e-Projection Sales Forecast Report

Japanese Hepatitis C Market Forecast: Methodology and Implications

This article was originally published in the Japanese journal, International Pharmaceutical Intelligence (**国際医薬品情報**), on May 9, 2016.

Updates to the report as of August 2018

The actual sales of Harvoni and Sovaldi in Japan in the fiscal year 2016 were 1.6 billion yen and 713 hundred million yen, respectively, according to IQVIA Topline Market Data report (2017 figures are not disclosed). There were no significant price cuts to Harvoni and Sovaldi in April 2018.

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Executive Summary

Hepatitis C is a serious burden to the Japanese society, and the treatment of the disease represents a crucial issue. Recent advances in technology have made highly effective drugs with fewer side effects available to the patients. The development and the commercialization of direct antiviral agents (DAAs) have become a hallmark to the hepatitis C virus (HCV) treatment paradigm. These drugs have achieved a sustained virological response (SVR) rate as high as almost 100% in clinical trials, meaning virtually eliminating the virus from most of the patients. Driven by the performance of these drugs, the market for antiviral agents in Japan has almost reached five billion dollars in 2015, representing an astonishing growth rate of 125% per year.

To predict the dynamics of the HCV DAA market, we have employed a simple stochastic process model to project the patient population from 2016 to 2025. In this model, we included multiple scenarios based on various assumptions about patient behavior, pricing, reimbursement, and market access. As a result, our forecast suggests that the HCV market's total annual sales would have been the peak around 300B JPY in 2015 to 2016 despite the "Special Repricing" applied in April 2016, and the market will dramatically contract beyond peak year. Sofosbuvir based treatments, namely Sovaldi and Harvoni, will continue to be dominant among the competitors. The market size will become insignificant for entrants after the estimated launch of grazoprevir/elbasvir in late 2016.

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Background

HCV infection is known to be the most significant cause of liver cancer, and the number of HCV carriers in Japan is estimated to be around 1.5 to 2.0 million[1,2]. Despite the screening and diagnosis efforts, in 2012 liver cancer caused the death of more than 30,000 people[3]. Thus Hepatitis C still represents a significant burden to the Japanese society[4].

Due to the innovation in pharmaceutical and clinical science, new drugs have been continuously introduced to the market since the discovery of the HCV in the late 1980s[5,6]. This array of promising new products contributed to improving the performance of the HCV treatments in the clinical front by increasing the SVR rates, by reducing the side effects, by shortening the treatment period and by enabling a more patient-friendly route of administration - each helping to remove the burden on the patients. However, this innovation in patient experience, together with the high prices of these treatments, brought the market to expand significantly. According to the IMS Health Topline Data[7], the Systemic antiviral market (ATC code J05) in Japan reached 497,172 million yen (approximately 50 billion US dollars) in 2015, growing at an impressive 125.3% per year. The rapid growth of this massive market not only will have commercial implications to the manufacturers but certainly will have a major impact on the national health insurance budget.

Here, we have forecasted the sales of DAAs for the treatment of HCV infections in Japan, including sofosbuvir based treatments, namely Harvoni and Sovaldi. Both medicines were subject to the "Special Repricing" which took place in April 2016 and the National Health Insurance price (NHI price). Both drugs were cut approximately 35% only several months after their commercial launch. Due to the high SVR rates, the improved safety profiles of DAAs, the already declining number of HCV carriers due to the aging population and virtually no new infection cases, the prices on these drugs are expected to decrease even faster. The purpose of this report is three fold: to explain in detail the methodology we have applied in our forecasting process, to describe the sensitivities of the outcomes to the multi-dimensional scenarios including patient behavior, pricing and market access on our model, and to suggest the strategic implications of our projection from the manufacturer as well as the public health funding perspective.

Overview of the Methodology

To develop a flexible and intuitive patient population forecast, we have employed a simple stochastic model based on the observation of the insurance claims data which is commercially available in Japan. Next, we have compared the profile of the products included in the forecast and calculated the user preference/peak patient share of the respective products. We multiplied the patient numbers with the assumed prices of each product and modified it with the reimbursement and market access factors to come up with an annualized forecast of the 5 DAA products up to 2025.

Patient Population Dynamics

We observed the health insurance claims data to identify any historical trends in the number of diagnosed, drug-treated and antiviral drug-treated patients. Population data were provided by the Japan Medical Data Center (JMDC, Tokyo, Japan). In brief, JMDC data comprises of health insurance claims of an aggregated 3.7 million subjects sampled from the social insurance system in Japan, including ICD-10 classified diagnosis and medical treatment information. The figures used in this report are all 5-year age and sex group extrapolations to the general population. Table 1 shows the historical population data extracted from the JMDC database.

Table 1. Annual historical HCV population estimates in Japan

	2010	2011	2012	2013	2014
a) Diagnosed patients	914,877	847,948	829,149	765,275	712,587

b) Drug treated patients*	415,356	369,527	333,610	291,639	259,996
c) Drug treated rate (c=b/a)	*45%*	*44%*	*40%*	*38%*	*36%*
d) Antiviral drug treated patients**	48,653	32,094	39,346	28,600	34,502
e) Antiviral drug treated rate (e=d/b)	*12%*	*9%*	*12%*	*10%*	*13%*

*: Drug-treated patients is defined as the number of subjects who had received any drug treatment during the relevant year periods. **: Antiviral drugs include pegylated interferon (peg-Ifn), ribavirin, telaprevir, simeprevir, asunaprevir, and daclatasvir.

The following trends could be recognized by observing the population estimates.

- The diagnosed patient population is decreasing at an annual average rate of 49,000 subjects.
- The number of drug-treated patients, as well as the ratio against diagnosed patients, are decreasing.
- The antiviral drug-treated rate is relatively stable at around 9-13%.

Based on these trends, we have developed a stochastic population dynamic model described in Figure 1.

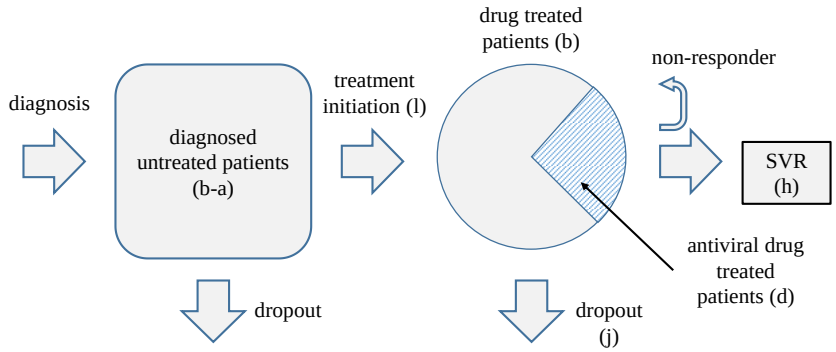


Figure 1. Schematic of hepatitis C population dynamic model

In this model, we have applied the following assumptions.

