Aestimo
Innovator's Briefing
Hepatitis C

AFRICA & MIDDLE EAST

www.aestimo.ie

About the disease

Epidemiology

Global incidence
21 to 28 per 100000 people
(route of transmission dependent)

Prevalence in this geography
3 928 158
(chronic cases)

Phases and stages of Chronic Hepatitis C Virus (HCV) infection	
Acute phase	Patient is infected; for the first 6 months patients are typically asymptomatic and around 30% of patients will clear the viral infection naturally
Chronic phase	70% of acute phase patients (50% to 90%) will progress to the chronic phase, representing long term infection, with the body unlikely to clear the infection without intervention During this phase patients are also likely to develop fibrosis, measured using the METAVIR score for fibrotic staging: Stage 0: no fibrosis Stage 1: portal fibrosis (mild fibrosis) Stage 2: periportal fibrosis (moderate fibrosis) Stage 3: septal fibrosis (bridging fibrosis and scarring) Stage 4: cirrhosis (severe scarring)
25% of chronic patients will develop cirrhosis; 20% of cirrhotic patients will develop Liver Cancer	

Key characteristics

- >70 million people worldwide have Chronic phase Hepatitis C infection, killing 700,000 people annually through cirrhosis and liver cancer
- Viral transmission occurs via intravenous based drug use, iatrogenic exposure, body piercing, and rarely through high risk sexual behaviour or vertical (perinatal) transmission from mother to neonate (around 5% of chronically infected mothers will transfer the virus to their child, with serological testing performed on the child when they are >1 year of age)
- HCV infection often co-presents with HIV infection, with coinfection endemic in Asia and Africa. For intravenous drug users coinfection rates are up to 92%.
- Acute to chronic phase transition is determined by a combination of age, gender, ethnicity, host genetics and immune status, viral genotype and subtype.
- There are 7 genotypes (1 through 7) of HCV, with each genotype having several subgenotypes, with geographies having specific prevalence for specific genotypes
- Genotypes and subgenotypes (around 100 different at present) are directly linked to possibility of progression from acute to chronic phases: subgenotype 1b infected patients have a 90% probability of progressing to chronic, while other types only have upto 50% probability.
- Within an infected patient, the specific subgenotype will exist as a mixed population of genetically distinct virions due to the high and rapid mutation rate (viral production occurs at 10^{12} virions per day with viral enzymes essential for its lifecyle that lack proofreading)

Genotype	1a & 1b	2	3	4	5 & 6	7
Percent of population (* this is a continent-wide average; each country has its own specific levels. See Botheju et al 2019, Nature Scientific Reports for details)	32%	7%	5%	42%	14%	So far only detected in DRC
Number of patients seropositive (1000's)	9858	1994	1279	13100	1375	-
RAV* frequency	Subtype 1a: 56% Subtype 1b: 34% (10-15% of patients present with RAV at initial diagnosis)	88%	50%	85% (4r variants, specifically in Africa)	99%	unknown
Zepatier (elbasvir /grazoprevir) for patients without RAVs for elbasvir	Yes	No	No	Yes	No	No
Mavyret (glecaprevir /pibrentasvir)	Yes	Yes	Yes	Yes	Yes	No
Harvoni (ledipasvir /sofosbuvir. Typically for 12 wks; 8wks if HCV RNA level is <6 million IU/mL))	Yes	No	No	Yes	Yes	No
Epclusa (sofosbuvir/velpatasvir)	Yes	Yes	Yes	Yes	Yes	Yes
Vosevi -2nd line therapy (sofosbuvir/velpatasvir/voxilaprevir)	Yes	Yes	Yes	Yes	Yes	No

**Resistant Associated Variants*

- This results in the high probability of the existence of Resistant Associated Variants that are not responding to the Direct Acting Antivirals (an implication is that in clinical practice, genotype and subgenotype definition prior to therapy initiation plays an essential role in treating the infection).
- The risk is that treatment can result in the enrichment of a variant that are often undetectable using existing assays and may present asymptomatically.
- Greater than 50% of people infected with Hepatitis C virus have not been diagnosed, especially if they have a low socioeconomic status (independent of geography)

The Patient Journey

Patient visits primary care physician/family doctor with following symptoms*:

- Easy bleeding and bruising
- Fatigue and/or general malaise
- Ascites
- Dark urine
- Leg swelling
- Possible jaundice
- Abdominal pain
- Spider angiomas

Patient referred to specialist centre:

- Medical history check & Physical exam
- Liver function tests
- Hepatitis C virus tests (and other virus tests: HIV, Hep B)
- Abdominal ultrasound (elastography)
- MRE imaging
- Liver Fibrosis assessment (FIB-4)

confirmation

Patient referred for treatment:

- Direct acting antivirals (DAA), in varying combinations, that target nonstructural proteins

Treatment is recommended for all patients with chronic infection

Follow up patient care and management

- 3 months after end of therapy: HCV viral load testing
- Every 6- 12 months: liver function tests, blood tests.
- APRI testing if fibrosis is suspected
- Genotypic drug resistance testing
- Hepatitis B reactivation assessment (if relevant)

Disease continuation/Recurrence:

- Patient has not achieved a sustained virologic response
- Resistance Associated Variants (mutations) have occurred
- Dominant Resistance associated variants vary by genotype, with an average occurrence of nearly 60%

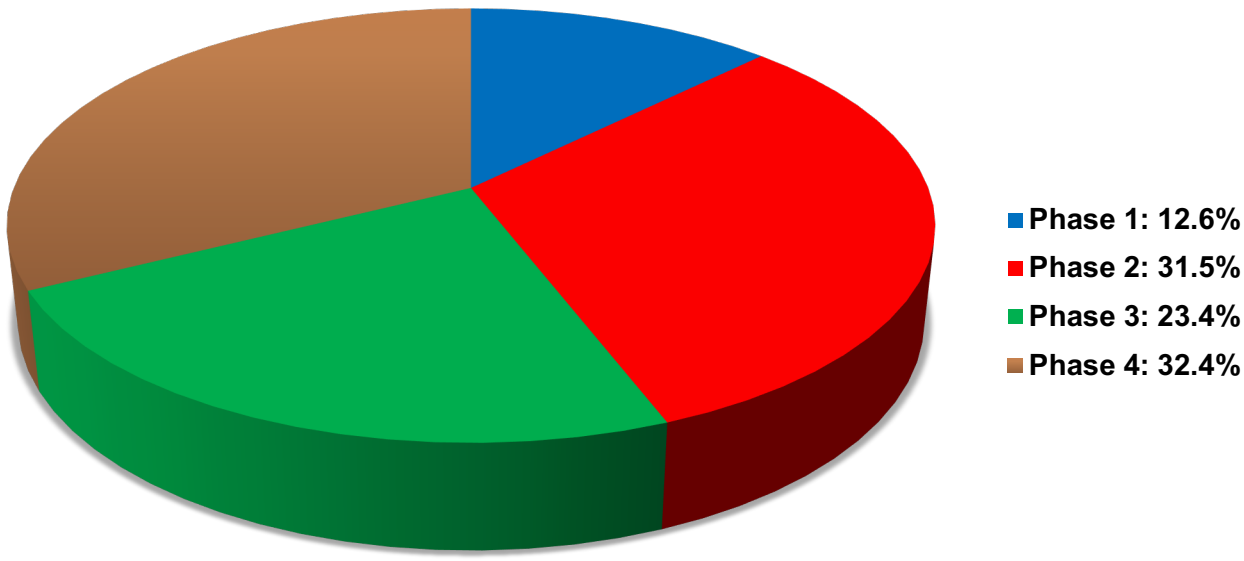
Standards-of-Care, Prices and Market size

- **Treatment Cost (TC)** represents the precise treatment regimen (annual or recommended duration if < 1year) multiplied by the price of the intervention(s) sourced from published prices from the marketplace geography and are indicated in $US equivalent values.
- The **market size** of the intervention, the **Serviceable Available Market (SAM)** value, are annual values and calculated as a function of the patient population eligible for that particular treatment multiplied by the TC.

