WHO Essential Medicines List Application

OMBITASVIR, PARITAPREVIR/RITONAVIR co-formulated tablet with or without DASABUVIR
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1) Summary statement of the proposal for inclusion, change or deletion

Ombitasvir/paritaprevir/ritonavir (25/150/100 mg) administered with or without dasabuvir (250 mg) is a newly approved all-oral regimen for the treatment of hepatitis C virus (HCV) developed by AbbVie Inc. The full regimen is comprised of four medications: ombitasvir, a potent NS5A inhibitor; paritaprevir, an inhibitor of the NS3/4A serine protease; dasabuvir, a non-nucleotide analogue inhibitor of NS5B polymerase; and ritonavir, used as a pharmacologic booster for paritaprevir. The regimen is used in combination with ribavirin in certain patient populations. It is proposed for inclusion in the WHO Model List of Essential Medicines (EML) as a treatment for adults with chronic HCV infection, either inclusive of dasabuvir for the treatment of genotype 1 (GT1), or without dasabuvir for treatment of genotype 4 (GT4).

The rationale for the inclusion of the regimen on to the WHO EML is as follows:

- Chronic HCV is of considerable public health interest from both a health and economic perspective due to the significant morbidity and healthcare costs associated with the disease
- Transmission of the disease is associated with major health inequity with the burden of the disease falling heaviest in low- and middle-income countries (LMICs) and marginalised groups
- Uptake of treatment for HCV has traditionally been very low due to the poor success rate, severe side effects, and long treatment durations
- New all-oral regimens have the potential to revolutionise treatment and monitoring, and moreover, are suitable for treatment scale-up in resource-limited settings
- Treatment with ombitasvir/paritaprevir/r ± dasabuvir ± ribavirin offers a number of potential benefits:
  - Optimal rates of sustained virologic response (SVR) in a variety of populations, including GT1 and GT4 treatment-naive and experience patients with or without cirrhosis, those co-infected with HIV-1, and recipients of liver transplants (>90% SVR in all treatment arms)
  - High tolerability with a favourable safety profile across all patient populations; the improved safety profile is expected to increase patient adherence to treatment minimising the development of viral resistance
  - First regimen to target three distinct stages in the lifecycle of HCV, and as such, when used in combination, confers high levels of resistance
- The major limitations of the regimen are its genotype-restricted activity, the necessity to include ribavirin in certain patient populations, the potential for major drug-drug interactions, and the high pill burden in comparison with other regimens
- Trials to examine the regimen in additional genotypes (GT2/GT3) and in a variety of populations, such as those with liver decompensation, and those with renal impairment or transplantation are in progress
- Ombitasvir/paritaprevir/r is currently being investigated in combination with alternative drugs which may widen the target population
- Inclusion of all-oral regimens on the EML will be crucial for treatment-scale up, providing the impetus for generic competition and increased dedicated national and international funding
2) Name of the focal point in WHO submitting or supporting the application (where relevant)

Nathan Ford

3) Name of the organisation(s) consulted and/or supporting the application

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4) International Nonproprietary Name (INN, generic name) of the medicine

- Ombitasvir, paritaprevir, and ritonavir
- Dasabuvir

5) Formulation proposed for inclusion; including adults and paediatric (if appropriate)

Ombitasvir/paritaprevir/ritonavir with or without dasabuvir, manufactured by AbbVie Inc. and approved as either Viekira Pak™ (complete multi-pill regimen) or Viekirax™ (ombitasvir/paritaprevir/ritonavir) used in combination with Exviera™ (dasabuvir), for oral administration for adults as follows:

Two ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg) co-formulated film-coated tablets once daily (total daily dosage: 50/150/100 mg) PLUS one dasabuvir 250 mg table twice daily (total daily dosage: 500 mg) for treatment of chronic HCV GT1 infection. Treatment of HCV GT4 does not require the addition of the dasabuvir tablet. Each dasabuvir film-coated tablet contains 270.3 mg dasabuvir sodium monohydrate equivalent to 250 mg dasabuvir.

The ombitasvir/paritaprevir/ritonavir plus dasabuvir regimen for GT1 is used in combination with weight-based ribavirin in certain patient subpopulations (1000 mg/day for patients ≤75 kg and 1200 mg/day for those >75 kg). Ombitasvir/paritaprevir/ritonavir for GT4 is routinely administered in combination with weight-based ribavirin.
The safety and efficacy of the regimen in children less than 18 years of age have not yet been established and thus no paediatric formulation is proposed for inclusion.