- HCV carriers will flow into the diagnosed untreated patient pool (b-a) once diagnosed. The incidence of diagnosis and the dropout rates from this stock of subjects are both stable.
- The diagnosed untreated patients will initiate drug treatment at a certain probability (l) and will flow into the drug-treated patient pool (b).
- A certain proportion of the drug-treated patients (b) will receive antiviral treatment (d). SVR (h) will happen at a certain probability based on the average profile of the drugs available at that time. SVR will only happen when a patient receives antiviral drug treatment. If the patient does not achieve SVR, they will flow back to the drug-treated patient pool (b).
- SVR achievement rate will increase from 50% in 2010 to 70% in 2014 and 95% in 2016, based on the improved performance of the emerging treatments.
- Patients in the drug-treated patient pool (b) will drop out (j) from treatment at a certain rate. We have assumed that the number of dropouts will be equivalent to the number of liver cancer deaths of each year (f). In table 2 we describe the actual deaths caused by liver cancer[8].

Table 2. Liver cancer deaths reported by the National Cancer Center Japan

	2010	2011	2012	2013	2014
f) Deaths from liver cancer	32,765	31,875	30,690	30,175	29,543
g) Deaths per drug treated patients (g=f/b)	*8%*	*9%*	*9%*	*10%*	*11%*

Table 3 describes some of the additional assumptions we plugged in to complete the model.

Table 3. Assumptions of the HCV patient population models

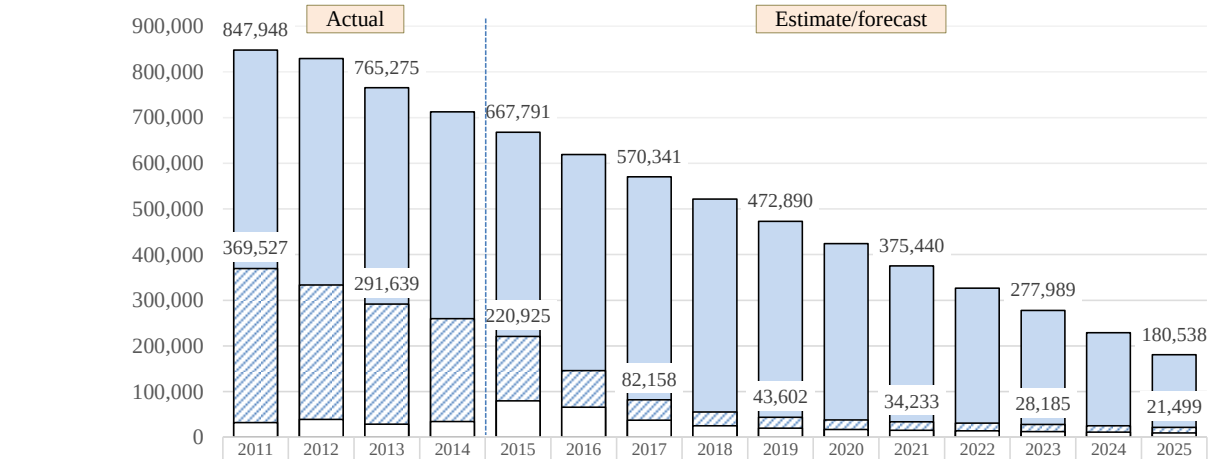
	2010	2011	2012	2013	2014
h) SVR achieved patients (h=d·i)	24,327	16,047	21,640	17,160	24,151
i) SVR achievement rate	*50%*	*50%*	*55%*	*60%*	*70%*
j) Dropout patients (j=f)	32,765	31,875	30,690	30,175	29,543
k) Dropout rate (k=j/b)	*8%*	*9%*	*9%*	*10%*	*11%*
l) Treatment initiated patients ($l=b_{dif}$-h-j*)	11,263	12,005	10,359	15,692	-
m) Treatment initiation rate (l÷(a-b)**)	*2.4%*	*2.5%*	*2.1%*	*3.3%*	-

*: The treatment initiated patients were calculated by subtracting the SVR achieved patients and dropout patients from the year on year difference in drug-treated patients.
**: The treatment initiation rate is the number of treatment initiated patients per diagnosed untreated patients

We have added another assumption for the year 2015 where JMDC information was not yet available. By analyzing the Early Postmarketing Phase Vigilance data (EPPV data) that was published by the manufacturers Gilead Sciences, Inc. (Tokyo, Japan) and Jannsen Pharmaceutical K. K. (Tokyo, Japan), we have estimated that the number of antiviral drug-treated patients jumped from 34,502 in 2014 to 80,000 in 2015.

Based on these assumptions, we have extrapolated the trends of the respective flows and developed a long-term patient forecast until 2025, as shown in Figure 2.

Figure 2. Patient forecast of the base case scenario

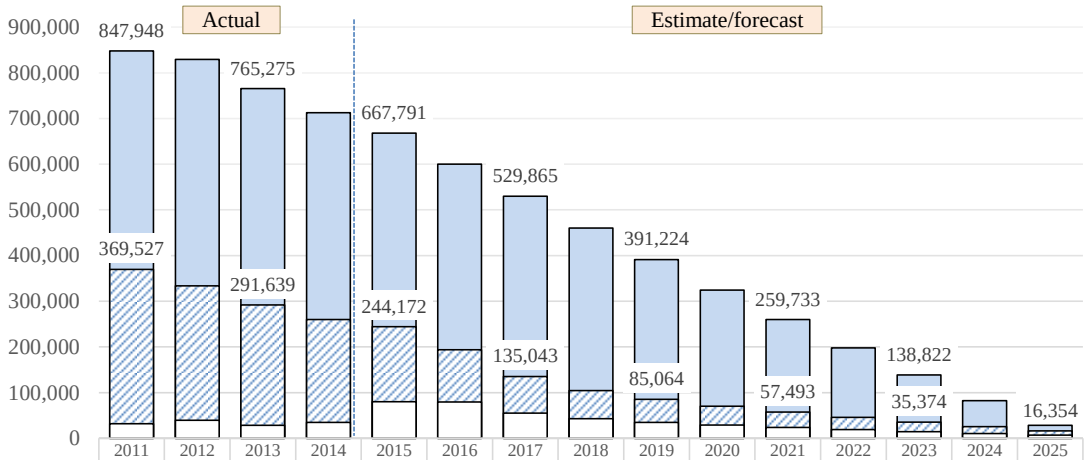


	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
diagnosed pats #	847,948	829,149	765,275	712,587	667,791	619,066	570,341	521,615	472,890	424,165	375,440	326,714	277,989	229,264	180,538
drug treated pats #	369,527	333,610	291,639	259,996	220,925	145,895	82,158	55,286	43,602	37,858	34,233	31,203	28,185	24,973	21,499
antiviral drug treated pats #	32,094	39,346	28,600	34,502	80,000	66,038	37,188	25,025	19,736	17,136	15,495	14,124	12,758	11,304	9,732

Here we can see that the number of drug-treated patients in 2018 will fall to a fifth of what it was in 2010.