Treatment description	Example (s)	TC ($US)	SAM ($US Mn)
NS5B	sofosbuvir	773	5069.1
NS5B + NS5A combination	zepatier	0	0
NS5A + NS3/4A combination	mavyret	286	1973.8
NS5B + NS5A combination	harvoni	382	2323.8
NS5B + NS5A combination	epclusa	722	4982.8

Global Innovation Development

Number of clinical trials ongoing: 111 globally



Clinical trial characteristics

Phase 1

CT cost $ 203 000

Median Patient No. 29
Median Duration: 2 (months)

Phase 2

CT cost $ 1 390 500

Median Patient No. 52
Median Duration: 4 (months)

Phase 3

CT cost $ 3 580 500

Median Patient No. 170
Median Duration: 3 (months)

Marketplace Forecasting and Development Risk

To estimate risk for innovation development, **forecasted SOM values** are calculated assuming the final product has a **14 year marketplace lifespan with a 21% SAM penetration**, which are then used in indication specific rNPV calculations; following the Health Economics caveat that **the innovative solution will be better than that standard of care (comparator product) but sold at the same price**

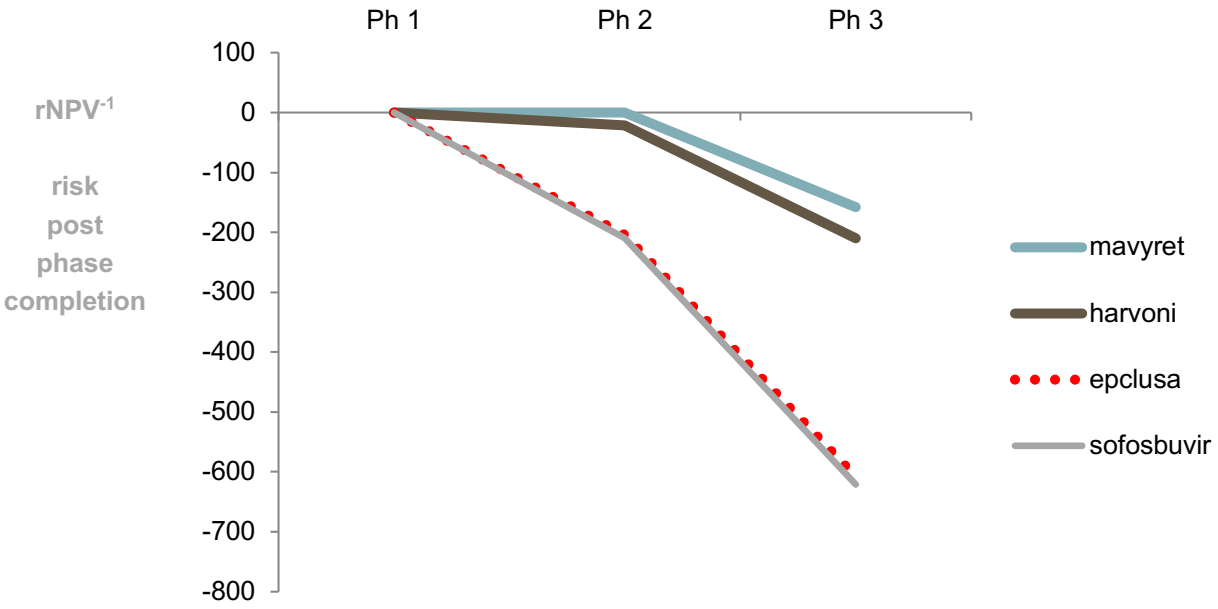
Treatment description	Example (s)	SOM ($US Mn)
NS5B	sofosbuvir	14903.2
NS5B + NS5A combination	zepatier	0
NS5A + NS3/4A combination	mavyret	5803.0
NS5B + NS5A combination	harvoni	6831.9
NS5B + NS5A combination	epclusa	14649.6

To reach a balance of zero following innovation investment, integrating in indication specific parameters, required lifetime SOMs are:

