

## Quantify HCV Clinical Outcomes Database Release 1.1 June 7 2009

### 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**

<b>Format</b>	Excel
<b>#Trials</b>	85
<b># Patients</b>	25,812
<b># Rows of Data</b>	5,824
<b>Last Updated</b>	07-Jun-09
<b>Compounds</b>	albinterferon alfa-2b, interferon alfa-2a, interferon alfa-2b, peginterferon alfa-2a, peginterferon alfa-2b, ANA958, BI 201335, BI 207127, Boceprevir, HCV-796, ITMN-191, MK-7009, PF-00868554, R7128, SCH-900518, TMC435, Telaprevir
<b>Key efficacy end points</b>	Viral load, SVR, RVR, ETR, histology (19 endpoints in total)
<b>Key safety/tolerability end points</b>	Adverse event percentages, laboratory values, dose reductions, dropouts for different reasons (59 endpoints in total)
<b>Strata</b>	Genotype, early response, baseline viral load and others

### 2. Features and benefits

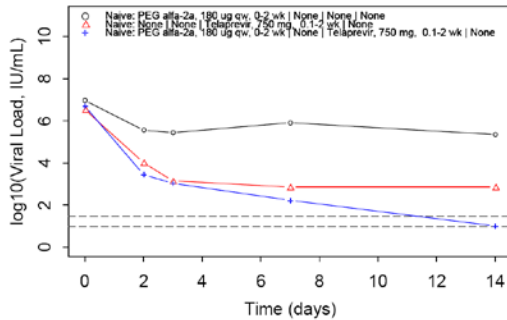
**Key Features:**

- **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

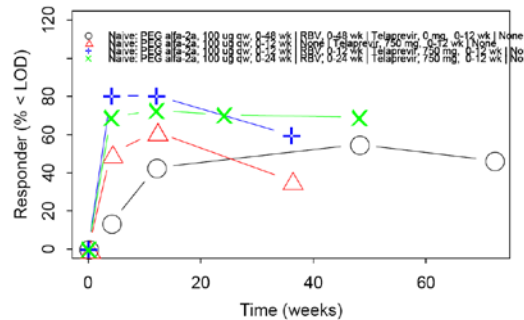
- **Model-friendliness:** designed and reviewed by experienced modelers to ensure highest quality and usability for modeling and simulation to support drug development strategies
- **Customizability:** can be augmented with clinical trial data proprietary to the client (this information goes into a separate proprietary database and will be owned by the client)

**Example Applications:**

[20] Forestier N (2007)

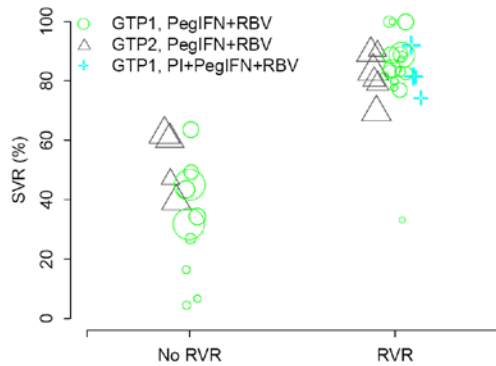


[32] Hezode C (2009) PROVE2



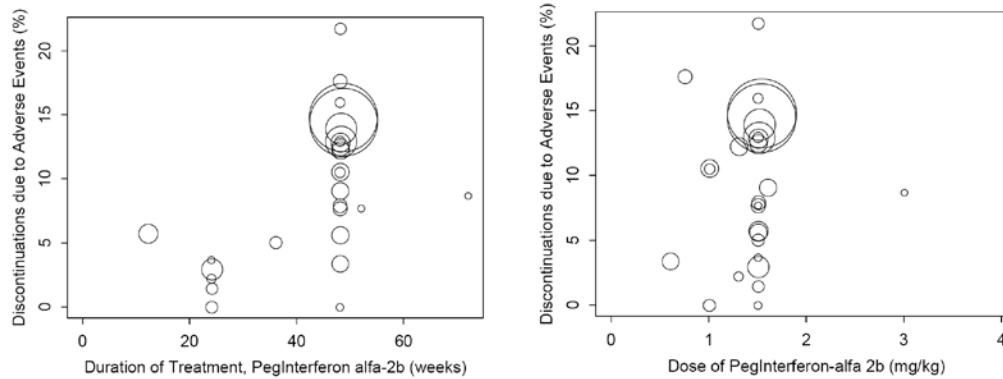
Question: What is the relationship between short-term viral decline and long-term viral response for a new protease inhibitor?

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.