In this first forecast, we have assumed that the rate of the patients who will initiate drug treatment will be constant over time. However, we can imagine a more aggressive case where patients may start to look for treatments more proactively once innovative drugs like Sovaldi or Harvoni should hit the marketplace. Under such conditions, treatment initiation rate (m) may increase from 3.3% to 10% in 2016. Based on this modified assumption, the forecast will look like Figure 3. We will refer to this the best case (best from the perspective of the patients and manufacturers).

Figure 3. Patient forecast of the best case scenario

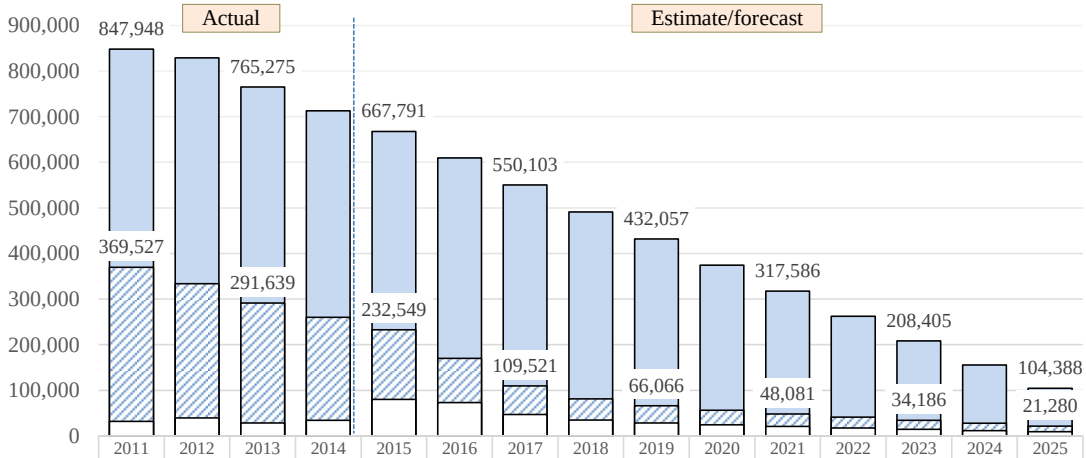


	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
diagnosed pats #	847,948	829,149	765,275	712,587	667,791	600,131	529,865	460,253	391,224	324,202	259,733	197,947	138,822	82,282	28,237
drug treated pats #	369,527	333,610	291,639	259,996	244,172	193,743	135,043	104,445	85,064	70,226	57,493	45,985	35,374	25,522	16,354
antiviral drug treated pats #	32,094	39,346	28,600	34,502	80,000	79,347	55,307	42,775	34,838	28,761	23,546	18,833	14,487	10,452	6,698

In the best case scenario, the number of antiviral drug-treated patients is larger in the early years but will exhaust faster and will be smaller in the later years, compared with the base case scenario.

Both scenarios are somewhat extreme, and we can think of another relatively moderate case which is in the middle. We will refer to this as a likely case, which is shown in Figure 4.

Figure 4. Patient forecast of the likely case scenario



	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
diagnosed pats #	847,948	829,149	765,275	712,587	667,791	609,598	550,103	490,934	432,057	374,183	317,586	262,331	208,405	155,773	104,388
drug treated pats #	369,527	333,610	291,639	259,996	232,549	170,206	109,521	81,240	66,066	56,057	48,081	40,940	34,186	27,652	21,280
antiviral drug treated pats #	32,094	39,346	28,600	34,502	80,000	73,192	47,096	34,935	28,410	24,106	20,676	17,605	14,700	11,891	9,151

Competitive Landscape and Market Share Assumptions

The scope of this report is limited to the DAAs and will not include other treatments such as liver supportive therapy (e.g., ursodeoxycholic acid) or Ifn with ribavirin only. As we have seen in the patient dynamics analysis, the number of antiviral drug-treated patients will start to decline in 2017 in any of the scenarios. Therefore, we have set the criteria of which regimen we should include to our analysis, as (i) containing at least one small molecule DAA (note that ribavirin will not be considered as DAAs) and, (ii) has been launched or is expected to launch before the end of 2016. Based on these criteria, products/pipeline listed in Table 4 will be covered in our analysis.

Table 4. The scope of this analysis (manufacturer)

Genotype 1	Genotype 2
• Harvoni (Gilead Sciences) • Viekirax (Abbvie) • Daklinza/Sunvepra (Bristol Myers Squibb) • grazoprevir/elbasvir (Merck Sharp & Dohme) • Ifn-containing triple therapy	• Sovaldi (Gilead Sciences) • Viekirax (Abbvie) • Ifn-containing triple therapy

Underscored products are filed but yet to be launched as of February 2016.

Note that since patients infected with HCV genotype 1 and 2 are managed based on distinct treatment strategies, we have segmented the products in this manner. However, other segmentations such as treatment naïve/2nd line or compensated/decompensated cirrhosis are not taken into consideration in this report. Emerging pan-genotypic treatments such as ABT-493/530, velpatasvir, and samatasvir are also out of scope due to their late launch.

Based on the latest hepatitis C treatment guidelines (which reflect the current perception of treatments in the physician community), we will now look into the profiles of the respective products.

1. Treatments for HCV Genotype 1
    a. Harvoni

Harvoni is manufactured and supplied by Gilead Sciences and was launched on September 1, 2015. Harvoni is a fixed-dose combination tablet of an NS5B inhibitor, sofosbuvir 400 mg, and an NS5A inhibitor ledipasvir 90 mg. Among the available treatments as of February 2016, only Sovaldi and Harvoni contain NS5B inhibitors. A summary of the product attributes is described as follows.

- Efficacy: Rate of SVR achievement at treatment week 12 (SVR12) was 99%, highest among competitors, and even reached 100% when used without ribavirin in the domestic clinical trials. Y93H variation in the NS5A region of the virus genome did not affect the SVR achievement rate, and there have been no reports of any specific genetic variation that may impact the efficacy of the treatment.

- Safety: No significant, treatment of specific safety concerns have been reported to date (as of Feb 2016). Sofosbuvir is a renal excretion type agent, and it is contraindicated in patients with severe renal dysfunction or with hemodialysis.

