16 (38%)	4/18 (22%)	23/68 (34%)
CT	5/16 (31%)	7/18 (39%)	10/16 (63%)	7/18 (39%)	29/68 (43%)
TT	6/16 (38%)	3/18 (17%)	0/16 (0%)	7/18 (39%)	16/68 (24%)

Most recent liver biopsy n(%)					
Bridging fibrosis	5/28 (17.9%)	7/25 (28.0%)	5/27 (18.5%)	5/26 (19.2%)	22/106 (20.8%)
Cirrhosis	9/28 (32.1%)	4/25 (16.0%)	3/27 (11.1%)	3/26 (11.5%)	19/106 (17.9%)

Table 2. Selected Baseline Characteristics of the mITT Population of Subjects.

Pharmacokinetics

The median serum IFN levels from the CSID and PEG-IFN arms are plotted in **Fig. 1**. The highest median serum IFN concentration (34.6 IU/mL) for the PEG-IFN control arm occurred at the visit (Day 3) scheduled to occur approximately midway between weekly bolus injections. After Day 3, the median IFN concentrations in the PEG-IFN arm are < 15 IU/mL and below the medians for the CSID arms. Interestingly, the IFN levels for the CSID arms appear to converge towards the 12 week time point. One possible explanation for this convergence is that subjects self-selected for a dose with improved tolerability through down-dosing or discontinuation. This observation motivated the selection of discontinuation before Week 12 as a PD response variable in the PD relationship analysis.

Descriptive statistics for select IFN exposure variables are presented graphically in **Fig. 2**. Comparison of the Week 4 and Week 12 IFN C_{avg} does not suggest accumulation ($p = 0.53$, paired t-test). The stability of serum IFN levels resulting from CSID therapy was characterized by the $PF\%$ of serum IFN concentrations for individual subjects from Day 3-Week 4 and Day 3-Week 12. The calculated values for $PF\%$ are summarized in **Fig. 2**. The values of $PF\%$ for the combined CSID arms from Day 3 through Week 4 and Week 12 of therapy are compared with historical controls in **Fig. 3**.

The power model analysis concluded that C_{avg} and C_{max} are proportionate to randomized weight-based dose over the investigated range (80-160 kIU/kg/day) through Weeks 4 and 12 of therapy (95% CI's for β include 1, exclude 0). C_{min} was found to be dose-proportionate through Week 4 (95% CI's for β include 1, exclude 0), but its dose-dependence and dose-proportionality through Week 12 were inconclusive (95% CI

includes both 0 and 1). Meanwhile, $PF^0\%$ was not found to be dose-dependent through Weeks 4 or 12 (95% CI's for β include 0, exclude 1). More detailed results of the power model analysis are illustrated in Figures 10-13.

Pharmacodynamics

5 The plasma HCV-RNA levels measured for the mITT population through Week 12 are presented in **Fig. 4**. Here, the enhanced viral kinetics of CSID relative to PEG-IFN with increasing dose is illustrated as the maximum line intensity is seen to shift from the upper right-hand to the lower left-hand corner of the sub-panels, moving from PEG-IFN to CSID 80, to CSID 120, and to CSID 160. Meanwhile, the number and
10 proportion of subjects in each treatment arm who exhibited selected PD responses are reported in **Table 3**, where statistically significant differences between individual CSID arms vs. the PEG-IFN arm are denoted. The number of mITT subjects in each study arm are provided in the column headings.

PD Response	Study Visit (Nominal Study Time)	PEG-IFN (N=28)	CSID		
			80 (N=25)	120 (N=27)	160 (N=26)
Undetectable	Day 3	0/28 (0%)	0/25 (0%)	2/27 (7%)	2/26 (8%)
HCV RNA	Week 1	0/28 (0%)	0/25 (0%)	2/27 (7%)	6/26 (23%)**
	Week 2	1/28 (4%)	3/25 (12%)	3/27 (11%)	7/26 (27%)**
	Week 4, RVR	2/28 (7%)	4/25 (16%)	7/27 (26%)	11/26 (42%)**
	Week 8	7/28 (25%)	11/25 (44%)	12/27 (44%)	11/26 (42%)
	Week 12, cEVR	7/28 (25%)	15/25 (60%)**	13/27 (48%)	11/26 (42%)
Discontinuation (cumulative, any reason before efficacy criteria)	Week 4	0/28 (0%)	4/25 (16%)*	3/27 (11%)	3/26 (12%)
	Week 12	3/28 (11%)	6/25 (24%)	9/27 (33%)*	10/26 (38%)*

15 * $p < 0.05$ vs. PEG; ** $p < 0.01$ vs. PEG

Table 3. Number and Proportion of Subjects with PD Responses Relevant to the PK/PD Analysis.

At Day 3, undetectable HCV RNA levels are reported for 2 subjects in each of the CSID 120 and CSID 160 arms, but not in the CSID 80 or PEG-IFN arms. At Week 4, the RVR rate of the CSID 160 arm (42%) is significantly ($p < 0.01$) higher than the RVR rate of the PEG-IFN control arm (7%), which is in agreement with the RVR rates reported for PEG-IFN- α -2a/b in literature (11-12%) (see, e.g. McHutchison JG, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. N Engl J Med 2009;361:580-593). Across the 3 CSID arms, the RVR rate monotonically increases with increasing randomized dose ($p < 0.05$, Cochran-Armitage test). The discontinuation rate through Week 4 was similar across the 3 CSID arms (11%-16%), with the CSID 80 arm being significantly larger than the PEG-IFN control (0%; $p < 0.05$).

At Week 8, the proportions of subjects with undetectable HCV RNA are similar across the 3 CSID arms (42%-44%) and trend higher than the PEG-IFN control (25%, $p > 0.05$). At Week 12, the cEVR rate of the CSID 80 (60%) arm is significantly higher ($p < 0.01$) than the cEVR rate of the PEG-IFN control (25%). The discontinuation rate through Week 12 for the CSID 120 (33%) and 160 (38%) arms are significantly higher than the PEG-IFN control (11%, $p < 0.05$). Across the 3 CSID arms, the apparent trends in the cEVR and cumulative discontinuation rates are not statistically significant ($p > 0.20$, Cochran-Armitage test).

The following PD relationships were found to be significant by multivariate logistic regression analysis: 1) Week 4 C_{min} and RVR ($p < 0.05$), and 2) Week 4 C_{min} and discontinuation before Week 12 ($p < 0.05$). The Week 12 exposure variables were not significant predictors of cEVR. Detailed results from the multivariate regression analysis are illustrated in Figure 14. The univariate relationships between Week 4 C_{min} and both RVR and discontinuation before Week 12 are presented in Table 4, as analyzed by recursive partitioning and Fisher's exact test. The results from the recursive partitioning analysis were confirmed using Receiver Operating Characteristic curves (Figures 15 and 16). Of the 78 CSID subjects in the mITT population, 60 met the prospective exclusion rules for Week 4 C_{min} . Two of the 60 subjects with Week 4 C_{min} values had missing Week

4 HCV RNA levels. Therefore, there are 58 subjects in the RVR contingency table and 60 subjects in the discontinuation contingency table. A multivariate contingency table is provided in Figure 17 that shows the distribution of RVR and discontinuation in relation to both of the critical values for Week 4 C_{min} .

RVR	Week 4 C_{min} (Critical Value = 32.8 IU/mL)	
	< Critical	≥ Critical
No	26	13
Yes	4	15
P-value	0.002	
Negative Predictive Value	26/30 (87%)	NA
Positive Predictive Value	NA	15/28 (54%)

Discontinuation Before Week 12*	Week 4 C_{min} (Critical Value = 60.7 IU/mL)	
	< Critical	≥ Critical
No	47	1
Yes	8	4
P-value	0.004	
Negative Predictive Value	47/55 (85%)	NA
Positive Predictive Value	NA	4/5 (80%)

- 5 * Due to the exposure variable exclusion rules, the analysis for C_{min} effectively considered discontinuations between 4 and 12 weeks.

Table 4. Contingency Tables for Week 4 C_{min} as a univariate predictor for RVR and Therapy Discontinuation.

- 10 Time-averaged neopterin response (neopterin E_{avg}) was significantly higher in each of the CSID arms verses the PEG-IFN arm through 4 and 12 weeks ($p < 0.01$), but

CSID dose did not have a significant effect ($p>0.05$). Across the 4 study arms, the correlation of viral decay with neopterin E_{avg} was modest and statistically significant through 4 ($R = 0.28$, $p<0.01$) and 12 weeks ($R = 0.28$, $p<0.05$). Across the 3 CSID arms, the correlation of IFN C_{avg} with neopterin E_{avg} was modest and statistically significant through 4 weeks ($R = 0.30$, $p<0.05$), but not through 12 weeks ($R = 0.27$, $p>0.05$). Additional details regarding neopterin E_{avg} are illustrated in Figures 25-28.

PERCENT FLUCTUATION CALCULATIONS FOR HISTORICAL CONTROLS AND COMPARISON WITH CSID

10 *IFN- α -2b (TIW)*

The percent fluctuation (PF%) of IFN- α -2b administered according to its label (3 MIU TIW; see, e.g. INTRON A. (Interferon-alfa-2b, recombinant) for Injection Product Insert. In. Schering-Plough (now Merck); 2008) was estimated using data published by Glue and co-workers (see, e.g. Glue P, et al. Pegylated interferon-alpha2b: pharmacokinetics, pharmacodynamics, safety, and preliminary efficacy data. Hepatitis C Intervention Therapy Group. Clin Pharmacol Ther 2000;68:556-567) for a single bolus during the fourth week of therapy. Percent fluctuation was calculated using the mean values reported in Table I from Glue and co-workers (see, e.g. Glue P, et al. Pegylated interferon-alpha2b: pharmacokinetics, pharmacodynamics, safety, and preliminary efficacy data. Hepatitis C Intervention Therapy Group. Clin Pharmacol Ther 2000;68:556-567) and the Equation:

$$PF\% = (100\%) \times (168 \text{ hrs}) \times (C_{max} - C_{min}) / (3 \times AUC_{0-168})$$

It was inferred that $C_{min} \approx 0$, since T_f (final quantifiable sampling time) < the dosing period ($\approx 168/3$ hours).

25 *PEG-IFN- α -2a (QW)*

The percent fluctuation of PEG-IFN- α -2a administered according to its label (180 mcg QW; see, e.g. PEGASY. (peginterferon-alfa-2a) Product Insert. In. Roche Pharmaceuticals; 2008) was estimated using the PK model and model parameters reported by Dahari and co-workers (see, e.g. Dahari H, Affonso de Araujo ES, et al.

Pharmacodynamics of PEG-IFN- α -2a in HIV/HCV co-infected patients: Implications for treatment outcomes. Journal of Hepatology 2010;53:460-467). Estimates for individual PK parameters (k_e , k_a and FD/V_d) were provided in the publication for the first 7 and 84 days of therapy for 17 individual subjects. For the present analysis, $PF\%$ was calculated from 3 days through 4 weeks and 3 days through 12 weeks of therapy using individual IFN concentration vs. time profiles calculated using the published PK model and PK parameters derived from the first 84 days of therapy.

PEG-IFN- α -2b (QW)

The percent fluctuation of PEG-IFN- α -2b administered according to its label (1.5 mcg/kg Q; see, e.g. PEGIntron. (Peginterferon-alfa-2b) Powder for Injection Product Insert. In. Schering-Plough (now Merck); 2008) was estimated using the PK model and model parameters reported by Talal and co-workers (see, e.g. Talal AH, et al. Pharmacodynamics of PEG-IFN alpha differentiate HIV/HCV coinfectd sustained virological responders from nonresponders. Hepatology 2006;43:943-953). Estimates for individual PK parameters (k_e , k_a and FD/V_d) were provided in the publication for week 1 and week 2 of therapy for 21 individual subjects. For the present analysis, $PF\%$ was calculated from 3 days through 4 weeks and 3 days through 12 weeks of therapy using individual IFN concentration vs. time profiles calculated using the published PK model and PK parameters derived from week 2 of therapy.

DISCUSSION

The first premise of CSID therapy for chronic HCV infection is that continuous subcutaneous infusion of IFN can achieve circulating IFN concentrations that are relatively stable compared to repeated bolus injections of IFN or PEG-IFN. The second premise of CSID is that the relatively stable levels of non-pegylated IFN, with its high level of biopotency and unrestricted volume of distribution, will result in enhanced PD response. The PK results presented herein support the first premise. The $PF\%$ through week 4 of CSID is significantly less than historical controls for IFN TIW, IFN- α -2b QW, and IFN- α -2a QW (**Fig. 3**, left). Through week 12, the $PF\%$ of CSID is significantly less than IFN TIW and PEG-IFN- α -2b QW, while the $PF\%$ of CSID is similar to PEG-IFN-

α -2a QW (**Fig. 3**, right). Nevertheless, PEG-IFN- α -2a, with its relatively large and more branched polyethylene glycol moiety, has a sub-optimal PD profile as it has been shown to require approximately 8-fold higher circulating IFN concentrations than PEG-IFN- α -2b to achieve 50% viral suppression in patients who achieve SVR (see, e.g. Talal AH, et al. Pharmacodynamics of PEG-IFN alpha differentiate HIV/HCV coinfectd sustained virological responders from nonresponders. Hepatology 2006;43:943-953; Dahari H, et al. Pharmacodynamics of PEG-IFN- α -2a in HIV/HCV co-infected patients: Implications for treatment outcomes. Journal of Hepatology 2010;53:460-467).

The PK results presented here support the feasibility of CSID therapy in that IFN exposure variables were found to be dose-proportionate through 4 (C_{avg} , C_{max} , C_{min}) and 12 (C_{avg} , C_{max}) weeks of therapy. Dose-proportionality is an ideal characteristic of any drug therapy, as it implies that the pharmacokinetics are amenable to control, the importance of which is highlighted by the critical values for Week 4 C_{min} discussed below. Considered with the half-life of IFN (~4 hours, see, e.g. Zeuzem S, et al. Pharmacokinetics of Peginterferons. SEMINARS IN LIVER DISEASE 2003:023), these results position CSID as a rapidly adjustable and individually tailorable therapy for the treatment of chronic hepatitis C.

The PD results presented here support the second premise of CSID, in that subjects in the CSID arms exhibited both accelerated viral kinetics (**Fig. 4**) and an increased proportion of subjects with undetectable HCV RNA (**Table 3**), relative to the PEG-IFN control. Furthermore, time-averaged neopterin response (E_{avg}) was significantly higher at 4 and 12 weeks in each of the CSID arms versus the PEG-IFN control ($p < 0.01$), providing evidence that CSID at the investigated doses results in increased activation of cellular immunity relative to PEG-IFN (see, e.g. Hoffmann G, et al. Potential role of immune system activation-associated production of neopterin derivatives in humans. Inflamm Res 2003;52:313-321). Interestingly, it has also been suggested that elevated neopterin levels play a role in some of the side-effects associated with IFN therapy (see, e.g. Hoffmann G, et al. Potential role of immune system activation-associated production of neopterin derivatives in humans. Inflamm Res 2003;52:313-321). Meanwhile, each of the 3 CSID arms exhibited significantly ($p < 0.05$)

higher rates of discontinuation through 4 or 12 weeks relative to the PEG-IFN control, for reasons other than lack of efficacy. Considered together, these results suggest a need to find a balance between the enhanced efficacy and reduced tolerability of CSID. Embodiments of the invention address this need.

5 Statistical analysis of various PD relationships identified a critical serum IFN level of approximately 33 IU/mL for the first 4 weeks of therapy for the COPE-HCV study population (**Table 4**). Subjects who reached Week 4 and had a C_{min} value ≥ 32.8 IU/mL had a 54% chance of attaining RVR, whereas subjects below this value had only a 13% chance of attaining RVR (87% NPV). The analysis also identified a critical value for
10 Week 4 C_{min} as a significant predictor of discontinuation before week 12, for reasons other than treatment futility ($< 2\text{-log}_{10}$ drop HCV RNA, **Table 4**). While 80% of subjects with Week 4 $C_{min} \geq 32.8$ IU/mL discontinued before Week 12, only 15% of subjects below this value discontinued before Week 12 (85% NPV).