6) International availability – sources, of possible manufacturers and trade names

Ombitasvir/paritaprevir/ritonavir co-formulated tablet (12.5/75/50 mg) plus dasabuvir tablet (250 mg):
Trade name: Viekira Pak™; Manufacturer: AbbVie Inc., US FDA approved December 19th 2014.

Dasabuvir tablet (Trade name: Exviera™; Manufacturer: AbbVie Inc.) and the ombitasvir/paritaprevir/ritonavir co-formulated tablet (Trade name: Viekirax™, Manufacturer: AbbVie Inc.) received separate European (EMA) approval on January 16th 2015.

Ribavirin, which is recommended for use with the regimen in specific patient populations, is off patent and available from numerous companies in generic formulations.

7) Whether listing is requested as an individual medicine or as an example of a therapeutic group

The request for inclusion is for the ombitasvir/paritaprevir/ritonavir co-formulation with or without dasabuvir, dependent on patient genotype.

8) Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

8.1) Epidemiology and burden of disease

Infection with hepatitis C virus (HCV) causes both acute and chronic infection; of those initially infected, approximately 55-85% progress to chronic HCV, of whom 15-30% will develop cirrhosis within 20 years (Thein et al. 2008). As such, the infection is a major contributor to liver disease, responsible for approximately one third of all cases of liver cirrhosis and hepatocellular carcinoma (HCC), and resulting in around 700,000 deaths every year (Naghabi et al. 2015). When grouped together, viral hepatitis ranks in the top 10 causes of mortality worldwide, higher than both tuberculosis and malaria (Cooke et al. 2013). Moreover, HCV infection is associated with morbidity and mortality independent of liver disease and accelerates the progression of other diseases such as human immunodeficiency virus (HIV-1); as such, the HCV burden is likely underestimated in current evaluations (Pearlman & Traub 2011; Cooke et al. 2013).
Recent data suggests that as many as 185 million individuals have been infected with HCV, representing almost 3% of the world population (Mohd Hanafiah et al. 2013). The prevalence of the infection varies considerably worldwide. It is most prevalent in Central and East Asia (3.8% and 3.7%, respectively), and in North Africa/Middle East (3.6%). In terms of number of people infected, the burden is heaviest in South and East Asia, each with over 50 million people living with HCV (Mohd Hanafiah et al. 2013). The burden falls disproportionately on LMICs where an estimated 85% of those chronically infected live (Londeix & Forette 2014).

HCV exhibits a high degree of genetic diversity with six major genotypes, each with several distinct subtypes (Messina et al. 2015). Therapy options need to be tailored to suit each genotype in terms of treatment options and duration. GT1 is most prevalent worldwide (46%), followed by GT3 infection (30%). Estimates suggest that GT2, 4, and 6 combined account for almost one-quarter of all infections, predominantly in LMICs despite being underserved by current therapy options. The AbbVie regimen is currently licensed for use in GT1 infection, which is prevalent worldwide, and GT4, which is most prevalent in sub-Saharan Africa and North Africa and the Middle East.

The significance of transmission routes varies widely between geographical populations and behaviour groups. Transmission of the disease is associated with major health inequity; the burden is heaviest in LMICs and marginalised groups. In LMICs, HCV is transmitted primarily through unsafe injection practices and procedures in both healthcare and community settings (Hauri, Armstrong & Hutin 2004). Risk factors include unsafe blood transfusions, non-sterilised medical equipment, traditional healing practices, and circumcision procedures. Due to improved infection control practices, HCV transmission has decreased significantly in high-income countries over the past two decades (Armstrong et al. 2006). The majority of new HCV infections in middle- and high-income countries are associated with injection drug use, and it is becoming an ever more significant risk factor for transmission in low-income countries. Recent estimates suggest that over 10 million of the 16 million injecting drug users (IDUs) worldwide are infected with HCV, with the prevalence in IDUs peaking over 90% in certain Eastern European and South and East Asian countries (Nelson et al. 2011). Other important transmission routes included mother-to-child transmission, and sexual transmission, particularly in men who have sex with men (MSM) (Mast et al. 2005; Wandeler et al. 2015).