- Dosage and administration: One tablet is taken once daily for 12 weeks.

    b. Viekirax

In Japan, Viekirax is manufactured and supplied by Abbvie. It was launched on November 26, 2016. Viekirax is a fixed-dose combination tablet of an NS5A inhibitor, ombitasvir 12.5 mg, an NS3/4A protease inhibitor, paritaprevir 75 mg, and ritonavir 50 mg which works as a booster for ombitasvir.

- Efficacy: SVR12 was as high as 95.3% in the domestic clinical trials. However, SVR achievement rates are known to decline in NS5A-Y93H variants. Patients are recommended to test this variation before receiving Viekirax (this genetic testing is not covered by the national health insurance as of February 2016).
- Safety: Liver impairment cases are observed in patients treated with Viekirax; patients with Child-Pugh grade B or C liver damage are contraindicated from this treatment. Edema is also a known side effect.
- Dosage and administration: Two tablets are taken once daily for 12 weeks.

c. Daklinza/Sunvepra

Launched on September 3, 2014, Daklinza/Sunvepra is manufactured and supplied by Bristol Myers Squibb. Daklinza is a tablet containing 60 mg of an NS5A inhibitor, daclatasvir, and Sunvepra is an oral capsule containing 100 mg of an NS3/4 inhibitor, asunaprevir.

- Efficacy: SVR12 was 89.1% in treatment naïve patients, and 84.7% in Ifn contraindicated or intolerant patients with whom previous treatments were ineffective. There are known resistance viral mutations for both of the drugs, and it is particularly recommended to test Y93 and L31 mutations in the NS5A region before treating a patient with these drugs. Also, it is known that viruses will acquire multiple new resistance mutations once this treatment fails. There are no established treatments for these mutation-acquired viruses.
- Safety: Liver impairment cases are observed in patients treated with Daklinza/Sunvepra; patients with Child-Pugh grade B or C liver damage are contraindicated from this treatment.
- Dosage and administration: Both tablets are taken once daily for 24 weeks.

d. grazoprevir/elbasvir (sold as Zepatier outside of Japan)

Grazoprevir/elbasvir is being developed by Merck Sharp & Dohme. It was filed with the Japanese authorities on March 11, 2016. Grazoprevir is an NS3/4A protease inhibitor, and elbasvir is an NS5A inhibitor.

- Efficacy: Domestic clinical trial data are not available as of February 2016. SVR12 was 95% in foreign studies. We will assume grazoprevir/elbasvir to have a product profile equivalent to that of Viekirax since both treatments share the same mode of action.
- Safety: Domestic clinical trial data are not published as of February 2016. Foreign data suggest this drug be well tolerated in patients.
- Dosage and administration: Taken once daily for 12 weeks.

e. Ifn-containing triple therapy

Ifn-containing triple therapy for HCV Genotype 1 consists of peg-Ifn, ribavirin, and an NS3/4A protease inhibitor, either simeprevir or vaniprevir. Janssen Pharmaceutical and Merck Sharp & Dohme,

respectively, are manufacturing and supplying the product. Telaprevir seems to have finished its once important role as a treatment of this indication.

- Efficacy: Domestic clinical trial data are similar between simeprevir and vaniprevir, with both SVR24s being around 80~90%. Both have shown lower SVR rates in patients who had failed with previous Ifn containing treatments.
- Safety: Side effects and their frequencies were similar to what was seen in peg-Ifn and ribavirin combination therapy without DAAs. Flu-like symptoms which are side effects of Ifn, as well as hemolytic anemia of ribavirin, were observed. Ribavirin is mainly excreted in urine, and judicious use will be required for subjects with renal impairment. Ribavirin is contraindicated in hemodialysis patients.
- Dosage and administration: Simeprevir and vaniprevir are taken once and twice daily, respectively, for 24 weeks. Peg-Ifn is administered subcutaneously once every week. Ribavirin is taken twice daily.

2. Treatments for HCV Genotype 2
    a. Sovaldi

Sovaldi is manufactured and supplied by Gilead Sciences and was launched on May 25, 2015. Sovaldi is a tablet containing sofosbuvir 400 mg. Sofosbuvir monotherapy is insufficient in its efficacy and will be used together with ribavirin.

- Efficacy: SVR12 was as high as 97% in domestic clinical trials, and its efficacy is not affected by any known background factors.
- Safety: Contraindicated in severe renal impairment patients and hemodialysis patients.
- Dosage and administration: One tablet of Sovaldi is taken once daily for 12 weeks. Ribavirin is taken twice daily.

    b. Viekirax

Abbvie also filed for approval of Viekirax for the indication for HCV genotype 2 infection on December 17, 2015.

- Efficacy and Safety: Neither domestic nor overseas clinical trial data for HCV genotype 2 infection are available as of February 2016. In our assumptions, we will consider Viekirax to have an equivalent product profile in genotype 2 as well as in 1 in Japanese subjects.
- Dosage and administration: Two tablets are taken once daily for 12 weeks.

    c. Ifn-containing triple therapy

Ifn-containing triple therapy for HCV Genotype 2 consists of peg-Ifn, ribavirin, and an NS3/4A protease inhibitor telaprevir. Mitsubishi Tanabe is supplying this drug in the brand name of Telavic. This indication was approved on September 19, 2014.

- Efficacy: Domestic clinical trials suggested that the SVR24 for triple therapy was 85% in patients intolerant to or recurring from previous Ifn plus ribavirin therapy.

- Safety: High frequency of side effects including rash and anemia caused by telaprevir administration is observed.
- Dosage and administration: Telaprevir is taken three times a day for 12 weeks. Peg-Ifn and ribavirin will last for 24 weeks.

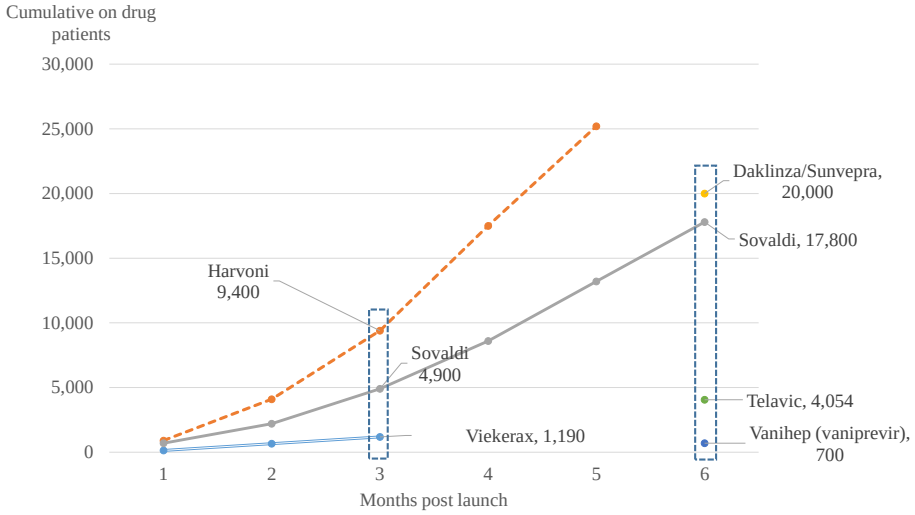
Profiles are quantified, and patient shares of each product are calculated using the e-Projection proprietary algorithm. Table 5 shows the calculated patient shares.