 The critical IFN concentration for attaining RVR of 32.8 IU/mL is 4-fold greater
15 than the mean C_{min} reported for week 4 of PEG-IFN- α -2b therapy (~ 8 IU/mL). For the PEG-IFN arm in the present study, the serum IFN concentrations after Day 3 represent an upper bound for the true C_{min} for each week for therapy, and it is notable that the median values (< 15 IU/mL, **Fig. 1**) are below the critical values of 32.8 and 60.7 IU/mL. These relatively low C_{min} values for the concurrent and historical controls
20 provide an explanation as to why PEG-IFN- α -2b is relatively well-tolerated, but also has relatively poor efficacy in terms of RVR.

 As noted above, a serum IFN concentration of approximately 33 IU/mL from a single blood sample a few (1.6 – 5.2) days after initiating CSID was identified as an early predictor of both RVR and discontinuation before 12 weeks. Contingent upon further
25 study, this finding could provide clinicians with the ability to more effectively tailor CSID therapy for improved efficacy and tolerability.

 The results presented here provide evidence that continuous subcutaneous delivery of non-pegylated IFN will result in more constant circulating levels of more biopotent IFN as compared to current standard of care and suggest a role for CSID in
30 the rapidly changing hepatitis B & C therapy landscapes. The relatively stable IFN levels

achieved by CSID are associated with accelerated viral kinetics and an increased proportion of patients achieving undetectable HCV RNA.

**EXAMPLE 2: SINGLE SERUM INTERFERON MEASUREMENT DURING
5 THE FIRST WEEK OF CONTINUOUS INTERFERON ALPHA-2B WITH
ORAL RIBAVIRIN PREDICTS RVR AND THERAPY DISCONTINUATION
IN PATIENTS WITH CHRONIC HCV-1**

This Example summarizes an analysis of data from the COPE-HCV clinical
10 trial. As noted above, COPE-HCV is an on-going, Phase II, multi-center, randomized,
open-label, active-control, dose-ranging study being conducted in the U.S. The study
includes a 4-arm randomized evaluation of 3 dose levels (80, 120 or 160 kIU/kg/day) of
IFN- α -2b delivered via continuous subcutaneous (SC) infusion compared with PEG-
IFN- α -2b given as once-weekly SC injections. Continuous SC delivery of IFN- α -2b is
15 being achieved via a wearable infusion system that is currently marketed for delivering
insulin.

Blood samples were collected from subjects during the first week of CSID
therapy. This sample collection is referred to as the mid-week 1 IFN ("MW1-IFN")
sample collection. The actual sample collection time varied across subjects (median=2.1,
20 range = 1.6 – 5.2 days). Serum interferon concentrations and plasma HCV RNA levels
were measured by ELISA (LLOQ = 5 IU/mL) or RT-PCR (LLOD = 18 IU/mL),
respectively.

Plasma HCV RNA levels were measured by a validated RT-PCR assay with an
LLOD = 18 IU/mL (COBAS® Ampliprep / COBAS® TaqMan® from Roche, or
25 equivalent). IL28B Genotyping. SNP analysis was performed by RT-PCR using Taqman
custom designed rs12979860 probes (Applied Biosystems), on an ABI HT-7900
instrument.

Study Outcome Definitions. Rapid virological response (RVR) was defined as
undetectable HCV RNA (< LLOD) after 4 weeks of therapy. Discontinuation was

defined as study discontinuation within the first 12 weeks for any reason other than failing efficacy continuation criteria.

Multivariate logistic regression (backward selection, exit p-value = 0.05) on RVR and discontinuation included baseline characteristics, as indicated in Table 2.

- 5 Critical values for predictive cutoff levels for MW1-IFN were determined by a single branching of univariate recursive partitioning and were confirmed by inspection of ROC curves. Fisher's exact test was used to calculate statistical significance of contingency tables.

- 10 MW1-IFN was initially found to be a significant predictor for both RVR and discontinuation within the first 12 weeks among subjects in the three CSID arms, as assessed by univariate logistic regression. In multivariate logistic regression, MW1-IFN concentration remained a statistically significant predictor of RVR (with baseline viral load and IL28B status) and discontinuation (with gender). Subjects with MW1-IFN concentrations ≥ 32.8 IU/mL had a 39% probability of attaining RVR, while subjects
15 below this value had a 5% chance of attaining RVR. Subjects with MW1-IFN concentrations ≥ 33.2 IU/mL had a 42% probability of discontinuation, while subjects below this value had a 9% chance of discontinuation (Table C).

- Figure 24B shows a detailed relationship of significant predictors of RVR or discontinuation from multivariate logistic regression analyses. The two significant
20 continuous variables (baseline HCV RNA and MW1-IFN concentration) are plotted against each other for each combination of the two significant categorical variables - IL28B genotype and gender. The critical value found for the achievement of RVR is 32.8. Genotypes are grouped into CC, CT, TT or unknown, which are indicated by "NA" in the figure.

- 25 In conclusion, a serum IFN concentration of approximately 33 IU/mL from a single blood sample a few (1.6 – 5.2) days after initiating CSID was identified as an early predictor of both RVR and discontinuation before 12 weeks. This finding provides clinicians with the ability to more effectively tailor CSID therapy for improved efficacy and tolerability.

30

TABLES A-D

A number of different SNPs that are associated with chronic HBV infection have been identified (see, e.g. Mbarek et al., Hum Mol Genet. 2011 Oct 1;20(19):3884-92, Obrien et al., Genes Immun. 2011 Sep;12(6):428-33; Zhang et al., Nat Genet. 2010 Sep;42(9):755-8; and Huang et al., Gut. 2011 Jan;60(1):99-107; the contents of which are incorporated by reference herein). In this context, databases such as the Entrez Global Query Cross-Database Search System provide search engines that allow users to search databases at the National Center for Biotechnology Information (NCBI) website. Those of skill in this art are aware, for example, that the Entrez SNP database provides a library of single nucleotide polymorphisms such as those disclosed in Mbarek et al. In this database, the sequences of various polymorphism are cataloged with a SNP designation (e.g. rs2856718 and rs7453920). Illustrative SNP sequences obtained using such SNP designations as a query are provided in Table A. In Table A, the polymorphic nucleotide in these SNP sequences is bracketed (nucleotide position 27).

15

TABLE A: ILLUSTRATIVE HBV ASSOCIATED SINGLE NUCLEOTIDE POLYMORPHISMS

rs2856718:
 GTGTGGGAGGACAGGCCATGGGATTA [A/G] ACAGCTCTTCTTAACCTGCCAGAGG (SEQ ID NO:
 20 16)

rs7453920:
 AGTGAAGAGGGCAGTCGGACCGATTTC [A/G] ACATTGACCTCTGCTCTTAGATCAG (SEQ ID NO:
 25 17)

rs3077
 TTCTTCTCACTTCATGTGAAAACCTAC [C/T] CCAGTGGCTGACTGAATTGCTGACC (SEQ ID NO:
 18)

rs9277535
 GACTGCAAATCTGCCTGATAGGACCC [A/G] TATTTCCACAGCACTAATTCAACAT (SEQ ID NO:
 30 19)

rs2284553

GCAGGGCTCAGAACTGTCCGGGTCCC [A/G] TCAGTGTGGGGCGGAAGAGGAAGA (SEQ ID NO: 20)

5

rs9808753

CAATAGCACGAGGCCTGTTGTCTACC [A/G] AGTGCAGTTTAAATAGTAAGCCGGT (SEQ ID NO: 21)

10

rs17401966

AAAACACATAGTGCTCTATGAGTCC [A/G] TATTGAGTCAAGTGTCTTAGAGGT (SEQ ID NO: 22)

In addition, a number of different SNPs that are predictive of factors associated with HCV infection including treatment induced viral clearance and the speed of a patients response to interferon- α have been identified (see, e.g. Ge et al., Nature 2009, 461(7262):399-401; Tanaka et al., Nat Genet. 2009 41(10):1105-9; Thomas et al., Nature 2009, 461(7265):798-801; Rauch et al., Gastroenterology 2010 138(4):1338-45; and McCarthy et al., Gastroenterology. 2010 138(7):2307-14, the contents of which are incorporated by reference herein). In this context, databases such as the Entrez Global Query Cross-Database Search System provide search engines that allow users to search databases at the National Center for Biotechnology Information (NCBI) website. Those of skill in this are aware, for example, that the Entrez SNP database provides a library of single nucleotide polymorphisms such as those disclosed in Ge et al., Nature. 2009; 461(7262): 399-401. In this database, the sequences of various polymorphism are cataloged with a SNP designation (e.g. rs12979860). Illustrative SNP sequences obtained using such SNP designations (e.g. rs12979860) as a query are provided in Table 2. In Table 2, the polymorphic nucleotide in these SNP sequences is bracketed (nucleotide position 27).

30

Table B: ILLUSTRATIVE HCV ASSOCIATED SINGLE NUCLEOTIDE POLYMORPHISMS

Illustrative SNP sequences obtained using such SNP designations (e.g. rs12979860) as a query are provided in Table B. In Table B, the polymorphic nucleotide in these SNP sequences is bracketed (nucleotide position 27).

5	rs12979860: CTGAACCAGGGAGCTCCCCGAAGGCG [C/T] GAACCAGGGTTGAATTGCACTCCGC (SEQ ID NO: 1)
10	rs12980275: CTGAGAGAAGTCAAATTCCTAGAAAC [A/G] GACGTGTCTAAATATTTGCCGGGGT (SEQ ID NO: 2)
	rs8099917: CTTTTGTTCCTTTCTGTGAGCAAT [G/T] TCACCCAAATTGGAACCATGCTGTA (SEQ ID NO: 3)
15	rs12972991 AGAACAAATGCTGTATGATTCCCCCT [A/C] CATGAGGTGCTGAGAGAAGTCAAAT (SEQ ID NO: 4)
	rs8109886 TATTCATTTTTTCCAACAAGCATCCTG [A/C] CCCAGGTCGCTCTGTCTGTCTCAAT (SEQ ID NO: 5)
20	rs4803223 CCTAAATATGATTTTCCTAAATCATAC [A/G] GACATATTTCCCTTGGGAGCTATACA (SEQ ID NO: 6)
25	rs12980602: TCATATAACAATATGAAAGCCAGAGA [C/T] AGCTCGTCTGAGACACAGATGAACA (SEQ ID NO: 7)
	rs8103142: TCCTGGGGAAGAGGCGGGAGCGGCAC [C/T] TGCAGTCCTTCAGCAGAAGCGACTC (SEQ ID NO: 8)
30	rs28416813: CAGAGAGAAAGGGAGCTGAGGGAATG [C/G] AGAGGCTGCCCCACTGAGGGCAGGGG (SEQ ID NO: 9)
	rs4803219: CTGAGCTCCATGGGGCAGCTTTTATC [C/T] CTGACAGAAGGGCAGTCCCAGCTGA (SEQ ID NO: 10)
35	rs4803217: TAGCGACTGGGTGACAATAAATTAAG [A/C] CAAGTGGCTAATTTATAAATAAAAT (SEQ ID NO: 11)
	rs581930: CTGTGGAGCACAGAACTGCCAGGAAC [C/T] AGGGCCCCCTGGATGACTGAGTGGGG (SEQ ID NO: 12)
40	rs8105790: CTTCCTGACATCACTCCAATGTCCTG [C/T] TTCTGTGGTTACATCTCCGCTAAT (SEQ ID NO: 13)
45	rs11881222: AGAGGGCACAGCCAGTGTGGTCAGGT [A/G] GGAGCAGAGGGAAGGGGTAGCAGGT (SEQ ID NO: 14)
	rs7248668: CATGGTCTCAGTCTGTAGCCCAAGCT [A/G] GAGCATAGTAGTGGCACAAATCGCCA (SEQ ID NO: 15)
50	

Table C: Subjects with MW1-IFN concentrations ≥ 33.2 IU/mL had a 42% probability of discontinuation, while subjects below this value had a 9% chance of discontinuation.

RVR	MW1-IFN (Critical Value = 32.8 IU/mL)	
	< Critical	$\geq$ Critical
No	21	30
Yes	1	19
P-value	0.003	
Odds Ratio	12.95	
Negative Predictive Value	21/22 (95%)	
Positive Predicted Value		19/49 (39%)
Discontinuation Before Week 12	MW1-IFN (Critical Value = 33.2 IU/mL)	
	< Critical	$\geq$ Critical
No	21	28
Yes	2	20
P-value	0.006	
Odds Ratio	7.32	
Negative Predictive Value	21/23 (91%)	
Positive Predicted Value		20/48 (42%)

5 MW1-IFN, Mid-Week 1 IFN concentration

Table D. Summary statistics of IFN exposure variables and viral kinetics for the first 4 weeks of continuous IFN therapy. Results are aggregated for the 3 dosing arms of continuous IFN. Data from 33 subjects were included in this analysis. Differences in defined data sets for different variables account for the disparity in N.

5

Variable	RVR	N	Mean	Median	Min	Max	CV% (%)
1. AUC (IU-hr/mL)	Combined	29	1400	1300	500	2200	34
	No	18	1400	1300	590	2200	32
	Yes	11	1400	1200	500	2100	38
C_{avg} (IU/mL)	Combined	29	49	46	18	79	34
	No	18	49	47	21	79	32
	Yes	11	49	43	18	76	38
C_{max} (IU/mL)	Combined	29	71	56	21	240	61
	No	18	67	56	27	140	45
	Yes	11	77	67	21	240	78
C_{min} (IU/mL)	Combined	32	38	34	17	70	39
	No	20	37	32	18	70	40
	Yes	12	40	37	17	68	38
PF% (%)	Combined	32	46	30	11	140	70
	No	20	52	38	15	140	68
	Yes	12	36	29	11	87	66
Baseline HCV RNA (log ₁₀ [IU/mL])	Combined	32	5.9	6.0	3.0	7.0	14
	No	19	6.2	6.3	5.4	6.8	6.2
	Yes	13	5.5	5.4	3.0	7.0	21
Viral Decay at Week 4 (log ₁₀ [IU/mL])	Combined	32	3.4	3.6	0.65	6.0	48
	No	19	3.5	2.2	0.65	4.8	53
	Yes	13	4.5	4.5	2.1	6.0	25

CLAIMS

1. A method of characterizing a pharmacokinetic profile resulting from a therapeutic regimen that comprises administering interferon- α to a patient via a continuous infusion device, wherein the pharmacokinetic profile correlates with a viral response to the therapeutic regimen, the method comprising the steps of:
- 5 obtaining a plurality of interferon- α serum concentration measurements from the patient following initiation of the therapeutic regimen;
- using the plurality of interferon- α concentration measurements to perform one or more determinations selected from the group:
- 10 (a) determine a percent fluctuation (PF%) of interferon- α concentrations in the patient;
- (b) determine a standard deviation of interferon- α concentrations in the patient;
- 15 (c) determine a coefficient of variation of interferon- α concentrations in the patient; and
- (d) determine a Cmin, Cavg or Cmax of interferon- α concentrations in the patient;
- so that the pharmacokinetic profile is characterized.
- 20
2. The method of claim 1, further comprising:
- determining if the pharmacokinetic profile conforms to a parameter that identifies the patient as more likely to exhibit a viral response as compared to patients having pharmacokinetic profiles that do not conform to the parameter; and
- 25 selecting a continued therapeutic regimen or course of action based upon said determination.
3. The method of claim 2, wherein the continued therapeutic regimen or course of action comprises one or more actions selected from the group:

(a) maintaining the therapeutic regimen for a duration of at least 4, 5, 6, 7, 8, 12, 24, 36 or 48 weeks;

(b) initiating a modified therapeutic regimen for the patient that comprises:

an increased dose of interferon- α ;

5 a decreased dose of interferon- α ; and

(c) discontinuing the therapeutic regimen.