Due to the common risk factors for transmission, co-infection with HIV-1 is common, and globally as many as 5 million persons may be co-infected with the two viruses (Alter 2006). This equates to approximately 20% of HIV-positive individuals living with HCV co-infection, though this prevalence varies considerably by risk group and is highest in individuals with history of IDU, haemophiliacs, and recipients of contaminated blood (Soriano et al. 2010). New WHO estimates of HIV-1/HCV co-infection prevalence are expected.
The high co-prevalence is especially important given that the relationship between the two viruses accelerates the progression of HCV infection compared to HCV mono-infection, leading to higher rates of cirrhosis, HCC, and mortality in this population. Since the introduction of antiretroviral therapy (ART), which has significantly increased the life-expectancy of HIV-positive individuals, it is estimated that patients co-infected with HCV are at a 35% increase risk of mortality compared with HIV-1 mono-infected patients (Chen et al. 2009). Furthermore, for those with a diagnosis of AIDS, chronic HCV co-infection was independently associated with a 50% increase in mortality (Branch et al. 2012). As such, chronic HCV is now the leading cause of death, after AIDS-related complications, among HIV-infected individuals in regions where ART is available (Weber et al. 2006). HCV infection may also impact the progression of HIV infection, although this evidence is less clear (Tedaldi et al. 2003; Rockstroh et al. 2005).

Eradication of infection is the most effective way to reduce the incidence of liver cirrhosis and HCC and can be achieved through drug therapy (van der Meer et al. 2012). As shown in a recent meta-analysis, treatment success, defined as undetectable HCV RNA 12 or 24 weeks post treatment (sustained virologic response; SVR), is associated with significantly improved survival 5-years post-treatment for both mono-infected patients and those co-infected with HIV-1 (Hill et al. 2014). The same study showed a decrease in risk of HCC and liver transplantation compared to non-SVR patients over the same time period. Additionally, life expectancy of patients with HCV infection and advanced fibrosis or cirrhosis who achieve SVR has been shown to be comparable to that of the general population (van der Meer et al. 2014).

Traditionally, treatment has consisted of weekly pegylated interferon (Peg-IFN) injections and daily ribavirin tablets for one year. Treatment uptake has been consistently poor in view of the poor success rates, long treatment duration, contraindications, and severe side-effects to therapy (Clark et al. 2014). A recent study was conducted to evaluate treatment uptake in 2013 in sixteen countries, including Australia, Brazil Canada, Egypt, and a number of European countries (Razavi et al. 2014). In nine of the countries, less than 1.5% of the HCV infected population received treatment and the treatment rate only exceeded 5% in France (5.2%).

New therapy options, known as direct-acting antiviral (DAA) regimens, offer the promise of increased success rates, complimented by shorter treatment durations, improve side-effect profiles, and simplified treatment monitoring. Combined, these qualities support treatment scale-up in resource-limited settings, where treatment outcomes have been shown to be similar to those in high-income countries (Ford et al. 2012). A recent study suggests that despite the improved treatment efficacy associated with new regimens, an increase in the level of diagnosis and treatment will be critical to achieve a substantial reduction in disease burden (Gane et al. 2015). This is particularly pertinent given that, despite a projected decline in the total number of HCV infections to 2030, the number of individuals with late-stage liver disease is expected to substantially increase, placing an unprecedented demand on health systems worldwide (Razavi et al. 2014).
It is these reasons that provide the rationale for DAAs, including the AbbVie ombitasvir/paritaprevir/r plus dasabuvir regimen, to be included on the EML. Inclusion will help to ensure timely access to HCV treatment worldwide, alleviating the future HCV health and economic burden. Furthermore, inclusion will promote health equity, given that the burden falls heaviest in those of low socioeconomic status, and marginalised groups with increased risk of all-cause mortality and poor access to health care (WHO 2014).

8.2) Assessment of current use

Ombitasvir/paritaprevir/r and dasabuvir with or without ribavirin is indicated for use as a treatment for chronic HCV GT1 infection in adults, regardless of fibrosis stage or treatment history. Additionally, in Europe a simplified regimen of ombitasvir/paritaprevir/r and ribavirin has been licensed for the treatment of chronic GT4 infected adult patients. The regimen is currently not indicated for children and adolescents due to the lack of safety and efficacy data in this population.