Table 5: Peak patient share assumptions for the respective products in the HCV DAA market

Genotype 1		Genotype 2	
Harvoni	66%	Sovaldi	78%
Viekerax	12%	Viekirax	18%
Daklinza/Sumvepra	6%	Ifn-containing triple therapy	4%
grazoprevir/elbasvir	10%		
Ifn-containing triple therapy	6%		

To cross check these assumptions with different data sources, we looked into the EPPV data published by each of the license holding companies. Figure 5 shows the uptake of cumulative patient numbers receiving the respective drugs post-launch, which was available as of February 2016. In this data, we can observe a striking difference in patient uptake between Viekirax and Harvoni, which the difference at three months after launch is 8 fold. We can hypothesize that the dominant product profile of Harvoni against Viekirax is reflected in the actual patient uptake.

Figure 5: Monthly patient uptake of HCV DAA products



Source: Early Postmarketing Phase Vigilance data available as of February 2016.

Pricing and Market Access Scenarios

The final process of forecast development will be constructing the pricing and market access assumptions. First, we will look into the current NHI price which is the listed price of the pharmaceuticals reimbursed in Japan. Note that in April 2016, the so-called “Special Repricing” policy was introduced, and this policy cut up to 35% of the price on Harvoni, Sovaldi, Viekirax and Daklinza/Sunvepra. Prices before and after the price cut are compared in Table 6.

Table 6: Prices and price assumptions of the HCV DAAs in Japanese Yen.

	Before Special Repricing		After Special Repricing	
	Price per day	Regimen price	Price per day	Regimen pricea
Genotype 1				
Harvoni	80,171	6,734,389	54,797	4,602,940
Viekirax	53,602	4,502,602	46,115	3,873,660
Daklinza/Sunvepra	15,747	2,645,563	13,598	2,284,414
grazoprevir/elbasvir	-	-	46,115	3,873,660
Genotype 2				
Sovaldi	61,799	5,191,141	42,240	3,548,126
Viekerax	-	-	46,115	3,873,660

We assume that grazoprevir/elbasvir and Viekirax for genotype 2 will be granted a price equivalent to the current Viekirax for genotype 1.

There is a high level of uncertainty regarding the future NHI pricing policies. One is the possibility of another "Special Repricing" (which will not be "Special" anymore if it happens this regularly; most likely the name of the policy should change) in April 2018 at the same timing with the regular biennial price cuts. Another is the viability of the so-called "New Premium System for the Promotion of Innovative Drug Discovery and Resolution of Off-Label Use" (or in short the "Innovative Drug Pricing") policy. In brief, this will exclude innovative new drugs from regular price cutting as exceptions and maintain their NHI prices until their exclusivity (e.g., patent life) expires. This was set up as a tentative policy in 2010, meaning that it is not guaranteed that the NHI prices of the DAAs will be maintained into the future, especially when the government is under an extremely tight budget constraint. Once this policy falls apart completely or even partially, we can assume that the drugs taken off of their exclusion will suffer from an average of 6% biennial price cut.

To deal with this uncertainty, we have considered two scenarios which are described in Table 7. These represent the best and worst cases of a probable outcome range, and most likely the reality will fall somewhere in between.

Table 7. NHI price scenario assumptions

Best case	Worst case
• No "Special Repricing" in 2018. • "Innovative Drug Pricing" will still be in place until 2025, NHI prices will be maintained in all HCV DAAs.	• "Special Repricing" happens once again and all NHI prices of HCV DAAs will be cut by 35%. • "Innovative Drug Pricing" abandoned in 2020 and 6% biennial price cut will happen to all HCV DAAs onwards.

Another uncertainty is regarding the market access of the HCV DAAs. Currently, local governments cover most of the patient co-pay (which is usually 30% of the NHI price in Japan) for HCV DAA treatments, and this financial support explains why the patients have relatively easy access to these extremely expensive drugs. Once again due to the tight national budget, we do not know if this coverage will last until the end of the forecast period. Here we can construct another pair of scenarios regarding the market access conditions of the HCV DAAs as shown in Table 8.

Table 8. Market access scenario assumptions

Best case	Worst case

• Local governments keep on supporting patient co-pay for HCV DAAs at least until 2025	• HCV treatment coverage will discontinue in 2020 and patients will be asked to cover 30% co-pay • Based on this decision in 2019 a rush demand will happen and will cause a 25% increase in the number of patients receiving HCV DAAs. However, the demand will be cut by 50% in later years.

Once again, most likely the real outcome will fall somewhere in between the two cases.

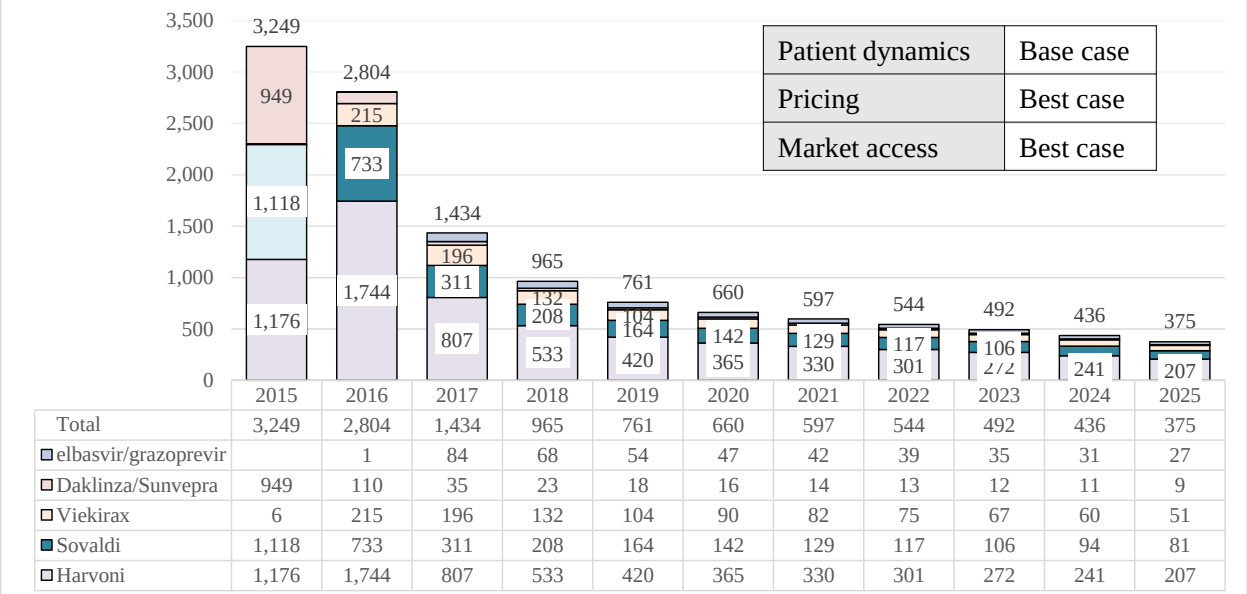
Scenario-based forecasts

Below are six scenarios depicting a various combination of three parameters; patient dynamics, pricing, and market access. We forecasted the respective sales of the products based on these scenarios.

