

Quantify HCV Clinical Outcomes Database

Release 3.0 February 8, 2011

1. Summary Information

The current version of the database includes clinical safety and efficacy information on all long-acting pegylated interferons as well as newer small molecules currently approved or in development for Hepatitis C Virus infection (HCV) with or without co-infection with Human Immunodeficiency Virus (HIV). Information on older treatment options (non-pegylated interferons) are included if they were used as active controls.

Table 1. Summary information

Format	Excel
#Trials /# Arms	139 /558
# Patients	36,426
# Rows of Data	11,629
Last Updated	20-June-2010
Compounds	albinterferon alfa-2b, consensus interferon, interferon alfa-2a, interferon alfa-2b, interferon alfacon-1, peginterferon alfa-2a, peginterferon alfa-2b, peginterferon lambda, ribavirin, taribavirin, ABT-072, ABT-333, ABT-450, ACH-1625, ANA598, BI 201335, BI 207127, BMS-790052, BMS-650032, Boceprevir, Danoprevir, Debio-025, GS-9256, GS-9450, HCV-796, IDX184, MK-3281, MK-7009, Narlaprevir, PF-00868554, PSI-7851, R1626, R7128, R7227, TMC435, Taribavirin, Telaprevir, VCH-222, ritonavir
Key efficacy end points	Viral load, SVR, RVR, EVR, ETR, etc
Key safety/tolerability end points	Adverse event percentages, histology endpoints, dose reductions, dropouts for different reasons
Key PK endpoints	AUC, Cmax, Trough, t1/2, Concentration
Strata	Genotype, early response, baseline viral load and others

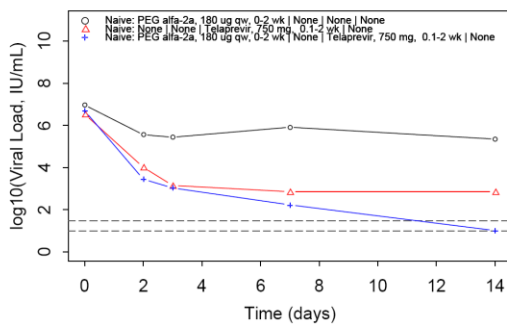
2. Features and benefits

Key Features:

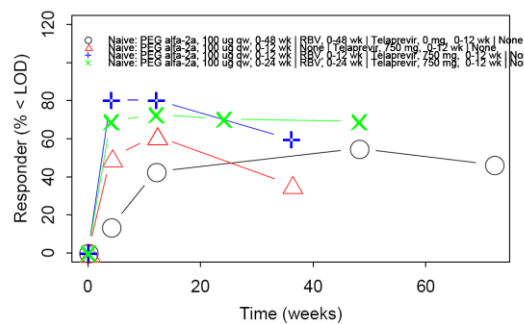
- **Comprehensive:** includes information for marketed drugs as well as drugs in development; data sources include journal publications, conference posters, regulatory reviews, etc.
- **Ease of tracking:** all clinical trial publications are listed in a separate source database and linked to unique clinical trial names
- **Flexibility:** the database design allows for quick updates as well as expansions to include additional indications/drugs/endpoints/trials
- **Model-friendliness:** designed and reviewed by experienced modelers to ensure highest quality and usability for modeling and simulation to support drug development strategies
- **Customizability:** can be augmented with clinical trial data proprietary to the client (this information goes into a separate proprietary database and will be owned by the client)

Example Applications:

[20] Forestier N (2007)