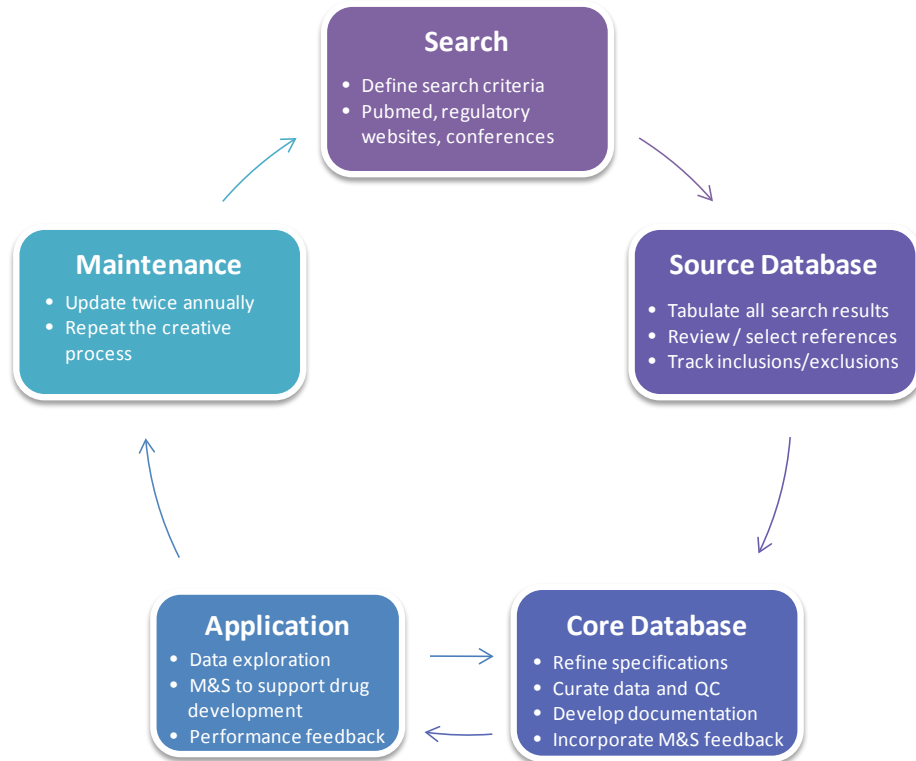
#### Why use our databases:

- Designed and managed by experienced modelers
- 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

285 references were identified and documented in the source database, of which a total of 85 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**

<b>Drug</b>	<b>Study</b>	<b>Description</b>
<b><i>Peginterferon alfa-2a</i></b>	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
<b><i>Peginterferon alfa-2b</i></b>	C/I98-580	Combotherapy
	C/I97-010	Combotherapy
	PO2080	Combotherapy, HIV
	PO1017	Combotherapy, HIV

The clinical outcomes database contains information from 85 trials, representing 292 unique treatment arms and about 25,812 patients. There are a total of 5,824 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	# Trials	# Arms	# Subjects
<i>albinterferon alfa-2b</i>	2	5	387
<i>interferon alfa-2a</i>	6	6	951
<i>interferon alfa-2b</i>	14	17	2,558
<i>peginterferon alfa-2a</i>	39	105	9,579
<i>peginterferon alfa-2b</i>	39	93	11,705
<i>Newer small molecules</i>			
<i>BI 201335</i>	2	8	53
<i>Boceprevir</i>	2	9	486
<i>ITMN-191</i>	3	19	155
<i>MK-7009</i>	2	12	129
<i>SCH-900518</i>	1	12	80
<i>TMC435</i>	2	10	87
<i>Telaprevir</i>	5	18	1,076
<i>ANA598</i>	1	4	35
<i>BI 207127</i>	1	5	48
<i>HCV-796</i>	2	12	167
<i>PF-00868554</i>	2	8	59
<i>R7128</i>	3	9	125

## 5. Outcome fields

The following endpoints are recorded in the database. The number of patients, percent of patients or rate (events per patient year) is recorded.

- Viral load endpoints (VL)
  - Breakthrough – detectable viral load after an initial period of undetectable viral load, all during treatment.
  - ETR (End of Treatment Response) – undetectable viral load at the end of treatment
  - EVR (Early Virological Response) – undetectable viral load 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
  - anorexia
  - chills
  - depression
  - diarrhea
  - dyspepsia
  - dyspnea
  - fatigue
  - flu-like illness
  - flu-like Symptoms
  - headache
  - hemoglobin
  - 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
- StudyDiscon – total number of subjects who discontinued the study and were not available for SVR measurement.
- StudyDisconAdverseEvents – total number of subjects who discontinued the study due to adverse events
- 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
- 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