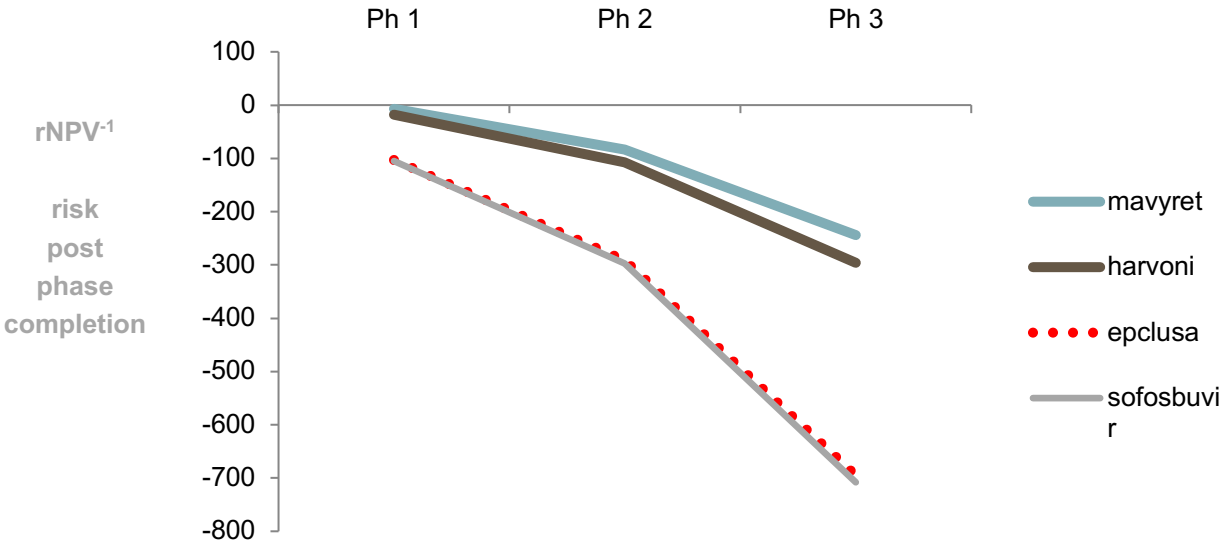
- **1100 $Mn for Repositioning**
- **2698 $Mn for De Novo**

Modeling the creation of a new solution, in which reimbursement agencies will use the standard-of-care as the comparator (clinical benefit and cost benefit), aiming towards generating a higher patient benefit but with the same overall cost, we can estimate the development risk of that new solution. Risk is presented as $rNPV^{-1}$ in which the lower the value the lower the risk. Any risk value above 0, arguably carries too high a development risk with consequent ROI's of <1. More details on the model parameters are explained below.

De Novo development risk:



Repositioning development risk:



Development Risk: model parameters

Development risk assessment was calculated using rNPV methods with the following most optimistic conditions:

De Novo and Repositioning risk measurement conditions

i) Product characteristics

- The new innovation will be superior to the existing standard of care, but will be priced equivalently (best case scenario)
- That the innovative product is a disruptive new 'best-in-class', compared to the standard of care
- That over its lifetime, the product, will achieve an overall 21% Serviceable Obtainable Market, equally over the studied geographic space, and that all citizens have equal access to the product
- The percent of the target population eligible for the intervention, based upon existing treatment regimens within the 'indication and intervention class' are used to create the market uptake

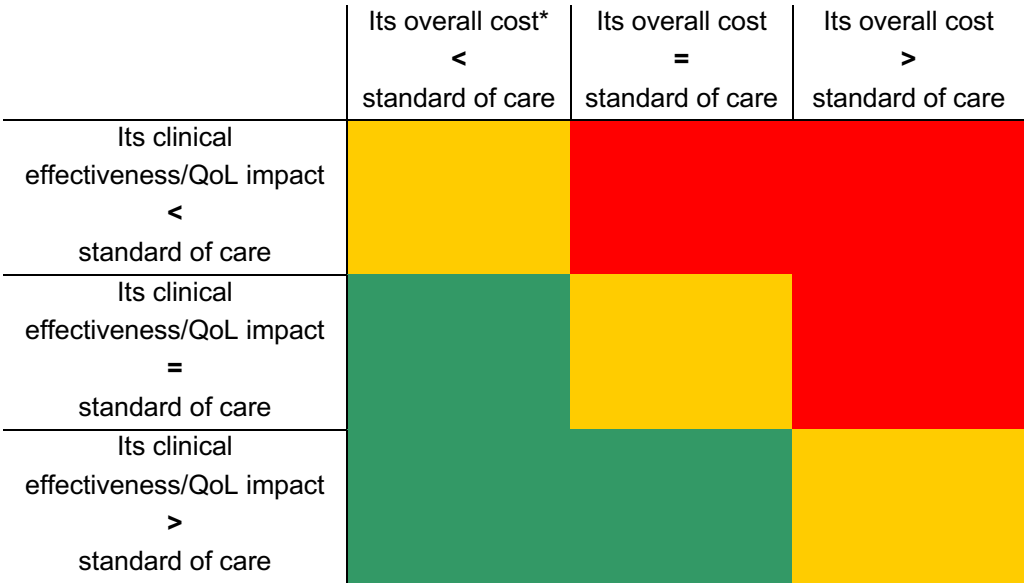
**detailed information on standards of care can be found at drugbank. go.drugbank.com (description, application, structure, DDI, development, manufacturer)*