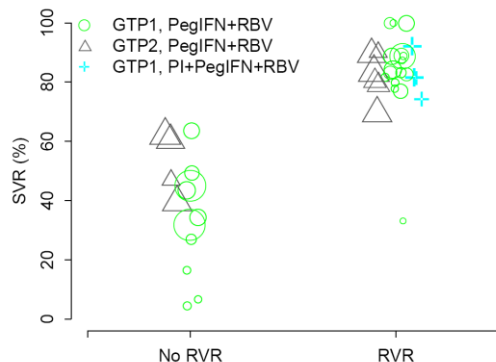


[32] Hezode C (2009) PROVE2



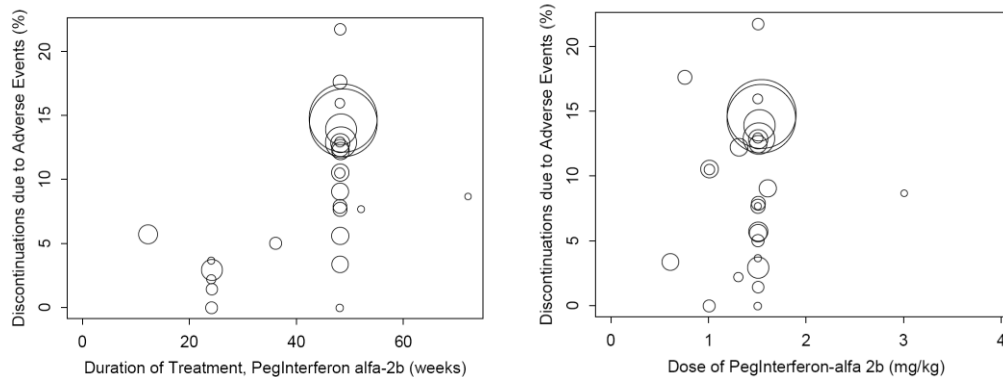
Question: What is the relationship between short-term viral decline and long-term viral response for a new protease inhibitor?

Approach: Use telaprevir (and other PIs) data to derive a viral dynamics model linking short-term (left) to long-term therapy (right).



Question: Can RVR be used to predict SVR for the newer protease inhibitors?

Approach: Compare SVR in responder populations to determine whether RVR to SVR correlations are consistent.



Question: For a new small molecule, is it better to decrease the dose or duration of concomitant interferons to minimize discontinuations due to adverse events?

Approach: Compare discontinuations due to adverse events vs. dose and duration of pegylated interferon trials.

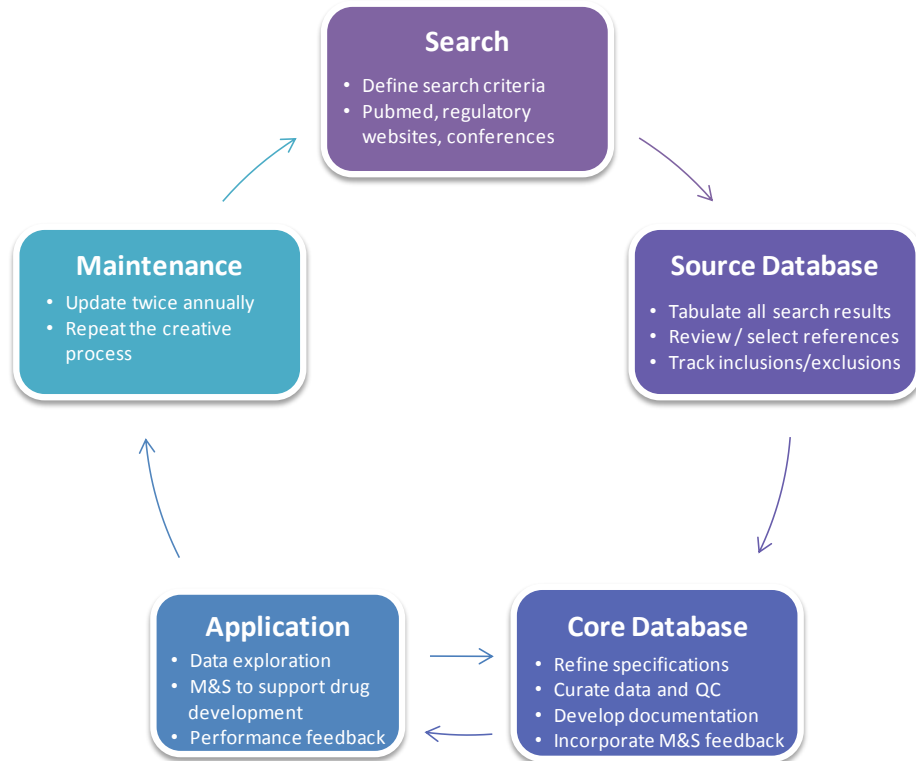
Why use our databases:

- Designed and managed by experienced modelers. There is a strong emphasis on making it easy to extract analysis datasets from the database
- Provides most relevant data to support clients' needs for quantitative decision making
- Contains up-to-date and high quality data so that it is always readily available to provide timely analysis required to support critical clinical trial decisions
- Supported by additional services such as modeling and simulation consulting services and custom curation services (by our partner, GVK Bio)

3. Organization and Structure

This product consists of two databases, the *HCV source database* and the *HCV clinical outcomes database*. The *source database* is a database that maintains the sources of information identified by searches and reviewed for inclusion or exclusion from the database. The *clinical outcomes database* contains the information on trial, treatment and patients characteristics and safety and efficacy results of the trials identified for inclusion in the database.

The following is a flowchart showing the process with which databases are created, optimized and updated.