4. The method of claim 2, wherein the parameter comprises one or more selected from the group:

10 (a) a maximum PF% of interferon- α concentrations not greater than 200%;

(b) a standard deviation of interferon- α concentrations not greater than 10 IU/ML; and

(c) a coefficient of variation of interferon- α concentrations not greater
15 than 20 %.

5. The method of claim 1, wherein the viral response to the therapeutic regimen comprises one or more responses selected from the group:

(a) a $\geq 1, 2$ or 3 log drop in viral particles observed in serum of the
20 patient; and/or

(b) an early virological response (EVR);

(c) a sustained virological response (SVR); and

(d) viral clearance.

25 6. The method of claim 1, wherein the pharmacokinetic profile comprises the percent fluctuation of interferon- α concentrations as determined using the formula:

percent fluctuation = $[C_{\max} - C_{\min}] / C_{\text{avg}}$; wherein:

$C_{\max}$ is maximum observed interferon- α concentration

$C_{\min}$ is minimum observed interferon- α concentration; and

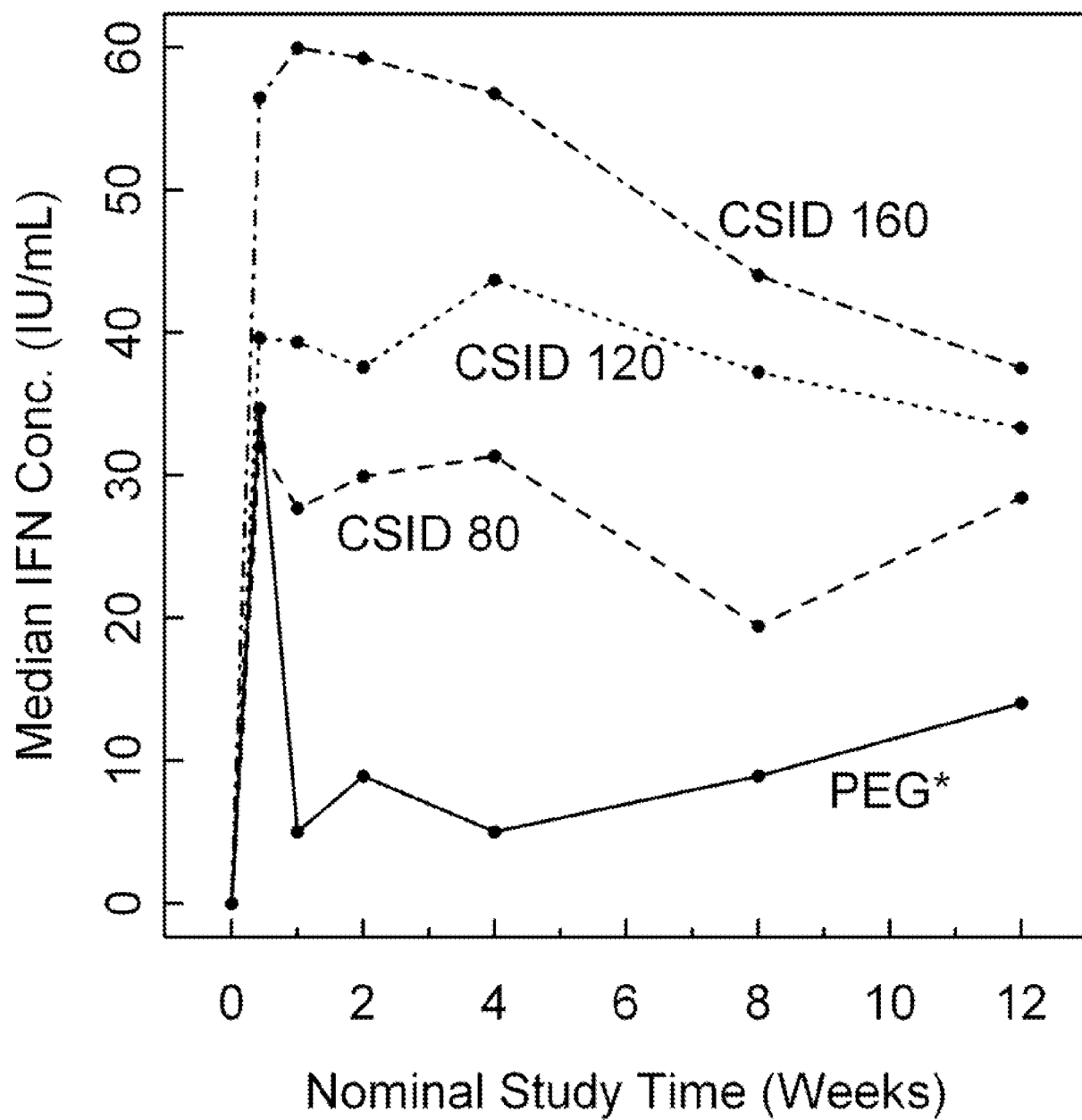
C_{avg} is average observed interferon- α concentration.

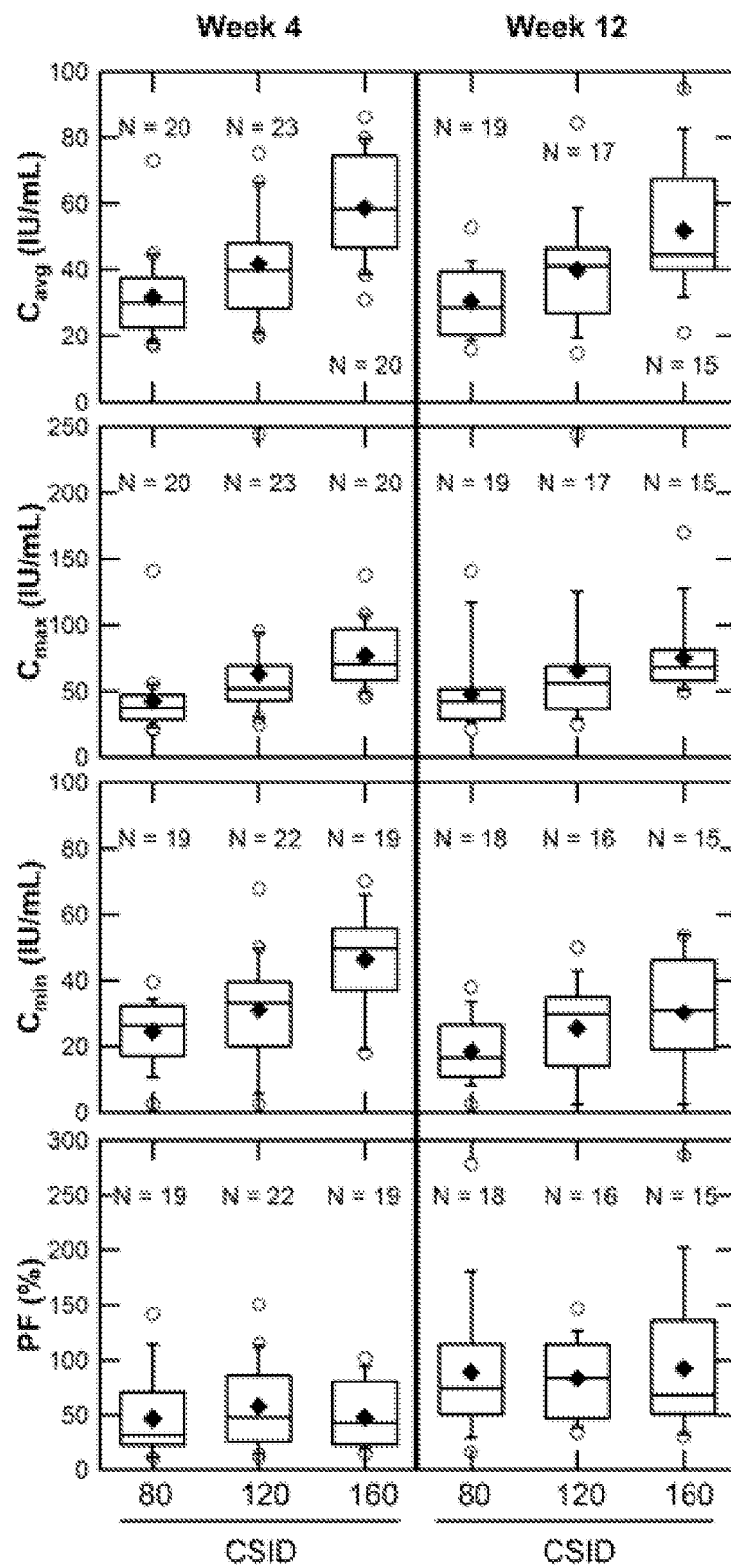
7. The method of claim 1, wherein the interferon- α is not pegylated.
- 5 8. The method of claim 1, wherein the patient is infected with:
 - a hepatitis B virus; or
 - a hepatitis C virus.
9. The method of claim 2, further comprising using an observation of a genomic
 - 10 sequence in the patient for selecting a continued therapeutic regimen or course of action, wherein:
 - the patient is infected with a hepatitis B virus and the genomic sequence comprises a single nucleotide polymorphism (SNP) designated rs2856718, rs7453920, rs3077, rs9277535, rs2284553, rs9808753 or rs17401966; or
 - 15 the patient is infected with a hepatitis C virus and the genomic sequence comprises a single nucleotide polymorphism (SNP) designated rs12979860, rs12980275, rs8099917, rs12972991, rs8109886, rs4803223, rs8103142, rs28416813, rs4803219, rs4803217, rs581930, rs8105790, rs11881222, rs7248668 or rs12980602.
- 20 10. A system for administering interferon- α to a patient, the system comprising:
 - a continuous infusion pump having a medication reservoir comprising interferon- α ; and
 - a processor operably connected to the continuous infusion pump and comprising a set of instructions that causes the continuous infusion pump to administer the
 - 25 interferon- α to the patient according to a patient-specific therapeutic regimen made by:
 - administering interferon- α to the patient via a continuous infusion pump according to a test therapeutic regimen;
 - observing concentrations of interferon- α present in the serum of the patient that result from the test therapeutic regimen so as to obtain information on one or more of:

- (1) a percent fluctuation (PF%) of interferon- α concentrations in the patient that result from the test therapeutic regimen;
- (2) a standard deviation of interferon- α concentrations in the patient that result from the test therapeutic regimen;
- 5 (3) a coefficient of variation of interferon- α concentrations in the patient that result from the test therapeutic regimen; or
- (4) a C_{min} , C_{avg} or C_{max} of interferon- α concentrations in the patient that result from the test therapeutic regimen;
- determining if an observed value of (1)-(4) conforms to a parameter that identifies the patient as more likely to exhibit a viral response to interferon- α as compared to patients having pharmacokinetic profiles that do not conform to the parameter; and
- 10 designing the patient specific therapeutic regimen using the observed value, wherein, (as compared to the test therapeutic regimen), the patient specific therapeutic regimen comprises:
- 15 an increased dose of interferon- α ; or
a decreased dose of interferon- α .
11. The system of claim 10, wherein the continuous infusion pump:
- 20 has dimensions smaller than 15 x 15 centimeters; or
is operably coupled to an interface that facilitates the patient's movements while using the continuous infusion pump, wherein the interface comprises a clip, a strap, a clamp or tape.
- 25 12. The system of claim 10, wherein:
- the interferon- α is not conjugated to a polyol; and/or
the patient-specific therapeutic regimen is sufficient to maintain circulating levels of the interferon- α in the patient above a mean steady state concentration of at least 100, 200, 300, 400, 500, 600 or 700 pg/mL

13. The system of claim 10, wherein the viral response comprises one or more of:
- (a) a ≥ 1 , 2 or 3 log drop in viral particles observed in serum of the patient; and/or
 - 5 (b) an early virological response (EVR);
 - (c) a sustained virological response (SVR); and
 - (d) viral clearance.
14. The system of claim 10, wherein the patient is infected with:
- 10 a hepatitis B virus; or
 - a hepatitis C virus.
15. A method of administering a therapeutic regimen comprising interferon- α delivered to a patient infected with a hepatitis C virus via a continuous infusion device,
- 15 the method comprising:
- (a) determining average serum interferon- α concentrations in the patient that are occurring on about a third day of administering interferon- α , wherein serum interferon- α concentrations of above about 30 IU/mL identify the patient as having a greater probability of achieving rapid virologic response (RVR) as compared to a patient having
 - 20 serum interferon- α concentrations below about 30 IU/mL; and
- using the serum interferon- α concentrations in the patient as determined in step
- (a) to:
- (i) adopt the therapeutic regimen for a duration of at least 4, 5, 6, 7, 8, 12, 24, 36 or 48 weeks; or
 - 25 (ii) design a modified therapeutic regimen for the patient that comprises:
 - an increased dose of interferon- α ; or
 - a decreased dose of interferon- α .

16. The method of claim 15, wherein the modified therapeutic regimen is designed to produce serum interferon- α concentrations in the patient above about 25-40 IU/mL and below about 60 IU/mL.
- 5 17. The method of claim 15, wherein the average serum interferon- α concentrations in the patient are observed by obtaining at least 3, 4, 5, or 6 different serum samples from the patient over the period of time.
18. The method of claim 17, wherein the period of time is 1, 2, 3, 4, 5 or more days.
- 10 19. The method of claim 15, wherein the interferon- α is not pegylated.
20. Use of interferon- α in the manufacture of a composition adapted for a continuous infusion apparatus, wherein the interferon- α composition is manufactured to
- 15 allow the continuous infusion apparatus to:
- maintain mean circulating levels of interferon- α in serum of a patient above a steady state concentration of at least 100 pg/mL when administered subcutaneously; and
- produce a maximum percent fluctuation (PF%) of interferon- α concentrations in the patient of not greater than 200%.

