



Ockham Technical Synopsis is a recurring series prepared for internal staff and consultants of Ockham Development Group. Highlighting current and emerging issues and challenges in clinical research, these publications are intended to disseminate intelligence captured during the execution of key clinical trials and are therefore updated on a continuous basis.

HEPATITIS C (HCV)

DISEASE DEFINITION

Hepatitis C is an infection caused by a virus that attacks the liver and leads to inflammation. Most people infected with the Hepatitis C virus (HCV) have no symptoms. In fact, most people don't know they have the Hepatitis C infection until liver damage appears, decades later, during routine medical tests.

Hepatitis C is one of several hepatitis viruses and is generally considered to be among the most serious of these viruses. Hepatitis C is passed through contact with contaminated blood — most commonly through needles shared during illegal drug use.

CAUSES AND RISK FACTORS

Hepatitis C infection is caused by the HCV, which is spread when a subject comes in contact with contaminated blood.

Examples of how HCV can be spread include:

- **Blood transfusions and organ transplants before 1992.** Improved blood-screening tests became available in 1992. Before that year, it was possible to unknowingly contract HCV through a blood transfusion or organ transplant.
- **Shared needles.** HCV can also spread through sharing contaminated needles when injecting drugs.
- **Childbirth.** A small number of babies born to mothers with HCV acquire the infection during childbirth.
- **Sexual contact.** In rare cases, HCV may be transmitted sexually.

Risk of Hepatitis C infection is increased for persons who:

- Have been exposed to infected blood
- Have ever injected illicit drugs
- Are HIV-positive
- Received a piercing or tattoo in an unclean environment using unsterile equipment
- Received a blood transfusion or organ transplant before 1992
- Received clotting factor concentrates before 1987
- Received hemodialysis treatments for a long period of time
- Were born to a woman with a Hepatitis C infection.

TESTING AND DIAGNOSIS

Screening Healthy People for Hepatitis C

Testing for Hepatitis C infection in people who have a high risk of coming in contact with HCV may help doctors begin treatment or recommend lifestyle changes that may slow liver damage. This is recommended because Hepatitis C infection often begins damaging the liver before it causes signs and symptoms.

People who may want to talk to their doctors about screening for HCV infection include:

- Anyone who has ever injected illicit drugs
- Anyone with unexplained, unusual liver function tests
- Babies born to mothers with Hepatitis C
- Health care and emergency workers who have been exposed to blood or accidental needle sticks
- People with hemophilia who were treated with clotting factors before 1987
- People who have ever undergone long-term hemodialysis treatments
- People who received blood transfusions or organ transplants before 1992
- Sexual partners of anyone diagnosed with Hepatitis C infection.

Blood Tests to Diagnose Hepatitis C

Blood tests may help to:

- Determine whether one is infected with HCV
- Measure the quantity of the HCV in the blood (viral load)
- Evaluate the genetic make-up of the virus (genotyping), which helps determine treatment options.

APPROVED TREATMENTS

Treatment Not Always Necessary

A diagnosis of Hepatitis C infection doesn't necessarily mean treatment is necessary. Someone with only slight liver abnormalities may not need treatment because the risk of future liver problems is very low. A doctor may recommend follow-up blood tests to monitor for liver problems.

Antiviral Medications

Hepatitis C infection is treated with antiviral medications intended to clear the virus from the body. Doctors may recommend a combination of medications taken over several weeks. Once the patient completes a course of treatment, the doctor will test the blood for HCV. If HCV is still present, the doctor may recommend a second round of treatment.

Antiviral medications can cause depression and flu-like signs and symptoms (e.g., fatigue, fever, and headache). In certain cases side-effects can be serious enough that treatment must be delayed or stopped.

Liver Transplant

If the liver has been severely damaged, a transplant may be an option. During a liver transplant, the surgeon removes the damaged organ and replaces it with a healthy liver. Most transplanted livers come from deceased donors, though a small number come from living donors.