3. Overview of the HCV Source Database

The primary data sources were controlled clinical trials published in the medical literature or available through FDA or EMEA websites. Additional data sources include information available from AASLD and EASL conferences obtained from natap.org.

705 references (PubMed search results, FDA and EMEA documents, abstracts from NATAP) were identified and documented in the source database, of which a total of 139 unique trials were selected for inclusion in the database after careful review of the abstracts. The detailed reference information as well as reasons for exclusion are recorded to facilitate future expansion of the database.

4. Overview of the HCV Clinical Outcomes Database

The following randomized controlled trials provided information on safety and efficacy that were used for registration with the FDA and EMEA as primary or supportive evidence.

Table 2. List of registration trials in the database

Drug	Study	Description
<i>Peginterferon alfa-2a</i>	NV15489	Dose-finding, monotherapy
	NV15495	Monotherapy
	NV15496	Monotherapy
	NV15497	Monotherapy
	NV15801	Combotherapy
	NV15942	Combotherapy duration, dosing by genotype
	NR16071	Combotherapy, normal ALT
	NR15961	Combotherapy, HIV
	<i>Peginterferon alfa-2b</i>	C/I98-580
C/I97-010		Combotherapy
PO2080		Combotherapy, HIV
PO1017		Combotherapy, HIV

The clinical outcomes database contains information from 139 trials, representing 558 unique treatment arms and about 36,426 patients. There are a total of 11,629 rows in the database. Each row contains the information for an endpoint in one arm of a trial at a specific point in time. The tables below provide an overview of the available data for randomized treatments. The following table shows the available information for interferon and newer small molecules. Information on consensus interferon and unknown interferon is not shown in the table. The table shows the number of trials, number of treatment arms and number of patients.

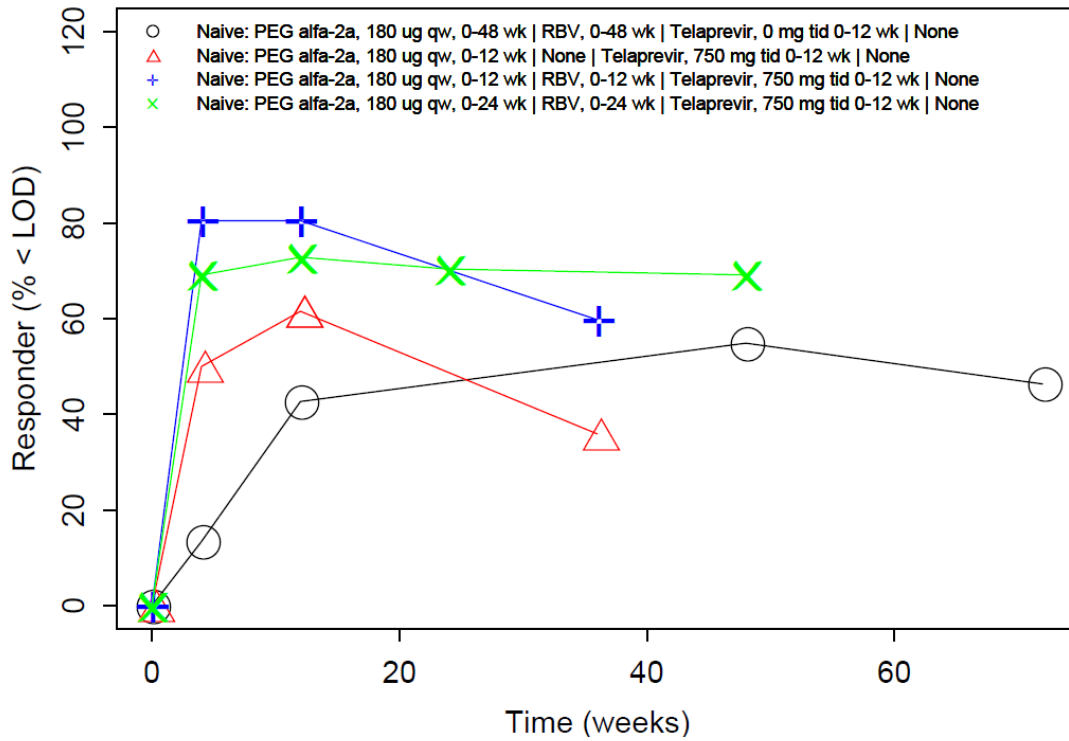
Table 3. Number of trials, treatment arms and patients for drugs in the database