**FIG. 1**

**FIG. 2**

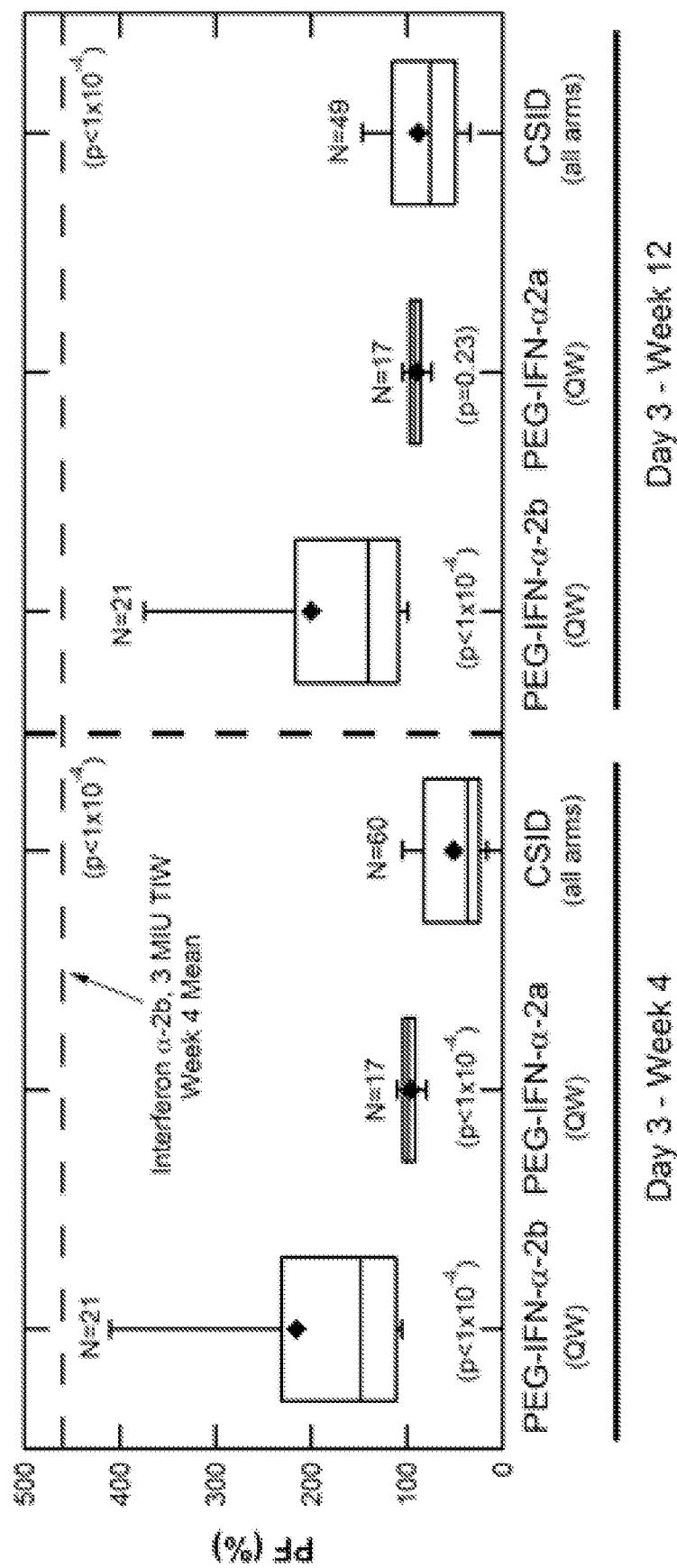
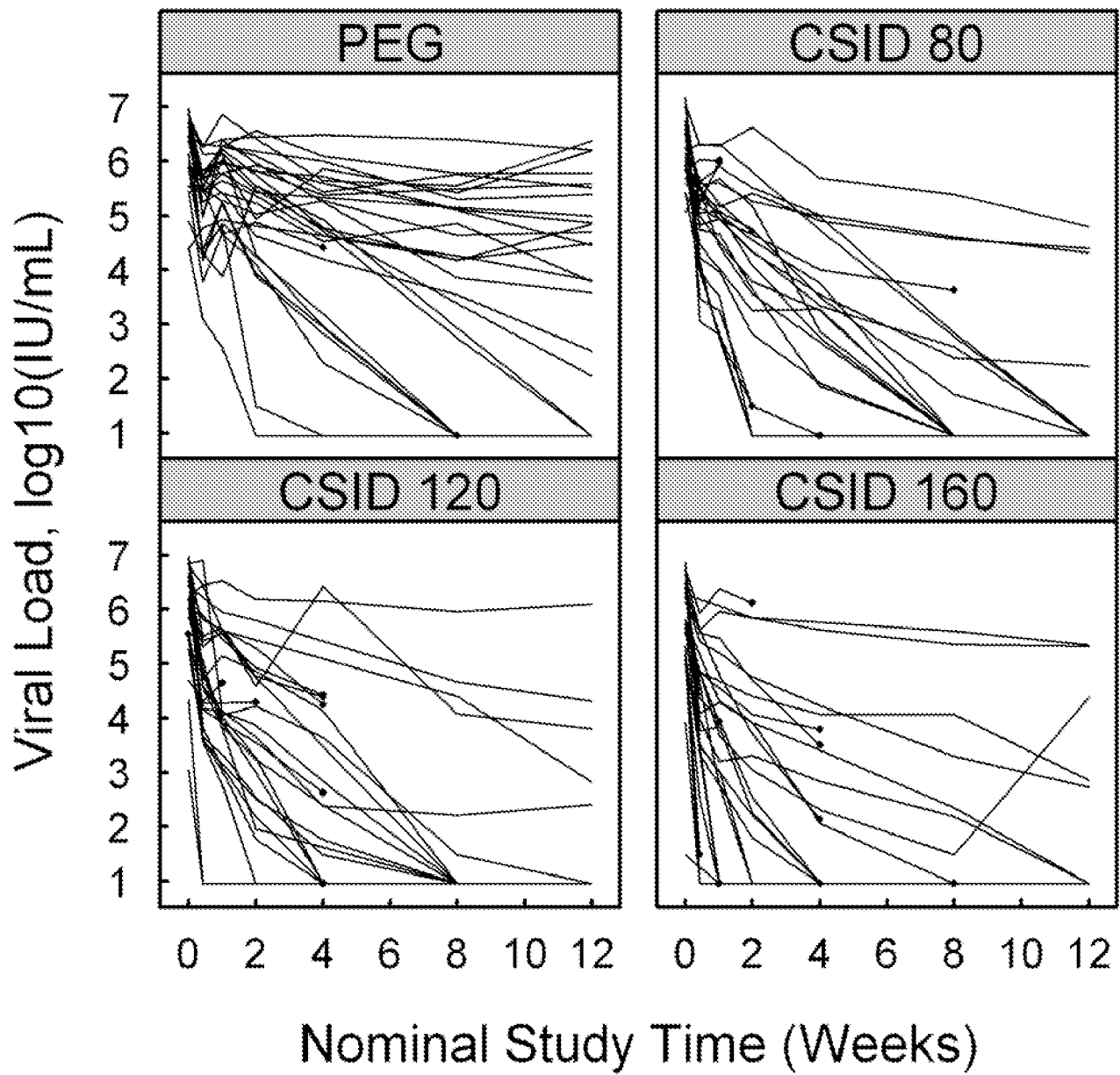


FIG. 3

**FIG. 4**

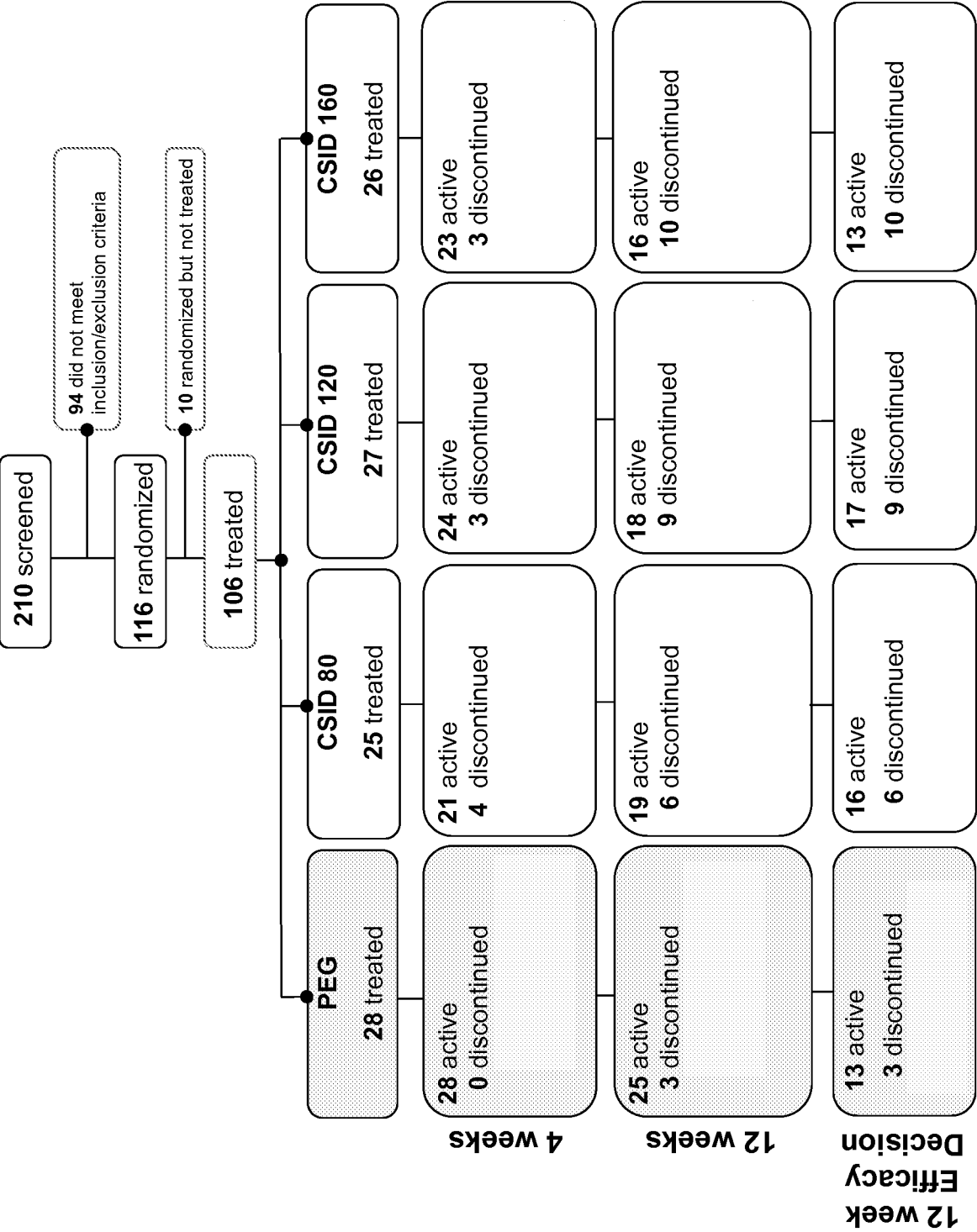


FIG. 5

Subject Disposition and Early Virologic Response (EVR) after 12 weeks of Therapy.

	PEG (N=28)	CSID 80 (N=25)	CSID 120 (N=27)	CSID 160 (N=26)
EVR * ($\geq 2\text{-log}_{10}$ Drop HCV RNA)	13/28 (46%)	16/25 (64%)	17/27 (63%)	13/26 (50%)
Failed Efficacy Criteria ($< 2\text{-log}_{10}$ Drop HCV RNA)	12/28 (43%)	3/25 (12%)**	1/27 (4%)**	3/26 (12%)**
Discontinuation (cumulative, any reason before efficacy criteria)	3/28 (11%)	6/25 (24%)	9/27 (33%)*	10/26 (38%)*

* $p < 0.05$ vs. PEG; ** $p < 0.01$ vs. PEG

FIG. 6

Serum IFN Concentration Detailed Summary Statistics.

The column headings provide the number of mITT subjects by arm (N). The number of IFN concentration measurements that are available for each study visit are also denoted (n).

Study Visit (Nominal Study Time)	PEG (N=28)	CSID 80 (N=25)	CSID 120 (N=27)	CSID 160 (N=26)
Baseline				
n	25	25	26	25
Mean (SD)	0.0 (0.0)	2.2 (7.0)	9.7 (47.8)	2.7 (7.6)
Median (Q1, Q3)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
(Min, Max)	0.0 (0.0)	(0.0, 30.5)	(0.0, 244.1)	(0.0, 29.2)
Day 3				
n	26	23	23	20
Mean (SD)	40.1 (24.0)	29.9 (18.0)	40.2 (17.7)	62.6 (21.2)
Median (Q1, Q3)	34.7 (27.5, 47.8)	32.0 (17.1, 34.3)	39.9 (31.8, 55.7)	60.0 (49.1, 68.0)
(Min, Max)	5.0 (130.3)	(2.5, 94.1)	(2.5, 69.0)	(33.4, 137.5)
Study Week 1				
n	26	24	23	25
Mean (SD)	17.2 (21.7)	27.8 (9.9)	38.9 (15.4)	59.7 (19.0)
Median (Q1, Q3)	5.0 (5.0, 18.2)	27.7 (22.8, 33.3)	39.4 (30.0, 49.9)	60.0 (48.3, 68.0)
(Min, Max)	5.0 (75.3)	(2.5, 50.6)	(2.5, 75.1)	(19.1, 99.9)
Study Week 2				
n	27	22	23	21
Mean (SD)	21.0 (29.3)	36.1 (25.1)	45.6 (21.1)	60.2 (20.0)
Median (Q1, Q3)	8.9 (5.0, 24.1)	29.9 (25.9, 39.7)	37.6 (35.6, 55.2)	59.3 (44.0, 73.2)
(Min, Max)	5.0 (139.0)	(18.0, 140.9)	(19.7, 95.4)	(33.8, 100.7)
Study Week 4				
n	27	21	24	20
Mean (SD)	20.3 (24.7)	33.8 (10.9)	43.8 (20.1)	60.7 (20.6)
Median (Q1, Q3)	5.0 (5.0, 23.1)	31.3 (24.5, 42.3)	43.7 (30.5, 53.1)	56.8 (48.2, 70.2)
(Min, Max)	5.0 (103.2)	(17.2, 52.0)	(12.9, 90.0)	(18.0, 108.3)
Study Week 8				
n	25	20	18	17
Mean (SD)	13.1 (12.0)	23.9 (11.1)	39.2 (21.0)	49.2 (26.5)
Median (Q1, Q3)	8.9 (5.0, 15.8)	19.4 (15.4, 36.1)	37.2 (24.4, 46.7)	44.1 (34.5, 74.3)
(Min, Max)	5.0 (45.1)	(7.6, 42.7)	(8.0, 106.3)	(2.5, 93.3)
Study Week 12				
n	24	19	18	15
Mean (SD)	15.9 (13.1)	35.0 (25.2)	39.0 (21.3)	46.6 (41.1)
Median (Q1, Q3)	14.0 (5.0, 20.8)	28.4 (19.0, 43.8)	33.3 (28.1, 39.3)	37.5 (22.4, 70.6)
(Min, Max)	5.0 (54.4)	(8.8, 117.1)	(7.0, 105.0)	(2.5, 170.4)

FIG. 7

Week 4 Interferon Exposure Variable Descriptive Statistics.

Interferon Exposure Variable	CSID 80 (N=25)	CSID 120 (N=27)	CSID 160 (N=26)	CSID Total (N=78)
AUC (day*IU/mL) #				
n (Missing)	20 (1)	23 (1)	20 (3)	63 (5)
Mean (SD)	888 (357)	1170 (435)	1650 (431)	1230 (508)
Median (Q1,Q3)	843 (644, 1030)	1110 (793, 1350)	1630 (1330, 2050)	1150 (821, 1640)
(Min,Max)	(475, 2050)	(554, 2110)	(867, 2410)	(475, 2410)
Cavg (IU/mL)				
n (Missing)	20 (1)	23 (1)	20 (3)	63 (5)
Mean (SD)	31.7 (12.7)	41.7 (15.5)	58.8 (15.4)	44.0 (18.1)
Median (Q1,Q3)	30.1 (23.0, 36.9)	39.8 (28.3, 48.0)	58.4 (47.5, 73.3)	41.0 (29.3, 58.7)
(Min,Max)	(17.0, 73.1)	(19.8, 75.3)	(31.0, 86.2)	(17.0, 86.2)
Cmax (IU/mL)				
n (Missing)	20 (1)	23 (1)	20 (3)	63 (5)
Mean (SD)	42.4 (25.4)	63.1 (44.4)	76.7 (23.6)	60.8 (35.5)
Median (Q1,Q3)	37.2 (28.9, 46.9)	51.8 (42.9, 69.0)	70.2 (58.4, 94.9)	51.8 (38.4, 70.7)
(Min,Max)	(20.7, 140.9)	(24.2, 244.1)	(45.9, 137.5)	(20.7, 244.1)
T_{max} (days)				
n (Missing)	20 (1)	23 (1)	20 (3)	63 (5)
Mean (SD)	17.3 (9.8)	15.9 (10.0)	16.1 (9.7)	16.4 (9.7)
Median (Q1,Q3)	14.0 (10.5, 28.0)	14.0 (7.0, 28.0)	14.0 (7.0, 28.0)	14.0 (7.0, 28.0)
(Min,Max)	(3.0, 28.0)	(0.0, 28.0)	(3.0, 28.0)	(0.0, 28.0)
C_{min} (IU/mL)				
n (Missing)	19 (2)	22 (2)	19 (4)	60 (8)
Mean (SD)	24.5 (9.3)	31.2 (15.2)	46.5 (15.8)	33.9 (16.3)
Median (Q1,Q3)	26.2 (17.1, 32.4)	33.3 (20.0, 39.4)	49.5 (37.1, 55.8)	32.8 (20.9, 44.3)
(Min,Max)	(2.5, 39.7)	(2.5, 67.8)	(18.0, 70.1)	(2.5, 70.1)

(Continued)

FIG. 8A

Week 4 Interferon Exposure Variable Descriptive Statistics (Continued)

Interferon Exposure Variable	CSID 80 (N=25)	CSID 120 (N=27)	CSID 160 (N=26)	CSID Total (N=78)
T_{min} (days)				
n (Missing)	19 (2)	22 (2)	19 (4)	60 (8)
Mean (SD)	7.6 (8.0)	13.4 (10.8)	12.7 (10.2)	11.4 (10.0)
Median (Q1,Q3)	3.0 (3.0, 7.0)	7.0 (3.0, 28.0)	7.0 (3.0, 28.0)	7.0 (3.0, 14.0)
(Min,Max)	(3.0, 28.0)	(3.0, 28.0)	(3.0, 28.0)	(3.0, 28.0)
PF%				
n (Missing)	19 (2)	22 (2)	19 (4)	60 (8)
Mean (SD)	46.8 (37.6)	58.1 (39.7)	47.9 (27.3)	51.3 (35.3)
Median (Q1,Q3)	31.9 (23.2, 70.2)	47.8 (27.2, 85.9)	43.2 (23.7, 80.7)	36.7 (24.5, 81.8)
(Min,Max)	(11.3, 141.6)	(11.1, 150.5)	(14.5, 102.1)	(11.1, 150.5)

FIG. 8B

Week 12 Interferon Exposure Variable Descriptive Statistics.