ii) Valuation characteristics

- Disease Indication and phase specific clinical success rates are used
- Cost of capital risk rates are used
- Disease specific clinical trial metrics are used
- HEOR (Health Economics and Outcome Research) clinical evidence multiple requirements is used
- SOMs are based upon local pricing structures (in this case imported from India)
- For '***De Novo***' Full value chain costs, from experimental development up to first scaled up manufacturing prior to market release are used
- For '***Repositioning***' Full value chain costs, from the end of phase 1, up to first scaled up manufacturing prior to market release are used
- Risk is presented as $rNPV^{-1}$

(During development, risk going down does not necessarily mean value going up due to long term aggregate market influencers)

Health Economics and Outcomes: how will your solution compare to the Standard-of-Care?



- If your solution has the characteristics of the cross-references in **red**, it is highly unlikely any agency or insurance company will agree to the purchase of your product
- If your solution has the characteristics of the cross-references in **amber**, the agencies or insurance companies will perform an Incremental Cost Effectiveness Review (ICER) to determine if it is worth purchasing your product
- If your solution has the characteristics of the cross-references in **green**, it is highly likely that all agencies and insurance company will agree to the purchase of your product

**Cost: this does not mean the price of the intervention exclusively. This includes evidence indicated below, that also includes operational costs for healthcare facilities, capital expenditures, staff training, procedure changes and monitoring, long term impact on quality of life and associated healthcare costs.*

To arrive at a point of reimbursement, and a customer paying for it, agencies attach a significant amount of emphasis to patient reported outcomes (PROs) that reflects an impact on the Quality of Life (QoL); these are not clinical efficacy endpoints. These are based upon questionnaires presented to the patient during the trial and when approved during treatment, that scales the impact of the intervention as a function of what the patient tells the doctor.

Common key HEOR evidence requirements

HEOR in Africa is a growing sector and perspective to healthcare solutions. This is linked to changes in the healthcare infrastructure itself to be able to provide sufficient quality health solutions to the population. Understandably, this will be a long journey.

There is clearly an impetus to develop better decision making in healthcare procurement, therefore we can anticipate that policy makers will be reviewing existing international processes and adapting them to their own locality. For the innovator, therefore, it would be logical to consider following the creation of HEOR data using standardized outputs and collect as much quality of life related information as possible during clinical trials following recognised approaches.

Recommended evidence that should be collected:

- Details of clinical trials and (if available) real world evidence for new product
- Clinical & economic systematic literature reviews (for new product and comparators and other required evidence)
- Comparative effectiveness vs. standard of care in clinical practice (often more than one comparator will be required)
- Pricing
- Cost-effectiveness analyses (of the new product vs. its comparators), for life years saved and cost-utility analyses using local currency per quality adjusted life year (QALY).
- Budget impact analyses (financial consequences/change in expenditure of adopting a new intervention)

Characteristics of HEOR requirements for Hepatitis C *

The HRQoL questionnaires used for assessing quality of life in sufferers of Hepatitis C are:

HepaDisk	Hepatitis C quality of life questionnaire
LDQOL	Liver Disease Quality of Life Questionnaire
CLDQ-HCV	Chronic Liver Disease Questionnaire-HCV version
PROQOL-HCV	Patient reported outcome quality of life survey for HCV
SF-36	RAND Medical Outcomes Study Short Form 36
EuroQOL EQ-5D	EuroQOL Group non-disease specific QoL instrument
WHOQOL-BREF	World Health Organization Quality of Life abbreviated version

**in addition to disease questionnaires, additional QoL questionnaires on fatigue (FIS) depression and anxiety are also used.*

Innovators need to carefully consider the patient outcome benefit from multiple perspectives to ensure their innovation is addressing all stakeholder needs.