Drug Name	NTrials	NArms	Nsubjects
albinterferon alfa-2b	5	14	2006
consensus interferon	1	1	30
interferon alfa-2a	6	6	951
interferon alfa-2b	14	17	2543
interferon alfacon-1	1	2	487
peginterferon alfa-2a	65	185	15112
peginterferon alfa-2b	50	122	13704
peginterferon lambda	1	9	56
ABT-072	2	15	116
ABT-333	4	26	213
ABT-450	1	7	41
ACH-1625	1	2	12
ANA598	2	5	88
BI 201335	5	15	704
BI 207127	3	15	131
BMS 790052	1	3	36
BMS-650032	1	7	32
Boceprevir	2	10	536
Danoprevir	1	3	25
Debio-025	3	10	138
GS-9256	1	5	44
GS-9450	1	11	64
HCV-796	2	10	123
IDX184	2	9	68
MK-3281	2	14	95
MK-7009	2	11	101
Narlaprevir	3	22	211
PF-00868554	2	7	50
PSI-7851	1	4	32
R1626	1	3	83
R7128	3	17	188
R7227	3	20	153
TMC435	4	12	98
Taribavirin	1	3	205
Telaprevir	7	20	958
VCH-222	1	5	29
ritonavir	4	21	213

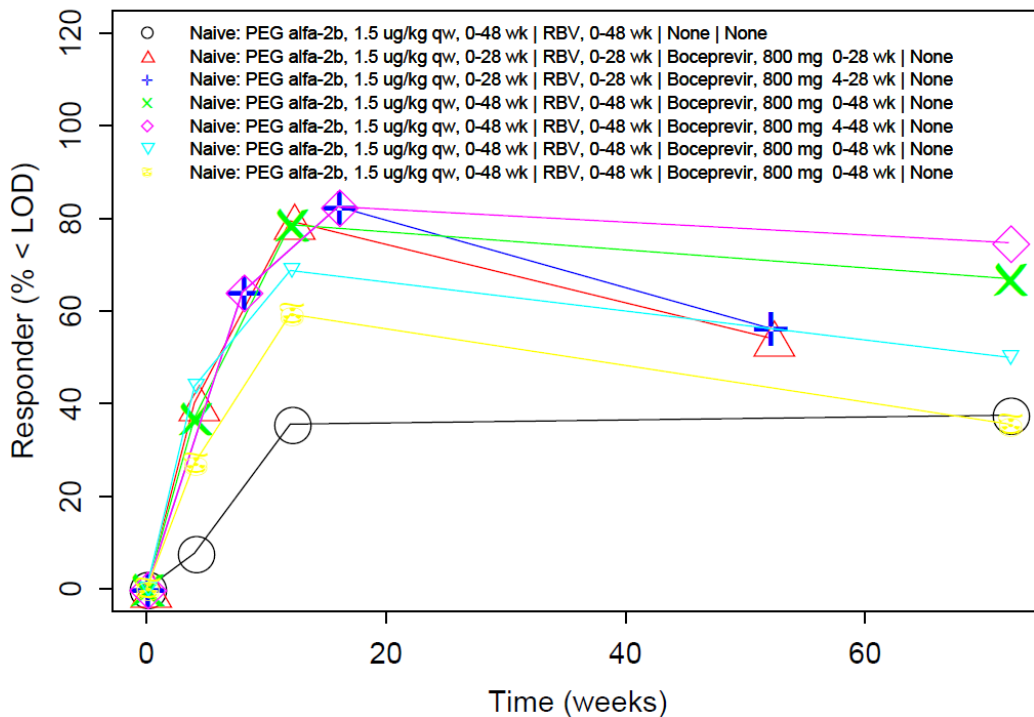
5. Example plots of actual trial data

The following graph shows examples of the time course of viral response as % patients with VL < LOD at a given time point. The graphs show the time course for each treatment arm and each trial that has information on this endpoint.

[19403903] PROVE2



[229] SPRINT-1



6. Outcome fields

Five endpoint types are recorded: viral load, treatment, adverse event, histology, and pharmacokinetic.

Viral load endpoints describe either the central tendency (mean, median etc.) of viral load at a particular point in time, or the percentage of responders relative to a threshold.

Treatment endpoints describe deviations to treatment, which are dose reductions for various reasons, discontinuations, and loss to followup.

Adverse Event endpoints describe the central tendency of laboratory values such as hemoglobin levels, the percentage of patients achieving a specified lab value, or the percentage of patients experience an adverse event.

Histology endpoints describe changes in liver status, either quantified by ALT measurements or by biopsy.

Pharmacokinetic endpoints include the central tendency of concentration at a particular point in time, or a PK parameter such as Cmax, AUC, or Ctrough.