Interferon Exposure Variable	CSID 80 (N=25)	CSID 120 (N=27)	CSID 160 (N=26)	CSID Total (N=78)
AUC (day*IU/mL) #				
n (Missing)	19 (0)	17 (1)	15 (4)	51 (5)
Mean (SD)	2560 (873)	3350 (1320)	4370 (1590)	3350 (1450)
Median (Q1,Q3)	2400 (1710, 3300)	3440 (2420, 3890)	3750 (3360, 5680)	3340 (2250, 3810)
(Min,Max)	(1330, 4440)	(1230, 7090)	(1760, 7980)	(1230, 7980)
C_{avg} (IU/mL)				
n (Missing)	19 (0)	17 (1)	15 (4)	51 (5)
Mean (SD)	30.5 (10.4)	39.9 (15.8)	52.0 (18.9)	39.9 (17.2)
Median (Q1,Q3)	28.5 (20.3, 39.3)	41.0 (28.8, 46.3)	44.7 (40.0, 67.7)	39.7 (26.8, 45.3)
(Min,Max)	(15.8, 52.9)	(14.7, 84.4)	(20.9, 95.0)	(14.7, 95.0)
C_{max} (IU/mL)				
n (Missing)	19 (0)	17 (1)	15 (4)	51 (5)
Mean (SD)	48.2 (31.3)	65.5 (50.2)	75.1 (29.6)	61.9 (39.1)
Median (Q1,Q3)	42.1 (28.4, 51.5)	55.9 (36.9, 68.6)	68.0 (57.6, 80.8)	54.5 (35.7, 70.7)
(Min,Max)	(20.7, 140.9)	(24.2, 244.1)	(49.9, 170.4)	(20.7, 244.1)
T_{max} (days)				
n (Missing)	19 (0)	17 (1)	15 (4)	51 (5)
Mean (SD)	41.9 (33.9)	35.2 (31.9)	27.7 (24.2)	35.5 (30.6)
Median (Q1,Q3)	28.0 (14.0, 84.0)	14.0 (14.0, 56.0)	14.0 (7.0, 56.0)	28.0 (14.0, 56.0)
(Min,Max)	(3.0, 84.0)	(0.0, 84.0)	(3.0, 84.0)	(0.0, 84.0)
C_{min} (IU/mL)				
n (Missing)	18 (1)	16 (2)	15 (4)	49 (7)
Mean (SD)	18.6 (9.5)	25.5 (13.8)	30.4 (17.9)	24.4 (14.5)
Median (Q1,Q3)	16.7 (11.0, 26.2)	29.6 (15.2, 34.0)	30.8 (19.1, 46.1)	25.4 (12.9, 33.1)
(Min,Max)	(2.5, 38.1)	(2.5, 49.9)	(2.5, 53.8)	(2.5, 53.8)

(Continued)

FIG. 9A

Week 12 Interferon Exposure Variable Descriptive Statistics (Continued)

Interferon Exposure Variable	CSID 80 (N=25)	CSID 120 (N=27)	CSID 160 (N=26)	CSID Total (N=78)
T_{min} (days)				
n (Missing)	18 (1)	16 (2)	15 (4)	49 (7)
Mean (SD)	41.8 (33.2)	25.9 (30.5)	56.5 (30.5)	41.1 (33.2)
Median (Q1,Q3)	56.0 (3.0, 56.0)	10.5 (3.0, 28.0)	56.0 (28.0, 84.0)	28.0 (7.0, 84.0)
(Min,Max)	(3.0, 84.0)	(3.0, 84.0)	(7.0, 84.0)	(3.0, 84.0)
PF%				
n (Missing)	18 (1)	16 (2)	15 (4)	49 (7)
Mean (SD)	89.4 (62.3)	83.7 (34.0)	92.5 (65.5)	88.5 (54.8)
Median (Q1,Q3)	73.9 (53.8, 114.0)	84.1 (47.2, 113.7)	68.0 (50.9, 135.6)	75.7 (50.9, 114.9)
(Min,Max)	(16.5, 277.7)	(34.3, 146.9)	(31.2, 286.0)	(16.5, 286.0)

FIG. 9B

Power Model Analysis – Detailed Results
Week 4 IFN Exposure Variable Power Model Analysis Results.

CSID arms only.

IFN Exposure Variable	β Estimate (95% CI)	95% CI for β Includes:		CI Interpreted as Evidence of:
		0	1	
C _{avg} (IU/mL)	0.91 (0.60, 1.2)	N	Y	Dose-Proportionality
C _{max} (IU/mL)	0.94 (0.56, 1.3)	N	Y	Dose-Proportionality
C _{min} (IU/mL)	0.95 (0.33, 1.6)	N	Y	Dose-Proportionality
PF%	0.22 (-0.44, 0.87)	Y	N	Dose-Independence

Note: None of the interferon exposure variables had a statistically significant ($p < 0.05$) quadratic term.

FIG. 10

Week 4 IFN Exposure Variable Power Model Analysis Results.
CSID arms only.

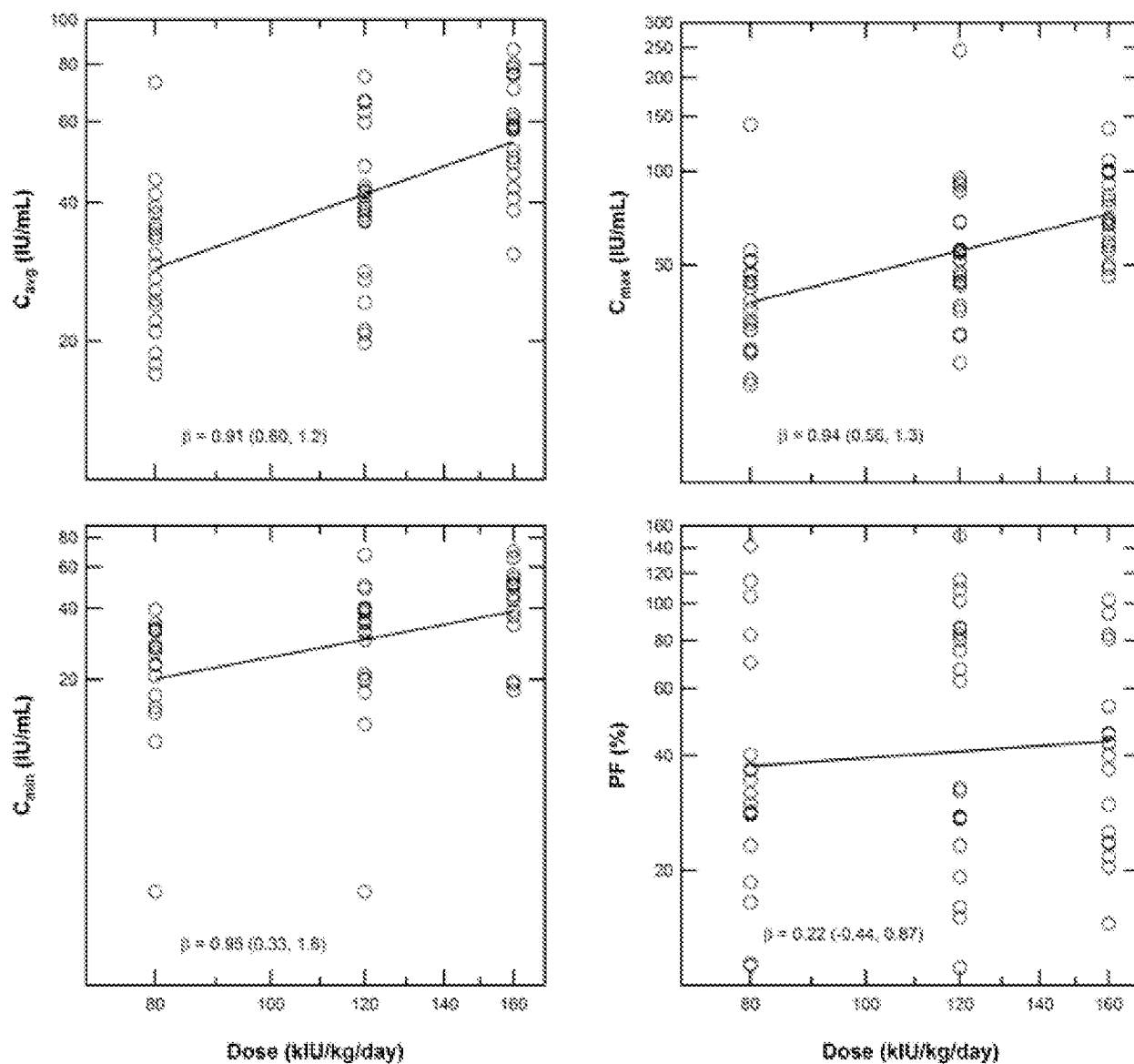


FIG.11

Week 12 IFN Exposure Variable Power Model Analysis Results.

CSID arms only.

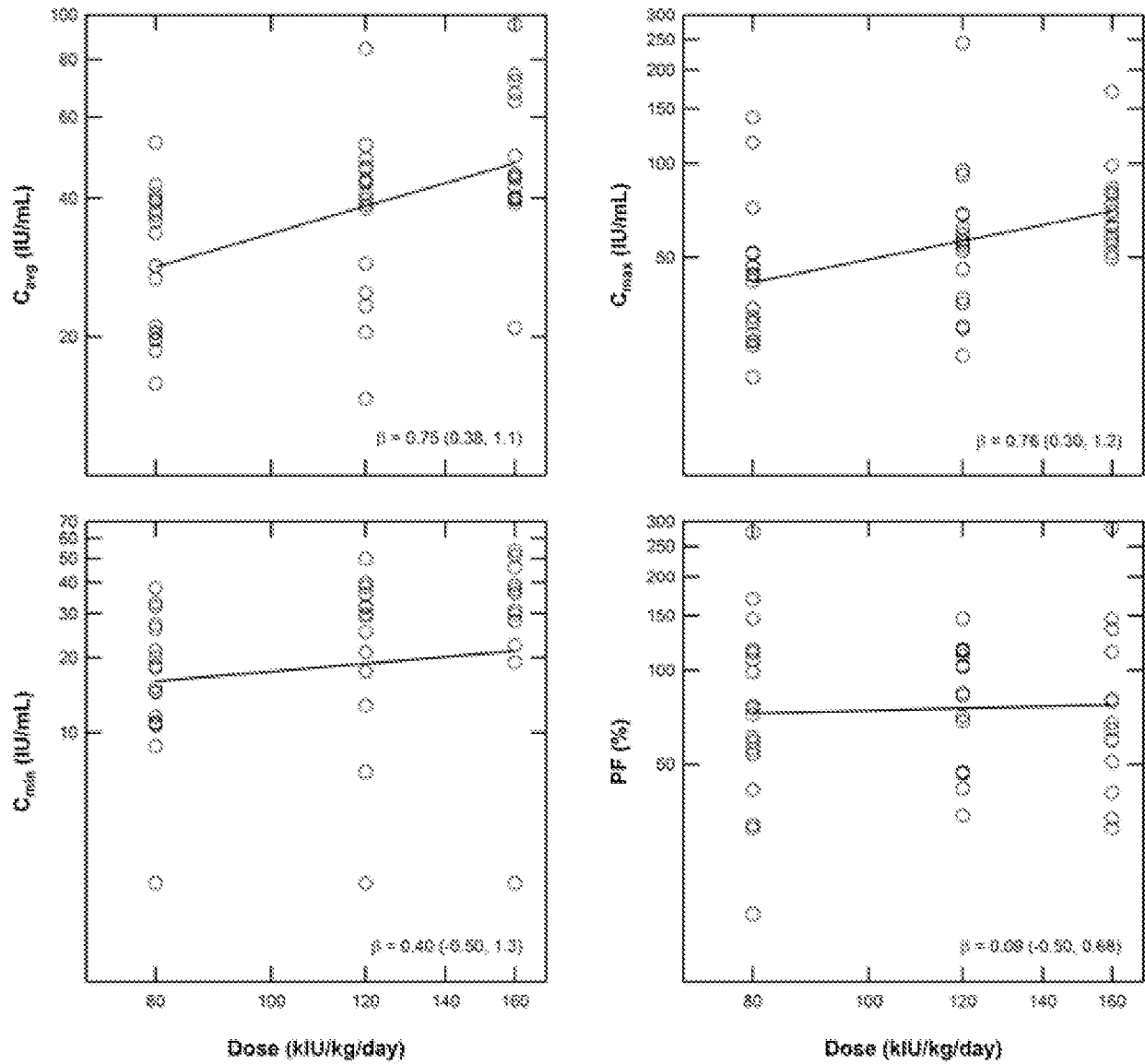
IFN Exposure Variable	β Estimate (95% CI)	95% CI for β Includes:		CI Interpreted as Evidence of:
		0	1	
C _{avg} (IU/mL)	0.75 (0.38, 1.1)	N	Y	Dose-Proportionality
C _{max} (IU/mL)	0.76 (0.30, 1.2)	N	Y	Dose-Proportionality
C _{min} (IU/mL)	0.40 (-0.50, 1.3)	Y	Y	Inconclusive
PF%	0.090 (-0.50, 0.68)	Y	N	Dose-Independence

Note: None of the interferon exposure variables had a statistically significant ($p < 0.05$) quadratic term.

FIG.12

Week 12 IFN Exposure Variable Power Model Analysis Results.

CSID arms only.

**FIG.13**

Analysis of PD Relationships

Multivariate Regression for Week 4 C_{min} as a Predictor of RVR and Discontinuation

(A) Independent Variables used in the Multivariate Regression Analysis.