	Scenario 1 (Fig 6-1)	Scenario 2 (Fig 6-2)	Scenario 3 (Fig 6-3)	Scenario 4 (Fig 6-4)	Scenario 5 (Fig 6-5)	Scenario 6 (Fig 6-6)
Patient dynamics	Base	Best	Likely	Likely	Likely	Likely
Pricing	Best	Best	Best	Worst	Best	Worst
Market access	Best	Best	Best	Best	Worst	Worst

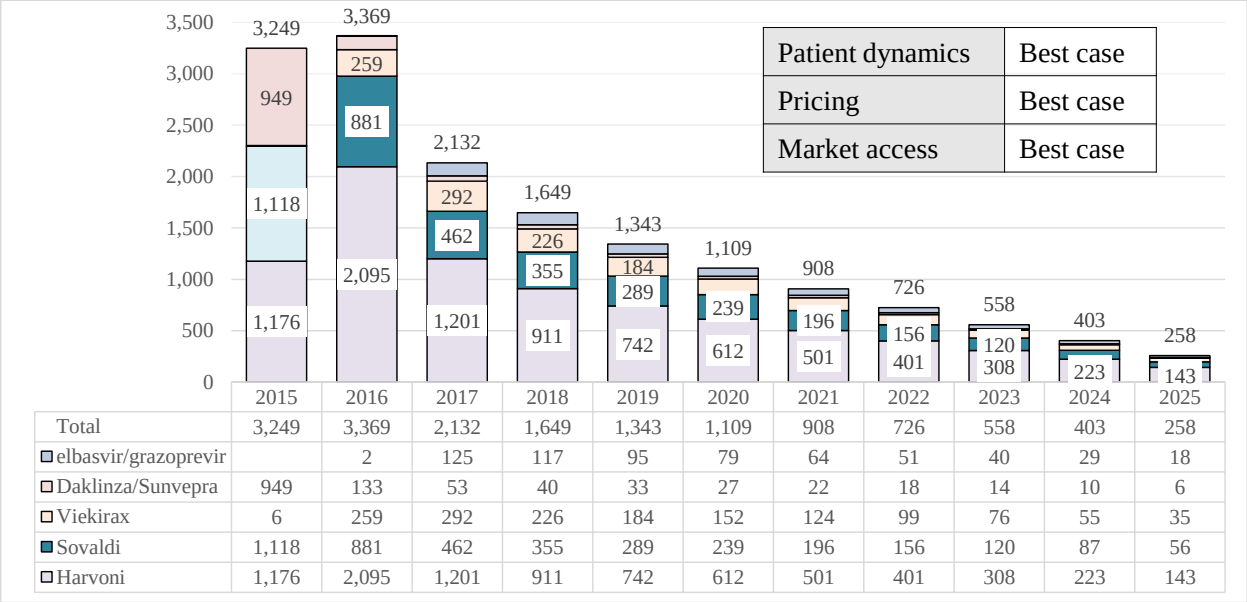
The first scenario shows how the patient dynamics will impact the forecast by fixing the scenarios in pricing and market access both to their best cases but change the patient dynamics.

Figure 6-1. Sales forecasts of the HCV DAAs (in hundred million yen ≈ million USD).



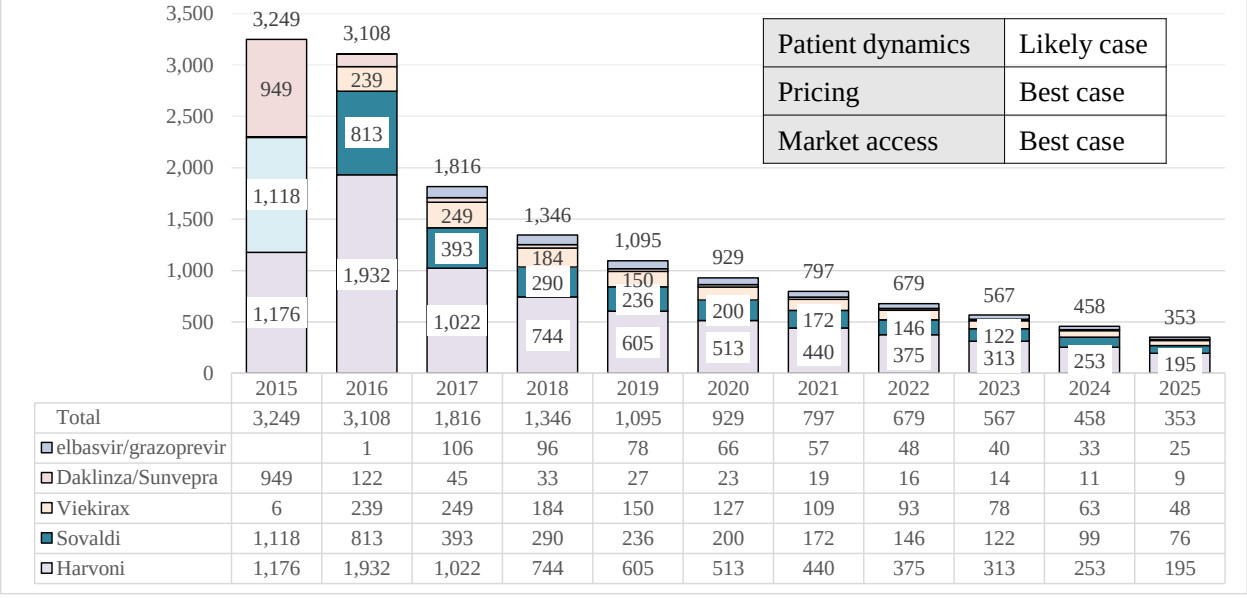
	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Total	3,249	2,804	1,434	965	761	660	597	544	492	436	375
elbasvir/grazoprevir		1	84	68	54	47	42	39	35	31	27
Daklinza/Sunvepra	949	110	35	23	18	16	14	13	12	11	9
Viekirax	6	215	196	132	104	90	82	75	67	60	51
Sovaldi	1,118	733	311	208	164	142	129	117	106	94	81
Harvoni	1,176	1,744	807	533	420	365	330	301	272	241	207

Figure 6-2. Sales forecasts of the HCV DAAs (in hundred million yen ≈ million USD).