We would recommend reviewing the outcomes that can be reported from the QoL questionnaires and address how to integrate them into the innovation development plan to address later stage needs, and increase the value of their solution.

Recommended reading

Subject matter	Type	Author	Link
*Understanding Hepatitis C and the patient care pathway	website	University of Washington	https://www.hepatitisc.uw.edu/page/hcv/biology
Geographic distribution of Hepatitis C by genotype	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5105050/
About Hepatitis C	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/books/NBK430897/
Treatment of Hepatitis C by genotype	website	University of Washington	https://www.hepatitisc.uw.edu/go/treatment-infection
Hepatitis C guidance	Guidelines	AASLD	https://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/AASLD-IDSA_HCVGuidance_August_27_2020.pdf
Cost effectiveness of DAA therapies for Hepatitis C	website	University of Washington	https://www.hepatitisc.uw.edu/go/evaluation-treatment/cost-access-medications/core-concept/all#price-direct-acting-antiviral-agents
Hepatitis C epidemiology	Peer reviewed publication	Scientific and medical specialists	https://www.who.int/news-room/fact-sheets/detail/hepatitis-c
Understanding Hepatitis C drug resistance	Peer reviewed publication	Scientific and medical specialists	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5935211/
Global prevalence of DAA resistant HCV variants	Peer reviewed publication	Scientific and medical specialists	https://www.nature.com/articles/srep20310
*DAA failures in treating HCV subtypes	Peer reviewed publication	Scientific and medical specialists	https://www.journal-of-hepatology.eu/article/S0168-8278(19)30587-2/fulltext
HEOR for Hepatitis C	Peer reviewed publication	Scientific and medical specialists	https://www.sciencedirect.com/science/article/pii/S1590865818313045
HEOR for Hepatitis C	Peer reviewed publication	Scientific and medical specialists	https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-016-1771-0
HTA in sub-saharan Africa 2020	Peer reviewed publication	Scientific and medical specialists	https://f1000research.com/articles/9-364
HTA in South Africa	website	Scientific and medical specialists	https://www.heroza.org
HTA in Africa	website	AFHEA	https://afhea.org/en/

Your next step

If you are motivated to design new solutions and products that will provide a better Standard of Care, Aestimo is able to provide tailored strategic insights, support and/or advice.

These solutions can provide **higher granularity information** on:

- Reimbursed interventions and solutions (all products in all classes: SOM, forecasted SAM and development risk)
- Solutions in development
- Disease subtypes; prevalence, evidence requirements, clinical trial design, measurements and outcomes
- Repositioning strategies: international growth, additional indications, new indications
- Country specific regulation and evidence requirements
- Feasibility assessments: stakeholders, opportunities, partners, non dilutive funding, product launches

And support the company to develop the evidence and engage with reimbursement authorities and payers.

To talk to us about your needs and plans, please contact Jonathan at jdando@aestimo.ie to schedule a webconference.

Aestimo Innovator's Briefings (AIB)

Bring together

- Marketplace specific standards of care (health products) for each class of intervention used within the indication
- Standard of care specific treatment regimens (dose and duration)
- Marketplace specific prices of standards of care
- Indication specific prevalence and incidence
- Eligible patient populations for each intervention and treatment
- Clinical trial logistic requirements
- Indication specific clinical trial success rates, durations and patient numbers
- Modeled optimal and realistic valuations based upon Serviceable Obtainable Market within a market place for each intervention class
- HEOR evidence requirements
- Development risk and opportunity calculations for *de novo* generation or repositioning of innovations, using full value chain economic costing.

These briefings link together all the key components of the value chain (concept to genericisation) in healthcare intervention development to enable any innovator to assess opportunity and risk for their idea, intellectual property, investment or intervention pipeline.

They also provide logistic and strategic insights that enable the innovator to design global innovation development and launch plans, by understanding what commercialisation action should be taken, when it should be done and where it should be made.