- Viral load endpoints (VL)
 - Breakthrough – detectable viral load after an initial period of undetectable viral load, all during treatment.
 - ETR (End of Treatment Responder) – undetectable viral load at the end of treatment
 - EVR (Early Virological Responder) – undetectable viral load during the initial phases of therapy, usually after 12 or 24 weeks.
 - EVnR (Early Virological non Responder) – detectable viral load and a minimal CFB during the initial phases of therapy, usually after 12 or 24 weeks.
 - NonResponder – patient who does not have undetectable viral load at any point during treatment
 - Raw VL (Raw Viral Load) – viral load
 - Relapse – patient who has undetectable viral load at the end of treatment but has detectable viral load during follow-up, typically 24 weeks.
 - Responder – undetectable viral load during treatment, but not at one of the times with a standard acronym, e.g. at 8 weeks
 - RVR (Rapid Virological Response) – undetectable viral load at 4 weeks
 - SVR (Sustained Virologic Response) – undetectable viral load, typically 24 weeks after stopping treatment.
- Adverse event endpoints (AE)
 - ALT – Alanine aminotransferase
 - SAE – Serious Adverse Events
 - Anemia – usually this is not associated
 - anorexia
 - chills
 - depression
 - diarrhea
 - dyspepsia
 - dyspnea
 - fatigue
 - flu-like illness
 - flu-like Symptoms
 - headache

- hemoglobin – usually this is a timecourse
- insomnia
- leukocytes
- leukopenia
- nausea
- nausea or vomiting
- neutropenia
- neutrophils
- platelets
- pruritis
- rash
- rash or pruritis
- rash severe
- thrombocytopenia
- tiredness
- vomiting
- Treatment Endpoints (TX)
 - DoseReduction – number of subjects with a dose reduction
 - DoseReductionAdverseEvents – number of subjects with a dose reduction because of adverse events
 - DoseReductionAnemia – number of subjects with a dose reduction because of anemia
 - DoseReductionIFN – number of subjects with an interferon dose reduction
 - DoseReductionIFNAdverseEvents – number of subjects with an interferon dose reduction due to adverse events
 - DoseReductionIFN.Anemia – number of subjects with an interferon dose reduction due to anemia
 - DoseReductionIFNLabs – number of subjects with an interferon dose reduction due to laboratory measurements, i.e. neutrophils, platelets, anemia
 - DoseReductionIFNNeutropenia – number of subjects with an interferon dose reduction due to neutropenia
 - DoseReductionIFNThrombocytopenia – number of subjects with an interferon dose reduction due to thrombocytopenia
 - DoseReductionLabs – number of subjects with a dose reduction due to laboratory measurements

- DoseReductionNeutropenia – number of subjects with a dose reduction due to neutropenia
- DoseReductionRBV – number of subjects with a RBV dose reduction
- DoseReductionRBVAdverseEvents – number of subjects with a RBV dose reduction due to adverse events
- DoseReductionRBVAnemia – number of subjects with a RBV dose reduction due to anemia
- DoseReductionRBVLabs – number of subjects with a RBV dose reduction due to laboratory measurements
- DoseReductionRBVNeutropenia – number of subjects with an ribavirin dose reduction due to neutropenia
- DoseReductionRBVThrombocytopenia – number of subjects with an ribavirin dose reduction due to thrombocytopenia
- DoseReductionThrombocytopenia – number of subjects with a dose reduction due to thrombocytopenia
- TXDiscon – number of subjects who discontinued treatment for any reason. Note that these subjects could still be available for SVR measurement.
- TXDisconAdverseEvents – number of subjects who discontinued treatment due to adverse events
- TXDisconLabs – number of subjects who discontinued treatment due to laboratory measurements
- TXDisconIFNAdverseEventsLabs – number of subjects who discontinued interferon due to adverse events or laboratory measurements
- TXDisconRBVAdverseEventsLabs – number of subjects who discontinued ribavirin due to adverse events or laboratory measurements
- TXDisconLackOfEfficacy – number of subjects who discontinued treatment due to lack of efficacy
- TXDisconOther – number of subjects who discontinued treatment for other reasons
- Histology Endpoints
 - ALT
 - Fibrosis
 - Hepatic Fibrosis
 - Hepatic Inflammation
 - Histological Improvement

- Histological Response
- Inflammation
- Inflammation Change
- Ishak Activity Score
- Metavir Activity Score
- Pharmacokinetic Endpoints
 - AUC
 - Half-life
 - Cmax
 - Clearance
 - Ctough