For people with HCV infection, a liver transplant is not a cure. Treatment with antiviral medications usually continues after a liver transplant, as Hepatitis C infection is likely to recur.

Vaccinations Against Other Forms of Viral Hepatitis

Doctors will likely recommend that affected patients receive vaccines against the Hepatitis A and B viruses. These are separate viruses that also can cause liver damage and complicate treatment of Hepatitis C.

PRODUCTS IN DEVELOPMENT

Products in R&D

Company	Product
Roche / Medivir	HCV polymerase inhibitor
Medivir / Tibotec	polymerase inhibitor
ViroChem Pharma	Polymerase inhib
Gilead	Protease polymerase inhib
GENimmune	GNI-104 - monoclonal antibody
Genelabs	NS5a NS4b & Replicase inhibitors
Enanta	Cyclophilin binder
Phenomix	protease inhibitor
Phenomix	Polymerase Inhibitor
Migenix	N-nucleoside Poly inhib
Merck / Metabasis	Polymerase inhib small molecule
PTC / Schering	IRES inhib
Vertex	Helicase inhibitor
Medivir / Roche	Polymerase inhibitor
Cetek	small molecule
Itherx (Immusol) / Novartis	ITX2155 I
Argos Therapeutics	Therapeutic Vaccine
Tibotec	Polymerase inhib.
Regulus Therapeutics	microRNA antagonism of miR-122
CombiMatrix	RNAi
Arrow Therapeutics	Polymerase inhibitor
Boehringer Ingelheim / Biota	Nucleoside analogues
Alios BioPharma	Small Molecule Antivirals
Biotron	targeting HCV-p7
NanoViricides	HepaCide-I
Hanall	Antihepatitis agents
Astex Therapeutics	Enzyme Inhibitor
Avexa / TargetDrug	replication inhib.
StemCells Inc	HCV resistant Human liver

Products in Pre-Clinical

Company	Product
Vertex	VX-813 2nd gen protease inhibitor
Intermune	2nd Gen. Protease inhibitor
Benitec / Tacere Bio / Pfizer	RNA interference TT033
Sirna Therapeutics	SIRNA-034 RNAi RNA interference
ViroChem Pharma	Polymerase inhib
iTherX	ITX4520 Entry Inhibitor

Idenix	Protease Inhibitors IDX136&316
Idenix	Non-Nuc Polymerase Inhibitor
Gilead / Achillion	ACH-1095 Protease inhibitor
Presidio	PPI-461 NS5A inhibitor
Arrow Therapeutics	A-689 NS5A Inhibitor
GENimmune	GNI-103 – Therapeutic vaccine
ChemDiv / IDialog	ID-12 small molecule
Biocryst	Polymerase inhibitor
Genelabs GL59728 & GL60667	Non-nucleoside & nucleoside
ViRex Medical	Hepavaxx C Therapeutic Vaccine
GenPhar	Vaccine
Genmab	HuMax-HepC antibody
Inhibitex	INX08189 Polymerase inhibitor
Pharmasset	PSI-938 nucleoside polymerase
Enanta	Polymerase Inhibitor
Dynavax	Type C TLR9 agonist
Protiva Biotherapeutics	siRNA
Samaritan Pharmaceuticals	SP-30 entry inhibitor
Presidio (acquired from XTL)	NS5A inhibitors
Avila Therapeutics	AVL-181 protease inhibitor
Altor BioScience	Soluble T-cell Antigen Receptor
Progenics	PRO 206 entry inhibitor