Categorical Variables	Continuous Variables
1. Black/Hispanic vs. Other	1. Week 4 C_{min}
2. Gender	2. Week 4 C_{avg}
3. IL28B Genotype (CC, CT, TT, unknown)	3. Week 4 C_{max}
4. HCV Genotype (1a, 1b)	4. Week 4 $PF\%$
5. Fibrosis Score (No or minimal fibrosis, Portal Fibrosis, Bridging Fibrosis, Cirrhosis)	5. Age
	6. Baseline HCV RNA
	7. BMI

(B) Multivariate Regression Results: Week 4 Exposure Variables & Baseline Characteristics as Predictors of RVR.

Variable	Odds Ratio: Point Estimate (95% Confidence Interval)	p-value
1. Week 4 C_{min}	1.083 (1.023, 1.146)	0.0060
2. Age	0.882 (0.802, 0.971)	0.0103
3. IL28B		0.0330
CC vs. CT	11.802 (1.617, 86.143)	
CC vs. TT	12.346 (1.011, 150.726)	

(C) Multivariate Regression Results: Week 4 Exposure Variables & Baseline Characteristics as Predictors of Discontinuation before Week 12.

Variable	Odds Ratio: Point Estimate (95% Confidence Interval)	p-value
1. Week 4 C_{min}	1.053 (1.009, 1.100)	0.0185

FIG.14

Receiver Operating Characteristic Curves for Week 4 Cmin as a Predictor of RVR and Discontinuation

Receiver Operating Characteristic Curve for Week 4 IFN Cmin as a Predictor for RVR.

CSID subjects only.

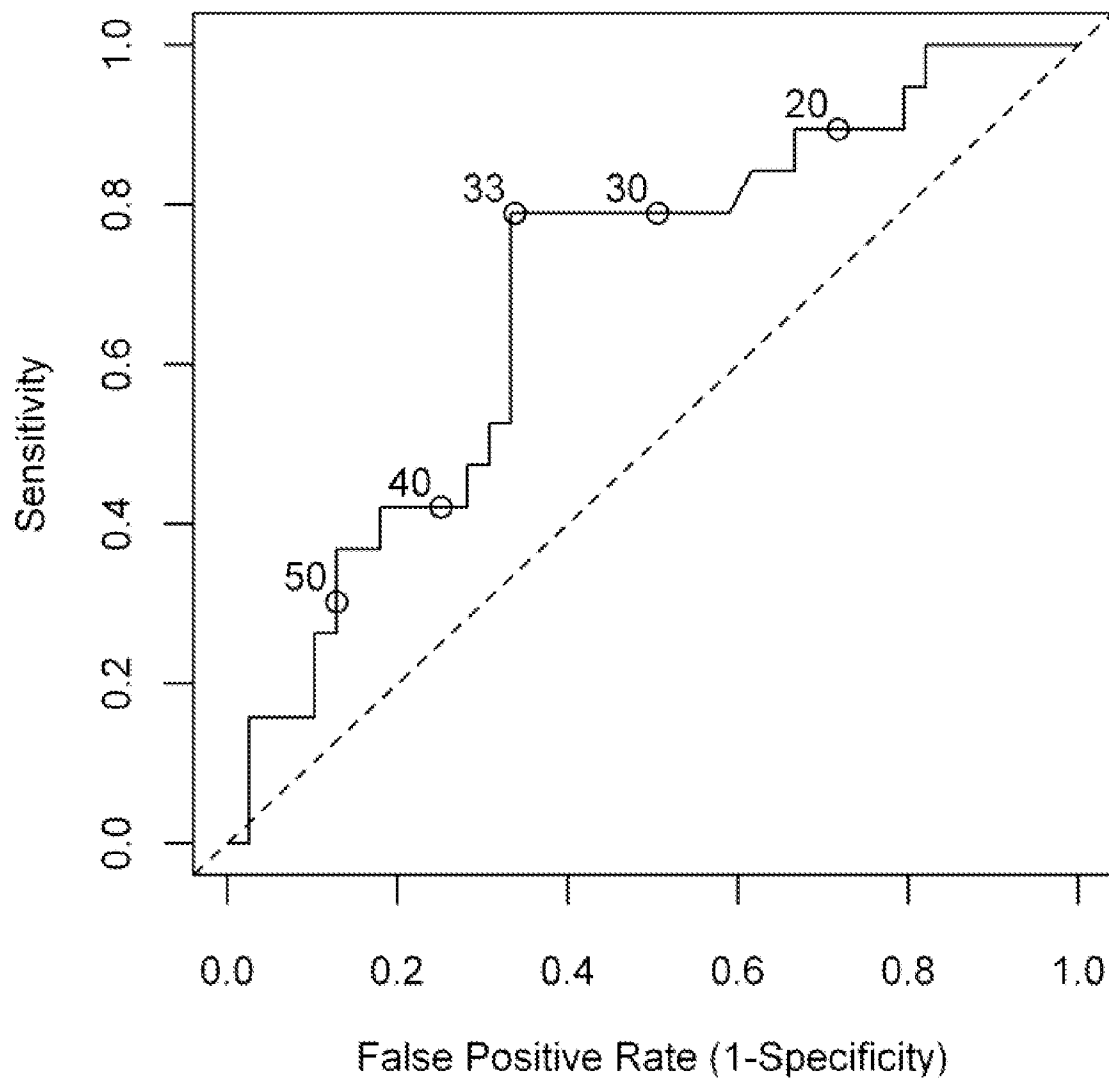


FIG.15

Receiver Operating Characteristic Curve for Week 4 IFN Cmin as a Predictor for Discontinuation before Week 12.

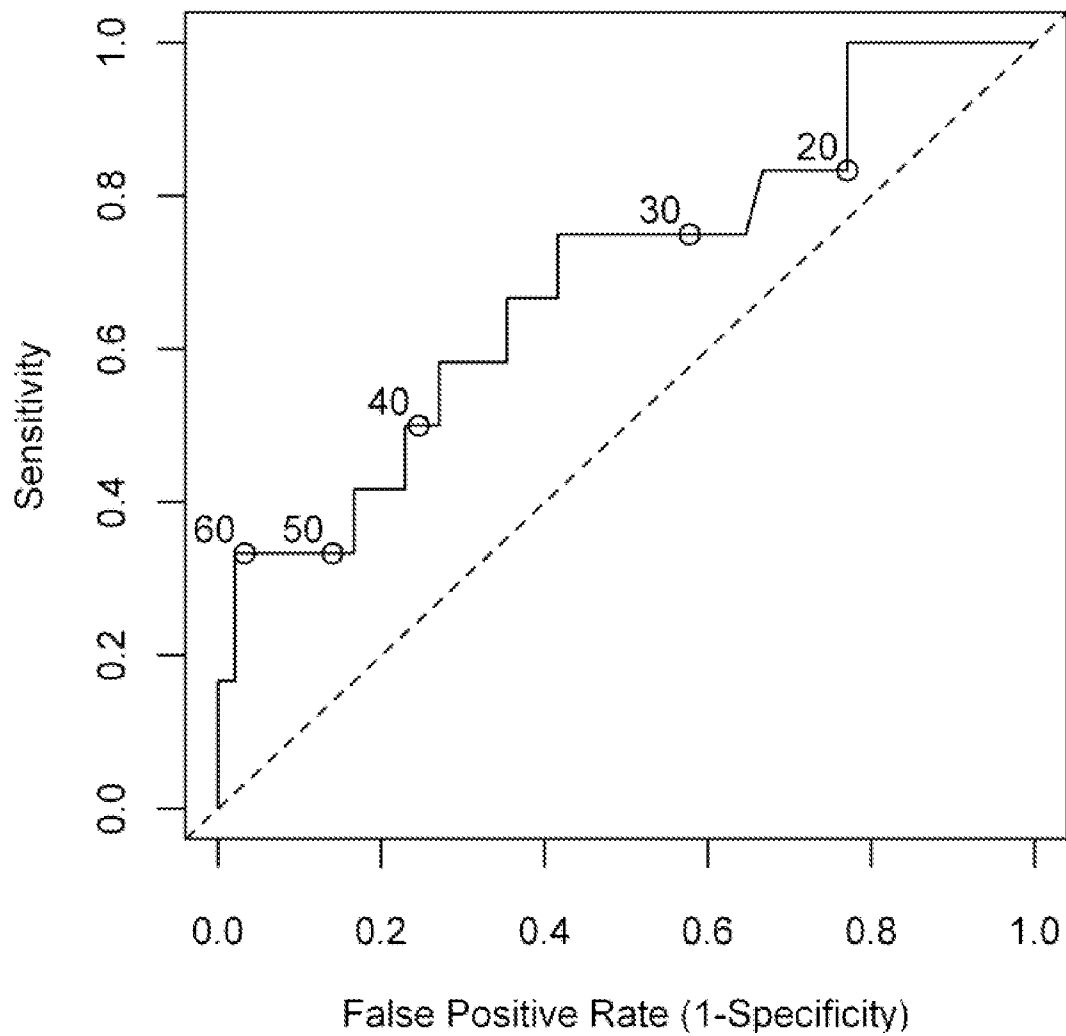


FIG.16

**Multivariate Contingency Table for Week 4 C_{min} as a Predictor for
RVR and Therapy Discontinuation**

		Total Number of Patients in C _{min} Range	Discontinued Between Weeks 4 and 12			
			No		Yes	
			RVR		RVR	
			No	Yes	No	Yes
Week 4 C _{min}	< 32.8 IU/mL	30	24/30 (80%)	3/30 (10%)	2/30 (7%)	1/30% (3%)
	32.8 - 60.7 IU/mL	23	8/23 (35%)	10/23 (43%)	3/23 (13%)	2/23 (9%)
	> 60.7 IU/mL	5	0 (0%)	1/5 (20%)	2/5 (40%)	2/5 (40%)

FIG.17

Day 3 IFN Concentration as a Predictor of RVR

(A) Independent Variables used in the Multivariate Regression Analysis.

Categorical Variables	Continuous Variables
1. Black/Hispanic vs. Other	1. Day 3 Serum IFN Concentration
2. Gender	2. Age
3. IL28B Genotype (CC, CT, TT, unknown)	3. Baseline HCV RNA
4. HCV Genotype (1a, 1b)	
5. Fibrosis Score	
(No or minimal fibrosis, Portal Fibrosis, Bridging Fibrosis, Cirrhosis)	

(B) Multivariate Regression Results: Day 3 Serum IFN Concentration & Baseline Characteristics as Predictors of RVR.

Variable	Odds Ratio: Point Estimate (95% Confidence Interval)	p-value
1. Day 3 IFN Concentration	1.034 (1.002, 1.067)	0.0389
2. Baseline HCV RNA	0.313 (0.108, 0.909)	0.0327
3. IL28B		0.0167
CC vs. CT	8.055 (1.528, 42.464)	
CC vs. TT	20.722 (1.647, 260.703)	

FIG.18

Contingency Table for Day 3 IFN Concentration as a Univariate Predictor for RVR and Therapy Discontinuation.

CSID Subjects only.

RVR	Day 3 IFN Concentration (Critical Value 32.8 = IU/mL)	
	< Critical	≥ Critical
No	21	30
Yes	1	19
P-value	0.003	
Negative Predictive Value	21/22 (95%)	NA
Positive Predictive Value	NA	19/49 (39%)

FIG.19

Receiver Operating Characteristic Curve for Day 3 IFN Concentration as a Predictor for RVR.

CSID subjects only.

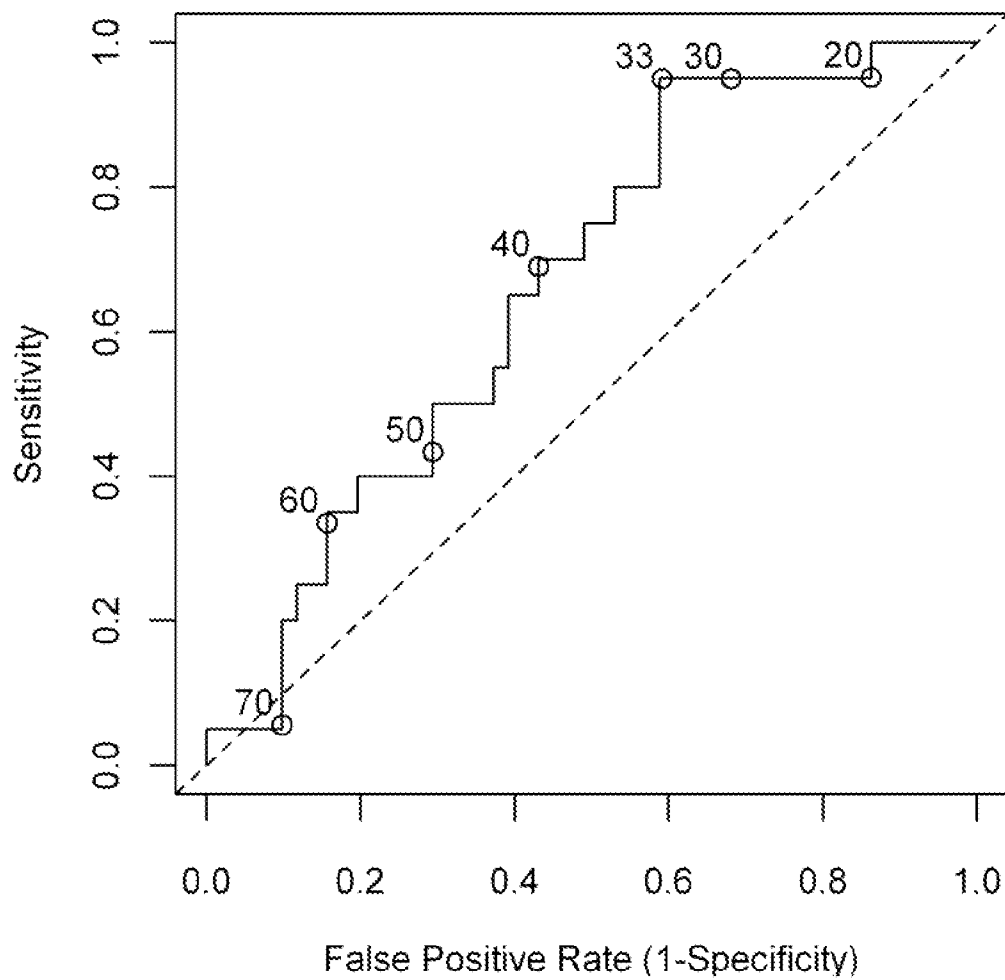


FIG. 20

Correlation of Week 4 Viral Decay with Week 4 IFN Exposure Variables

Correlation of Week 4 IFN Exposure Variables with Viral Decay.

CSID subjects only.

Interferon Exposure Variable	Correlation with Week 4 Viral Decay			Number of Observations Included
	Pearson's R (p-value)	Spearman's Rho (p-value)	Kendall's Tau (p-value)	
C _{avg} (IU/mL)	0.12 (0.345)	0.088 (0.504)	0.062 (0.483)	60
C _{max} (IU/mL)	0.17 (0.198)	0.065 (0.623)	0.051 (0.566)	60
C _{min} (IU/mL)	0.18 (0.170)	0.12 (0.376)	0.077 (0.394)	58
PF%	-0.23 (0.086)	-0.21 (0.112)	-0.16 (0.085)	58

FIG.21

Scatterplots of Week 4 Viral Decay vs. Week 4 IFN Exposure Variables.

CSID subjects only.