	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Total	3,249	3,369	2,132	1,649	1,343	1,109	908	726	558	403	258
elbasvir/grazoprevir		2	125	117	95	79	64	51	40	29	18
Daklinza/Sunvepra	949	133	53	40	33	27	22	18	14	10	6
Viekirax	6	259	292	226	184	152	124	99	76	55	35
Sovaldi	1,118	881	462	355	289	239	196	156	120	87	56
Harvoni	1,176	2,095	1,201	911	742	612	501	401	308	223	143

Figure 6-3. Sales forecasts of the HCV DAAs (in hundred million yen ≈ million USD).

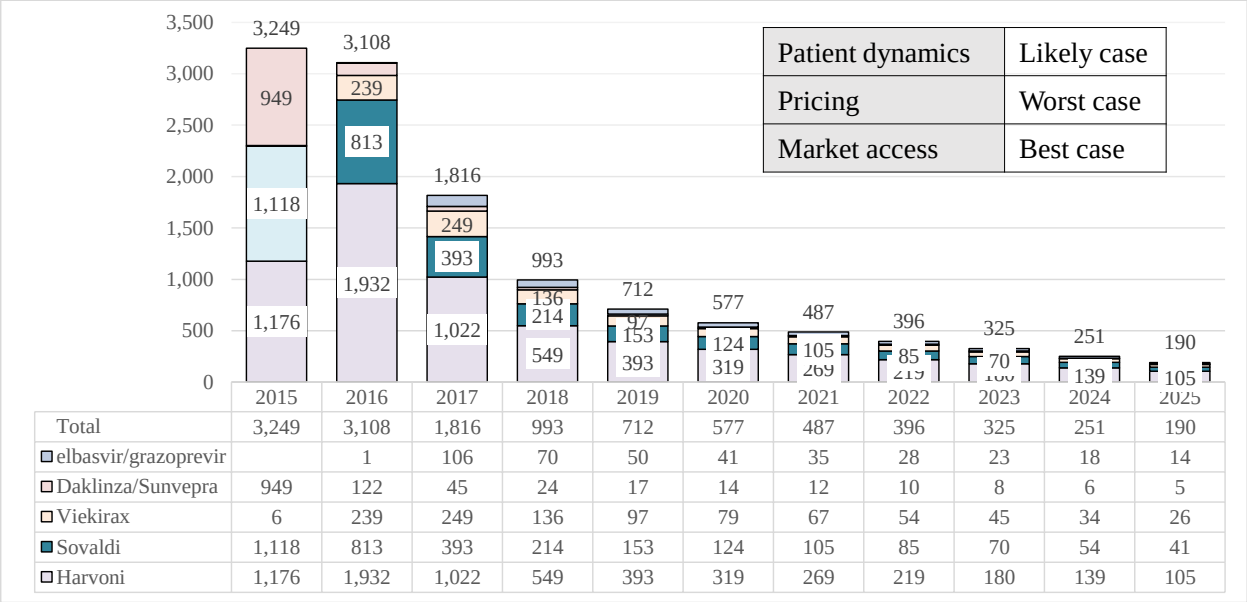


	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Total	3,249	3,108	1,816	1,346	1,095	929	797	679	567	458	353
elbasvir/grazoprevir		1	106	96	78	66	57	48	40	33	25
Daklinza/Sunvepra	949	122	45	33	27	23	19	16	14	11	9
Viekirax	6	239	249	184	150	127	109	93	78	63	48
Sovaldi	1,118	813	393	290	236	200	172	146	122	99	76
Harvoni	1,176	1,932	1,022	744	605	513	440	375	313	253	195

All else equal, there will be a difference of about 700 million USD in 2017 and 2018 between the best case and the base case.

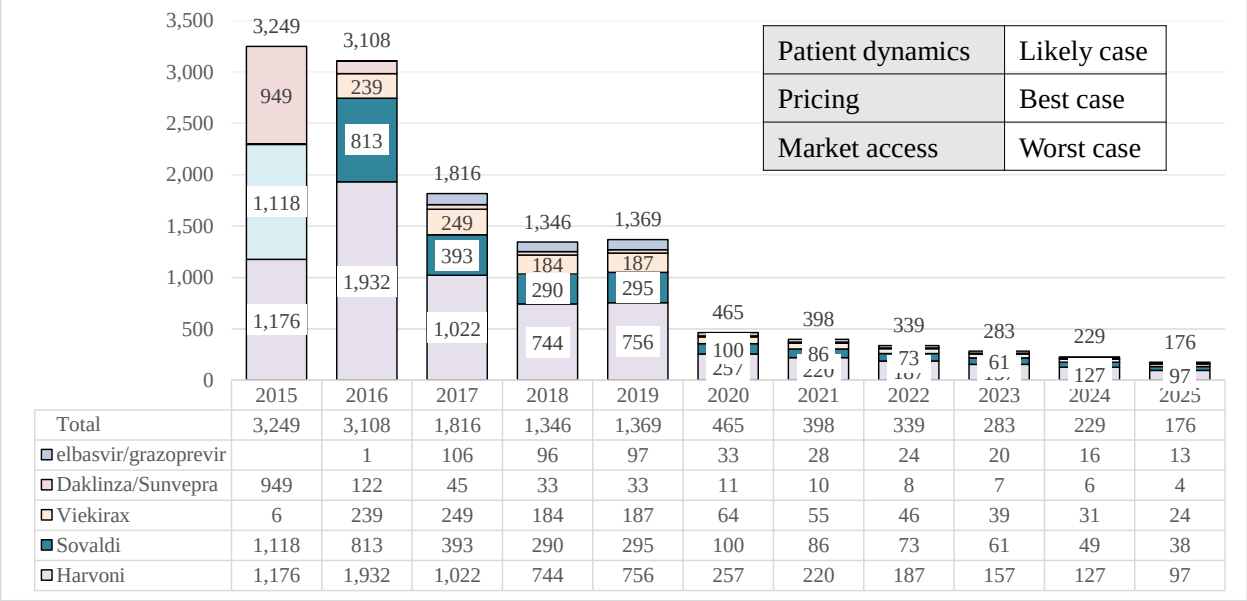
Now we will see the impact of pricing and market access by fixing the patient dynamics to the likely case but change the pricing and market access scenarios.