Products in Phase I

Company	Product
Vertex	VX-500 protease inhibitor
Pfizer	PF-4878691
Boehringer Ingelheim	BI 207127 Polymerase inhib.
Bristol-Myers Squibb	BMS-791325 Protease inhibitor
Bristol-Myers Squibb	BMS-650032 NS3 Inhibitor
Bristol-Myers Squibb	BMS-824393
Isis / Merck	MK-0608 nucleoside polymerase i..
Abbott	A-837093 Non-nuc polymerase inhib
Gilead	GS 9190 non-nuc polymerase i.
Achillion	ACH-1625 Protease inhibitor
Aethlon Medical	Hemopurifier
Transgene	TG4040 (MVA-HCV) Vaccine
Tripep / Inovio	Therapeutic Vaccine Chronvac-C
Arrow Therapeutics	ca) A-831 NS5A inhibitor
U of Mass. Med School	human monoclonal antibody
Eiger BioPharmaceuticals	NS4B-RNA Binding Inhibitor
Abbott / Enanta	ABT-450 Protease inhib
Pharmasset	PSI-7851 nucleoside polymerase i.
Phenomix	PHX1766 protease inhibitor

Products in Phase II

<i>Company</i>	<i>Product</i>
Intermune / Roche	Protease inhibitor ITMN-191 R7227
Roche / Pharmasset	R7128 nucleoside polymerase inhibitor
Medivir / Tibotec	TMC435 Protease inhibitor
Pfizer	Non-Nuc Polymerase inhibitor
Boehringer Ingelheim	BI 201335 protease inhibitor
Intercell Novartis	IC41 Therapeutic Vaccine
Chiron / CSL	Therapeutic Vaccine CSL123
Bristol-Myers Squibb	BMS-790052 NS5A Inhibitor
Merck	MK-7009 protease inhibitor
Anadys	ANA598 Polymerase inhib
ViroChem Pharma	VCH-759 Non nuc Polymerase inhib
Globeimmune	GI 5005 Therapeutic Vaccine
iTherX (formerly Immusol)	ITX5061 Entry Inhibitor

Products in Phase III

<i>Company</i>	<i>Product</i>
Vertex	Telaprevir (VX-950) Protease Inhibitor
Schering	Boceprevir (SCH503034) Protease inhibitor

ON-GOING TRIALS: LOCATION OF ACTIVE SITES**Active Phase I Studies**

<i>Country</i>	<i>Number of Sites</i>
United States	66
Germany	41
France	17
Spain	14
Canada	12
Italy	11
Poland	10
Australia	10
Israel	7
Taiwan	6
India	6
Belgium	5
Korea, Republic of	5
Slovakia	4
Russian Federation	4
Greece	4
Romania	4
United Kingdom	3

Switzerland	3
Puerto Rico	3
Czech Republic	3
Brazil	2
New Zealand	2
Japan	2
Egypt	2
Pakistan	2
Netherlands	1

Phase II Studies

<i>Country</i>	<i>Number of Sites</i>
United States	253
Germany	58
France	54
Canada	46
Australia	44
Spain	31
Italy	19
Belgium	18
United Kingdom	17
Poland	16
Israel	15
Russian Federation	14
Romania	14
Korea, Republic of	12
Austria	12
Argentina	10
Portugal	9
Norway	7
Bulgaria	7
New Zealand	7
Puerto Rico	7
Switzerland	6
Taiwan	6
India	6
Denmark	5
Thailand	5
Greece	5
Sweden	5
Czech Republic	3

Netherlands	3
Chile	1
Hungary	1
Lithuania	1
Japan	1

Phase III Studies

<i>Country</i>	<i>Number of Sites</i>
United States	151
France	99
Germany	62
Spain	37
Canada	34
Netherlands	27
Italy	23
Brazil	22
Australia	18
Belgium	14
Israel	10
United Kingdom	8
Russian Federation	8
Mexico	8
Taiwan	7
Austria	7
India	6
Switzerland	5
Argentina	5
Korea, Republic of	5
Japan	4
Slovakia	4
Romania	4
Greece	4
Czech Republic	4
Poland	4
Colombia	3
Puerto Rico	3
Pakistan	2
Hungary	2
Egypt	2
Sweden	1
Ireland	1

ENROLLMENT RATES

<i>Active or Planned HCV Studies</i>	<i>Enrollment Rate</i>
Phase I Studies	.09 – 1.34 pts/site/mn
Phase II Studies	.12 – 1.6 pts/site/mn
Phase III Studies	.06 - .21 pts/site/mn.