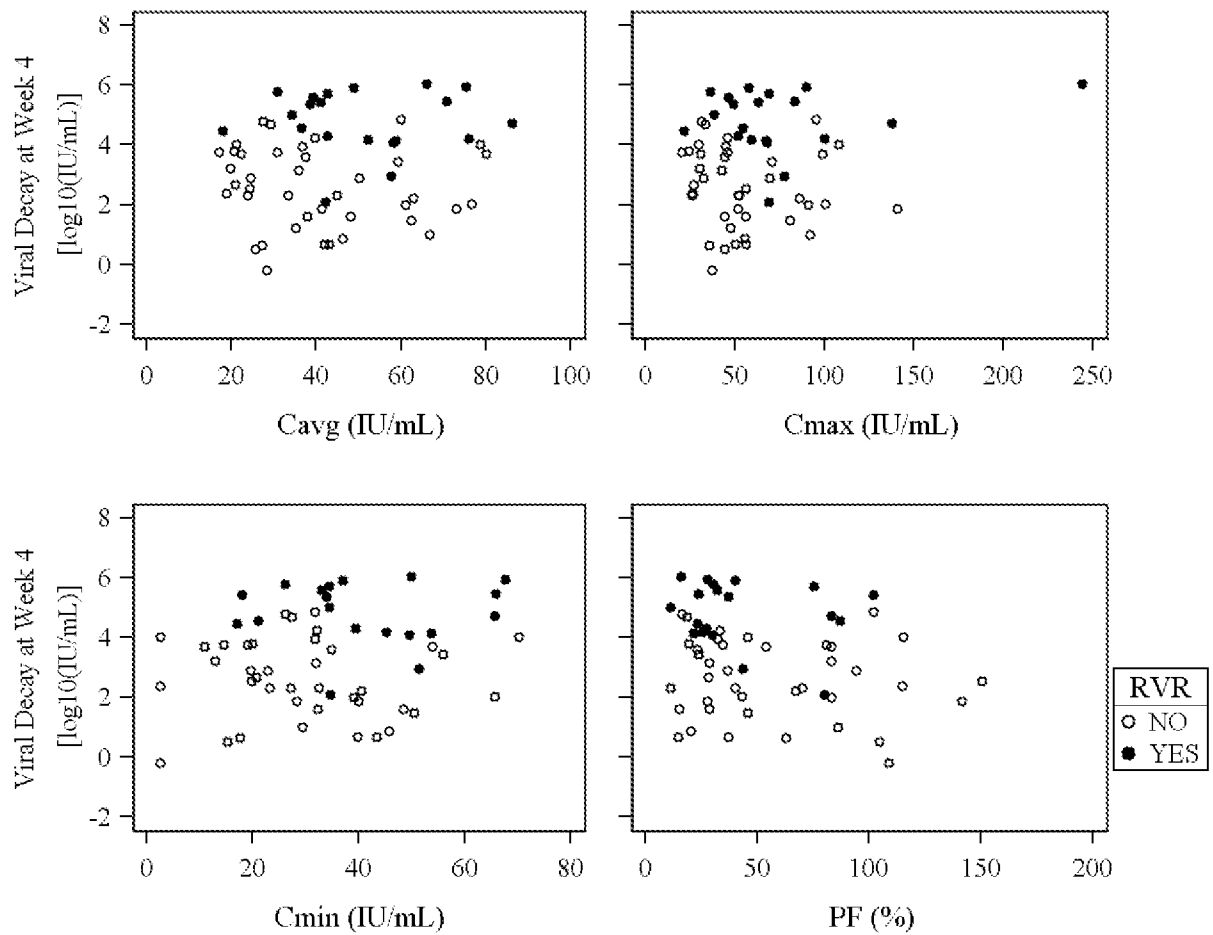


FIG.22

RVR and Viral Kinetics in Subjects with Refractory Host or Virus Genotypes

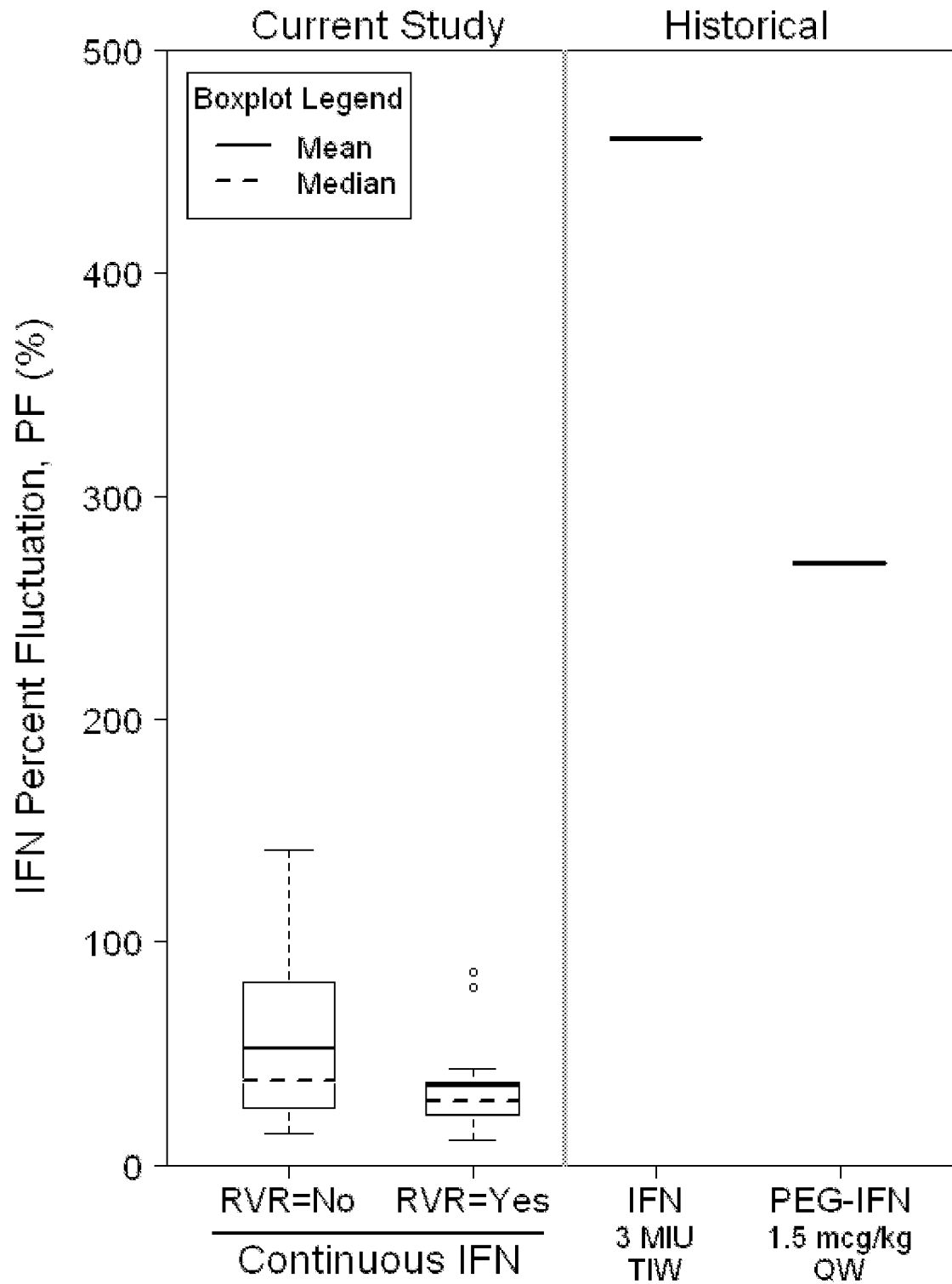
(A) RVR by Treatment Arm and Hepatitis C Virus Subgenotype.

HCV Subgenotype	PEG (N=28)	CSID		
		80 (N=25)	120 (N=27)	160 (N=26)
1a	2/24 (8%)	4/19 (21%)	6/23 (26%)	9/19 (47%)
1b	0/4 (0%)	0/6 (0%)	1/4 (25%)	2/7 (29%)

(B) RVR by Treatment Arm and Host IL28B Genotype.

IL28B Genotype	PEG (N=28)	CSID		
		80 (N=25)	120 (N=27)	160 (N=26)
CC	1/5 (20%)	4/8 (50%)	2/6 (33%)	4/4 (100%)
CT	0/5 (0%)	0/7 (0%)	3/10 (30%)	3/7 (43%)
TT	0/6 (0%)	0/3 (0%)	0/0 (NA)	2/7 (29%)

FIG.23

**FIG.24A**

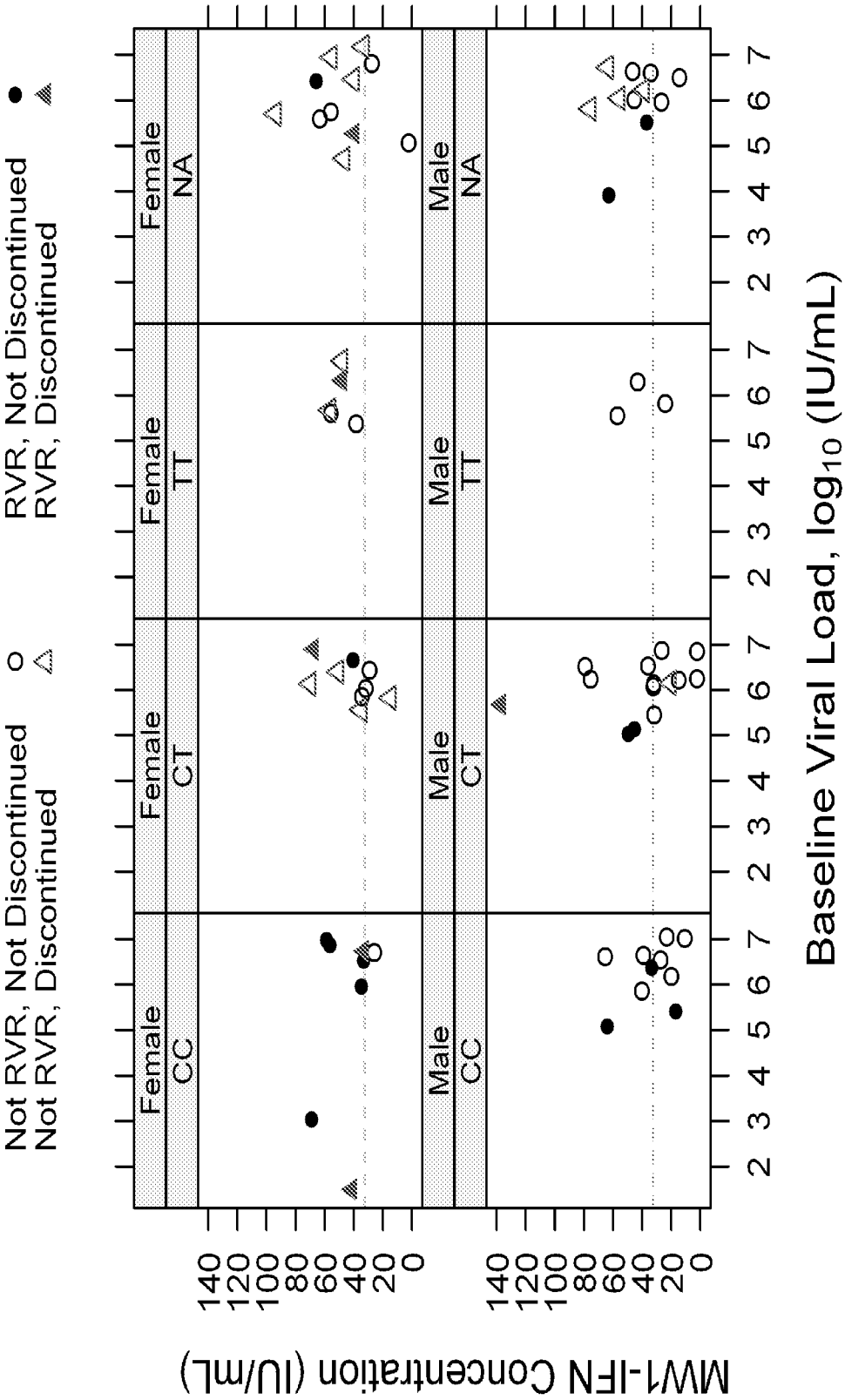


FIG. 24B

Neopterin PD Response

(A) Time-Averaged Neopterin Response from Individual Baseline (Eavg).

Neopterin E_{avg} (nmol/L)	PEG (N=28)	CSID			
		80 (N=25)	120 (N=27)	160 (N=26)	Total (N=78)
Week 4					
n (Missing)	24 (4)	21 (0)	22 (2)	21 (2)	64 (4)
Mean (SD)	9.3 (4.7)	16.9 (8.3)	17.5 (8.5)	16.9 (7.8)	17.1 (8.1)
Median (Q1,Q3)	9.0 (6.8, 10.5)	17.0 (10.4, 21.2)	16.7 (12.9, 20.2)	15.6 (11.8, 22.0)	16.6 (11.8, 20.7)
(Min,Max)	(2.1, 20.9)	(-1.0, 37.9)	(5.7, 41.5)	(7.7, 40.8)	(-1.0, 41.5)
Week 12					
n (Missing)	20 (5)	18 (1)	15 (3)	14 (5)	47 (9)
Mean (SD)	7.6 (3.5)	17.2 (9.4)	16.6 (8.7)	14.7 (10.0)	16.3 (9.2)
Median (Q1,Q3)	7.4 (5.8, 8.9)	16.9 (11.4, 21.5)	12.7 (11.2, 18.4)	13.6 (10.0, 16.5)	14.8 (11.1, 18.4)
(Min,Max)	(2.3, 15.7)	(-0.8, 42.4)	(8.2, 38.2)	(1.8, 46.2)	(-0.8, 46.2)

(B) Time-Averaged Neopterin Response from Individual Baseline (Eavg).

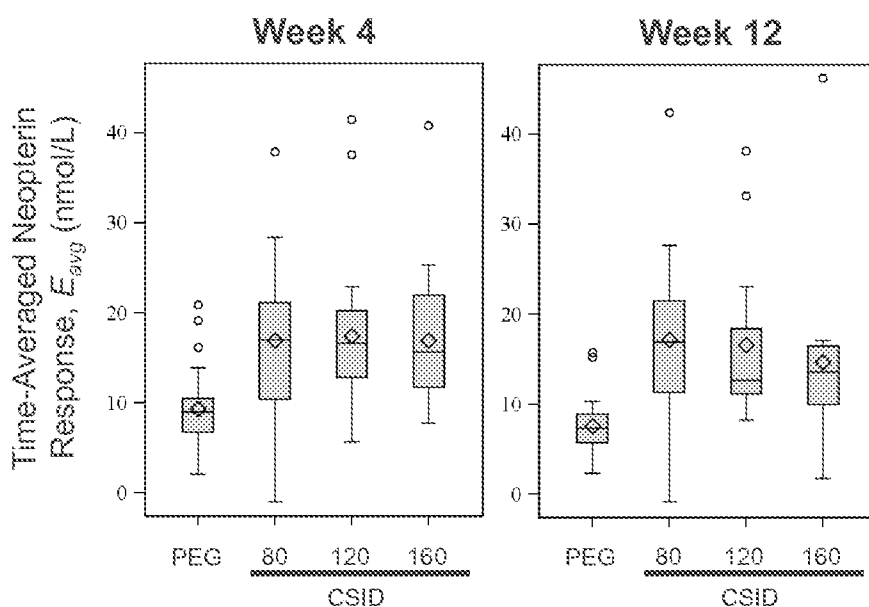


FIG.25

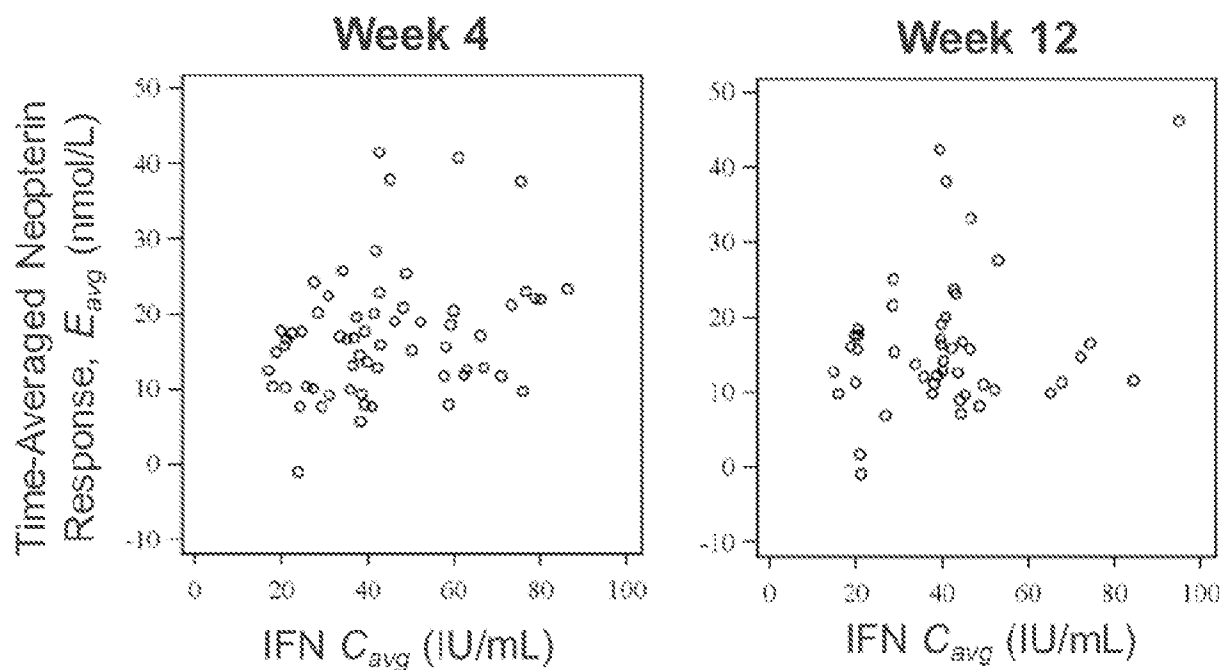
(A) Correlation of Neopterin Response with IFN Exposure.