Figure 6-4. Sales forecasts of the HCV DAAs (in hundred million yen ≈ million USD).



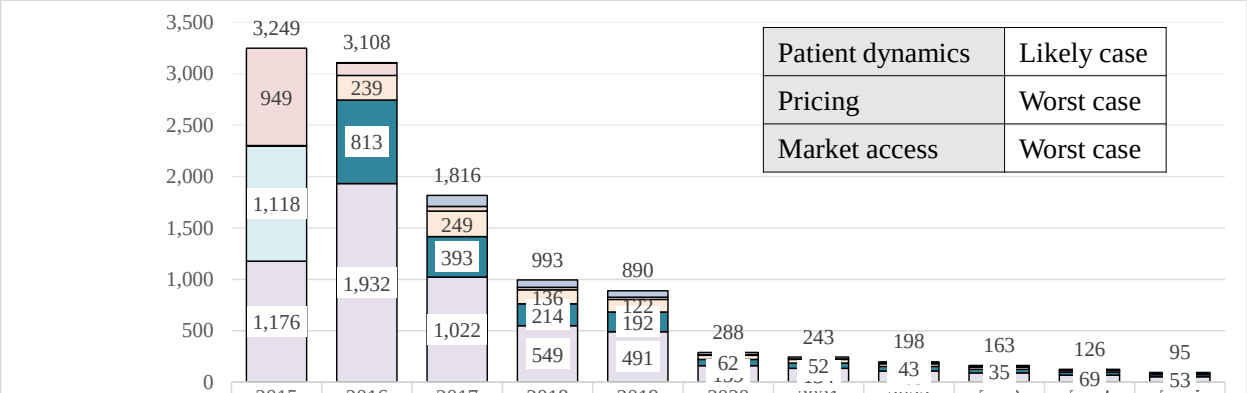
	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Total	3,249	3,108	1,816	993	712	577	487	396	325	251	190
elbasvir/grazoprevir		1	106	70	50	41	35	28	23	18	14
Daklinza/Sunvepra	949	122	45	24	17	14	12	10	8	6	5
Viekirax	6	239	249	136	97	79	67	54	45	34	26
Sovaldi	1,118	813	393	214	153	124	105	85	70	54	41
Harvoni	1,176	1,932	1,022	549	393	319	269	219	180	139	105

Figure 6-5. Sales forecasts of the HCV DAAs (in hundred million yen ≈ million USD).



	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Total	3,249	3,108	1,816	1,346	1,369	465	398	339	283	229	176
elbasvir/grazoprevir		1	106	96	97	33	28	24	20	16	13
Daklinza/Sunvepra	949	122	45	33	33	11	10	8	7	6	4
Viekirax	6	239	249	184	187	64	55	46	39	31	24
Sovaldi	1,118	813	393	290	295	100	86	73	61	49	38
Harvoni	1,176	1,932	1,022	744	756	257	220	187	157	127	97

Figure 6-6. Sales forecasts of the HCV DAAs (in hundred million yen ≈ million USD).



	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025
Total	3,249	3,108	1,816	993	890	288	243	198	163	126	95
elbasvir/grazoprevir		1	106	70	63	20	17	14	12	9	7
Daklinza/Sunvepra	949	122	45	24	22	7	6	5	4	3	2
Viekirax	6	239	249	136	122	39	33	27	22	17	13
Sovaldi	1,118	813	393	214	192	62	52	43	35	27	21
Harvoni	1,176	1,932	1,022	549	491	159	134	109	90	69	53

All else equal, there will be a difference of about 650 million USD in 2020 between the highest and the lowest case.

Implications of the forecast model

1. HCV DAA market size will shrink from 2016 onwards

In addition to the naturally decreasing patient population, emergence of new, highly effective drugs such as Harvoni and Sovaldi will reduce the number of the hepatitis C patients quickly, and the market left for products that will launch later than elbasvir/grazoprevir would be small in any of the scenarios discussed in this report.

2. Sovadi and Harvoni will prevail in the HCV DAA marketplace.

The EPPV data suggests that the two sofosbuvir based treatments will almost monopolize each genotypic market, which is presumably due to the dominant product profile against its competitors. There is virtually no tradeoff in their attributes except for the contraindications in renal impairment patients. This profile advantage is paramount in this nature of the treatment for hepatitis C where the drug is used effectively as prophylaxis of cirrhosis and liver cancer, and the majority of the HCV carriers are without any symptoms. Therefore, a small difference in product profiles will significantly affect the preference of the available alternatives. Also from the perspective of forecast modeling, the extremely high cure rates (SVR achievement rates) will free the analysis from taking further lines of treatments into consideration (i.e., will allow us to ignore the resistant patients looking for other treatment options).

3. Pricing and market access restriction policies will have significant implications

In the case of pricing and the market access policy both being at the worst cases, the market size will decrease by 69% from 929 million to 288 million yen, suggesting a significantly high level of sensitivity in sales of the HCV DAA products against political decisions. This may suggest the importance of lobbying activities for the manufacturers playing in this market.

Conclusions

Here we have developed a long-term forecast until 2025 for the HCV DAAs in Japan. Using a simple stochastic process model we have shown that the once expanded HCV DAA market as large as 300 billion yen (approx. 3 billion US dollars) will start to contract in the next couple of years due to the decreasing number of patients over time. The simplicity of the model allows the forecast to be flexible enough for certain modifications to the patient behavior assumptions. Our market share model quantified the product profiles into expected market (patient) shares which were externally validated by other independent data sources. We have employed multiple scenarios regarding patient dynamics, pricing, and market access, to deal with the high level of uncertainty. This multi-case approach was useful in visualizing the sensitivities of those external factors, helpful in suggesting strategic directions to maximize the product value, and in depicting the implications to the national social security budget.

Disclaimer: Neither Toshiaki Nagate nor e-Projection will be responsible to any extent of any decisions, including any stock purchase or sell, made by any third party, based on this report.

Declarations of potential conflict of interest: Neither Toshiaki Nagate nor e-Projection owns any of the stocks of the companies that are discussed in this report as of February 2016. Toshi Nagate was employed by Abbvie/Abbott from 2009 to 2013

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[7] https://www.ims-japan.co.jp/japanese/topline/ (confirmed on Sep 23, '16)
[8] http://ganjoho.jp/reg_stat/statistics/dl/index.html#incidence (confirmed on Sep 23, '16): note that liver cancer deaths are not the actual observed numbers of subjects that dropped out from drug treated patient pool. We used this data as a benchmark assumption due to lack of any other relevant data and hepatitis C patients who could not tolerate drug treatment would eventually decease from liver cancer. A supportive finding may be the fact that the rate of observed liver cancer deaths per drug treated patients (g) was stable over time.