CSID arms only.

Neopterin E_{avg} (nmol/L)	Correlation with IFN C_{avg} Through Week 4 or Week 12			Number of Observations Included
	Pearson's R (p-value)	Spearman's Rho (p-value)	Kendall's Tau (p-value)	
Week 4	0.30 (0.020)	0.32 (0.012)	0.21 (0.017)	62
Week 12	0.27 (0.068)	0.042 (0.782)	0.045 (0.653)	47

(B) Scatterplots of Neopterin E_{avg} vs. IFN C_{avg} .

CSID subjects only.

**FIG.26**

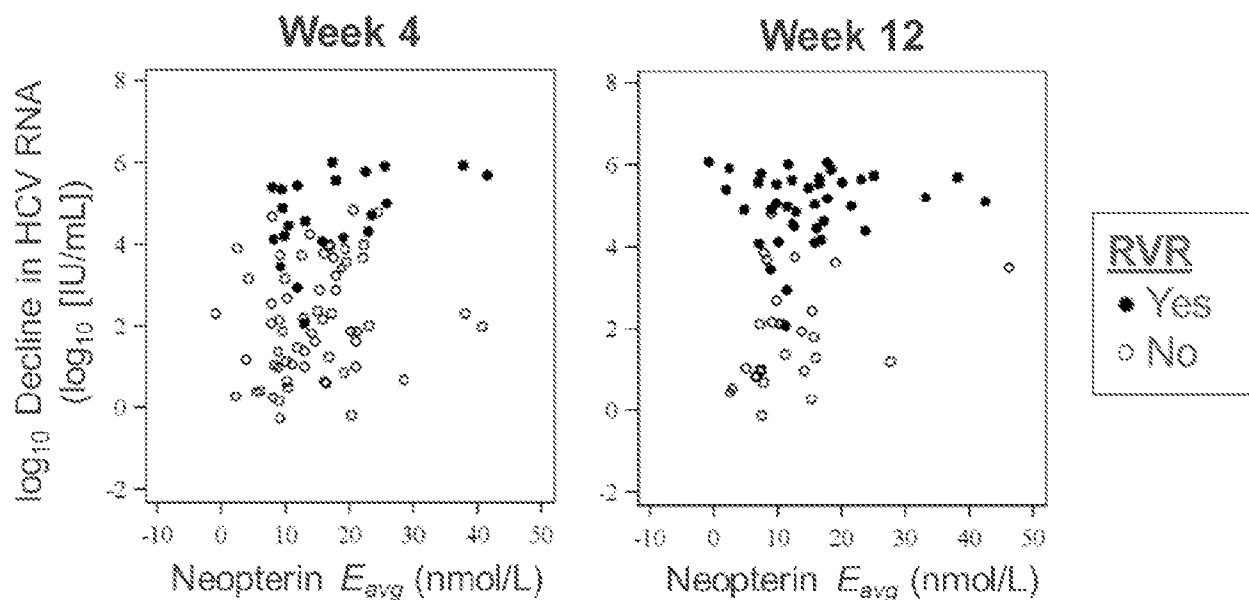
(A) Correlation of Neopterin Response with Viral Decay.

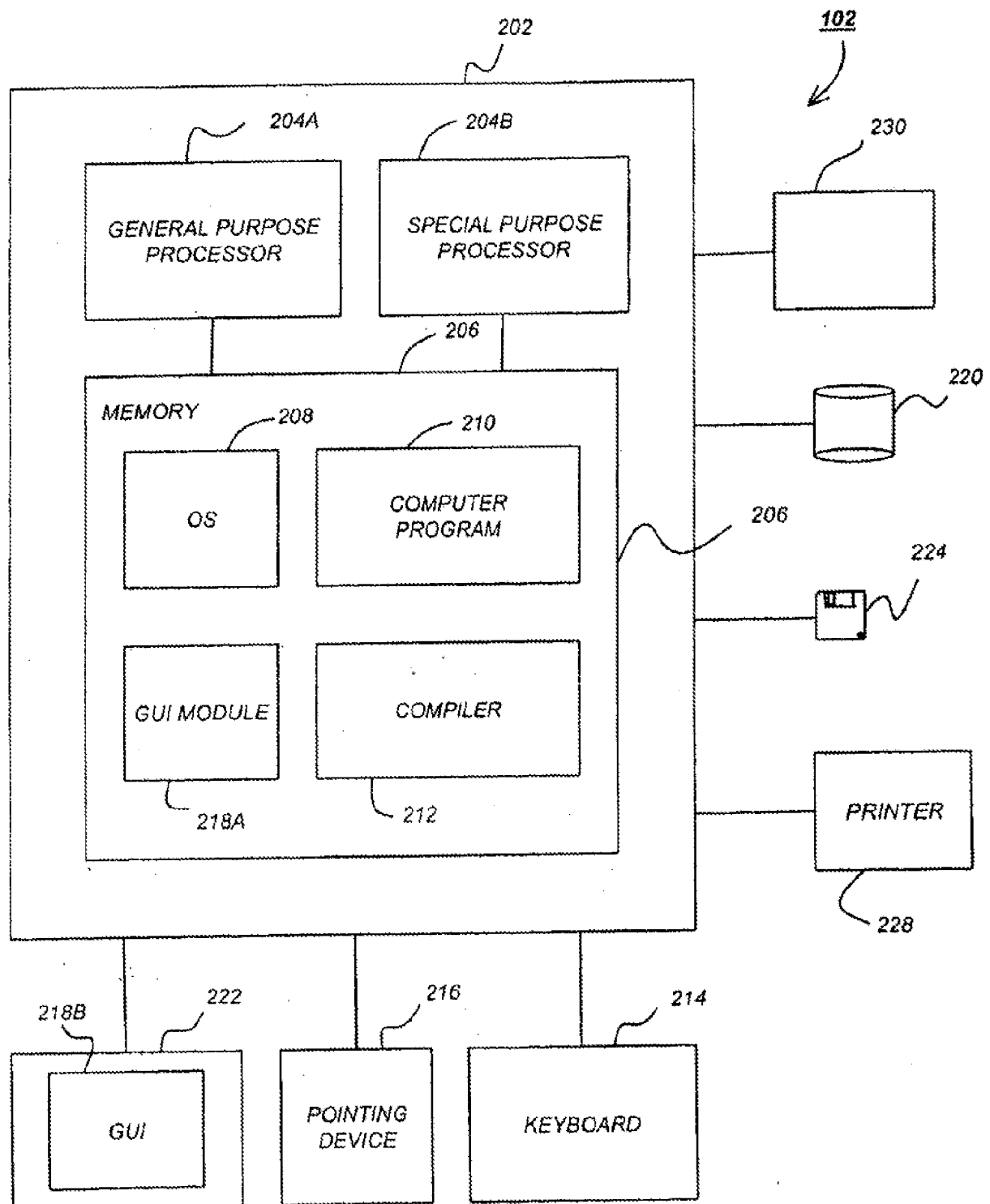
PEG and CSID subjects.

Neopterin E_{avg} (nmol/L)	Correlation with Viral Decay Through Week 4 or Week 12			Number of Observations Included
	Pearson's R (p-value)	Spearman's Rho (p-value)	Kendall's Tau (p-value)	
Week 4	0.28 (0.008)	0.28 (0.008)	0.20 (0.007)	86
Week 12	0.25 (0.044)	0.29 (0.018)	0.21 (0.013)	67

(B) Scatterplots of Viral Decay vs. Neopterin E_{avg} .

PEG and CSID subjects.

**FIG.27**

**FIG. 28A**

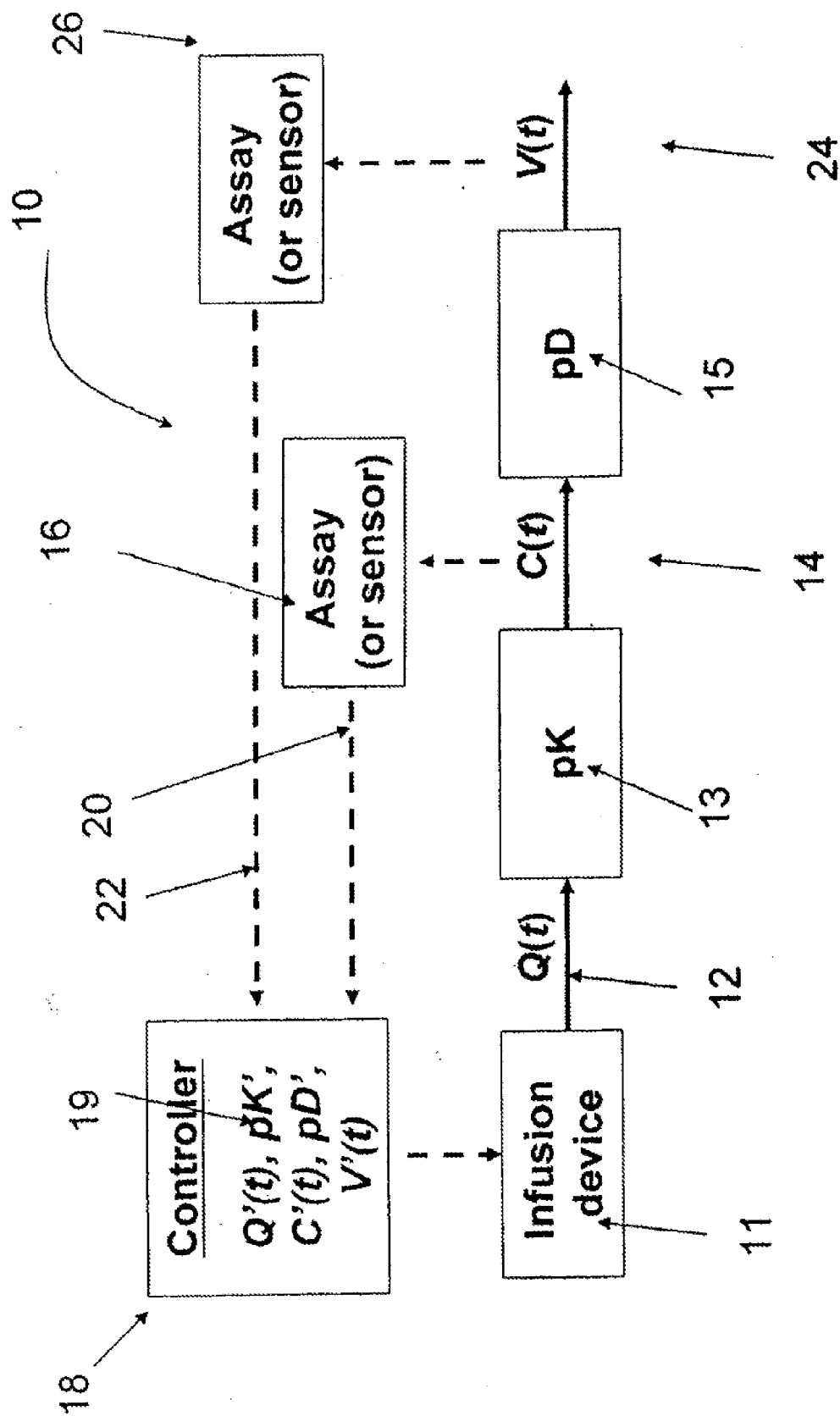


FIG. 28B

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/026792

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K38/21 A61P31/12 A61M5/172 G01N33/50 G06F19/00 ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K A61P A61M G01N G06F		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, COMPENDEX, EMBASE, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2011/027229 A1 (VAN ANTWERP WILLIAM P [US] ET AL) 3 February 2011 (2011-02-03) cited in the application abstract; claims 15-19; figures 1-8; examples 1-3 paragraph [0138]	1-20
X	WO 2009/120991 A2 (MEDTRONIC INC [US]; VAN ANTWERP WILLIAM P [US]; HAMLEN ROBERT C [US];) 1 October 2009 (2009-10-01) cited in the application abstract; claims 20-24; examples 1-2 ----- -/-	1-20
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 16 May 2012		Date of mailing of the international search report 24/05/2012
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Laffargue-Haak, T

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2012/026792

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. (means)

☐	on paper
☒	in electronic form
 - b. (time)

☒	in the international application as filed
☐	together with the international application in electronic form
☐	subsequently to this Authority for the purpose of search
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/026792

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/026792

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCHENKER S ET AL: "Activity and tolerance of a continuous subcutaneous infusion of interferon-alpha2b in patients with chronic hepatitis C", JOURNAL OF INTERFERON AND CYTOKINE RESEARCH, MARY ANN LIEBERT, NEW YORK, NY, US, vol. 17, no. 11, 1 November 1997 (1997-11-01), pages 665-670, XP002903597, ISSN: 1079-9907 abstract * p. 666, Study design * * Fig. 3, patient 208 * -----	1-4, 10-12, 15-20
T	HAMLEN C ET AL: "PK/PD modeling of continuous interferon therapy for HCV", HEPATOLOGY, WILLIAMS AND WILKINS, BALTIMORE, MD, US, vol. 48, no. 4 Suppl.S, 1 October 2008 (2008-10-01), page 534A, XP002602733, ISSN: 0270-9139 the whole document -----	1-20
X,P	WO 2011/059824 A2 (MEDTRONIC INC [US]; VAN ANTWERP WILLIAM P [US]; HAMLEN ROBERT C [US];) 19 May 2011 (2011-05-19) cited in the application abstract -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2012/026792

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2011027229 A1	03-02-2011	EP 2459211 A1	06-06-2012
		US 2011027229 A1	03-02-2011
		WO 2011014882 A1	03-02-2011

WO 2009120991 A2	01-10-2009	EP 2286359 A2	23-02-2011
		US 2011184379 A1	28-07-2011
		WO 2009120991 A2	01-10-2009

WO 2011059824 A2	19-05-2011	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-9, 15-20

Method of characterizing a pharmacokinetic profile and a method of administrating a therapeutic regimen comprising interferon-alpha

2. claims: 10-14

A system for administrating interferon-alpha comprising a continuous infusion pump and a processor