The regimen is an all-oral, short-duration therapy that does not require co-administration with Peg-IFN. These characteristics offer the potential for shortened and simplified treatment and monitoring regimens compared to traditional Peg-IFN based treatments, and the regimen is accompanied by reduced rates of adverse events and drug-drug interactions. Furthermore, the regimen offers the potential for treatment of patients that would typically have been contraindicated, such as those with autoimmune disease, or current IDUs. The regimen is the first approved treatment for chronic HCV to combine three DAA agents with distinct mechanisms of action to target the virus at multiple steps in its lifecycle. This combination approach increases the likelihood of treatment success and reduces the chances of relapse after treatment. Moreover, the three DAAs have non-overlapping resistance profiles and as such have a high barrier to resistance when used in combination (Kati et al. 2015). This is particularly important given the rapid mutation rate of the virus that can lead to limited treatment efficacy and cross-resistance to other antivirals (Strahotin & Babich 2012). The major limitation of the regimen is its genotype-restricted activity. Despite this, GT1 infection is responsible for almost half of HCV infections worldwide, and G4 is predominant in highly endemic regions such as Egypt and across Central and North Africa and the Middle East (Messina et al. 2015). As shown in

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ombitasvir, 25 mg</th>
<th>Paritaprevir, 150 mg</th>
<th>Ritonavir, 100 mg</th>
<th>Dasabuvir, 250 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV DAA drug class</td>
<td>NS5A inhibitor</td>
<td>NS3/4A protease</td>
<td>PK enhancer</td>
<td>Nonnucleoside NSSB polymerase inhibitor</td>
</tr>
<tr>
<td>In vitro antiviral activity, genotypes</td>
<td>1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a</td>
<td>1a, 1b, 2a, 3a, 4a, and 6a</td>
<td>n/a</td>
<td>1a and 1b</td>
</tr>
<tr>
<td>Potency (GT1)</td>
<td>High</td>
<td>Moderate</td>
<td>n/a</td>
<td>Low</td>
</tr>
<tr>
<td>Resistance barrier</td>
<td>Low</td>
<td>Moderate</td>
<td>n/a</td>
<td>Low</td>
</tr>
</tbody>
</table>
Table 2. Daily pill burden of DAA Peg-IFN free regimens

<table>
<thead>
<tr>
<th>DAA regimen</th>
<th>Daily pill burden</th>
<th>Total pills</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ombitasvir/paritaprevir/r + dasabuvir ± ribavirin (GT1)</td>
<td>2 x ombitasvir/paritaprevir/r (12.5/75/50 mg) OD = 2 tablets + [3 x dasabuvir (250 mg) BID = 6 tablets]*</td>
<td>Without ribavirin: 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>With ribavirin: 10</td>
</tr>
<tr>
<td>Ombitasvir/paritaprevir/r + ribavirin (GT4)</td>
<td>2 x ombitasvir/paritaprevir/r (12.5/75/50 mg) OD = 2 tablets + 3 x ribavirin (200 mg) BID = 6 tablets*</td>
<td>8</td>
</tr>
<tr>
<td>Sofosbuvir + ribavirin (GT2/3)</td>
<td>1 x sofosbuvir (400 mg) OD = 1 tablet + 3 x ribavirin (200 mg) BID = 6 tablets*</td>
<td>7</td>
</tr>
<tr>
<td>Sofosbuvir + ledipasvir (GT1/4)</td>
<td>1 x sofosbuvir/ledipasvir (400/90 mg) OD = 1 tablet</td>
<td>1</td>
</tr>
<tr>
<td>Sofosbuvir + simeprevir (GT1/4)</td>
<td>1 x sofosbuvir (400 mg) OD = 1 tablet + 1 x simeprevir (150 mg) OD = 1 tablet</td>
<td>2</td>
</tr>
<tr>
<td>Sofosbuvir + daclatasvir (GT1/2/3/4)</td>
<td>1 x sofosbuvir (400 mg) OD = 1 tablet + 1 x daclatasvir (60 mg) OD = 1 tablet</td>
<td>2</td>
</tr>
</tbody>
</table>

*Assuming weight ≥75 kg (1200 mg daily dose); patients <75 kg require 5 x 200 mg (1000 mg daily dose)
Abbreviations: OD, once daily; BID, twice daily

Table 1, both ombitasvir and paritaprevir have shown potent multi-genotypic activity in vitro which could widen the use of the regimen to other genotypes after further evaluation (Pilot-Matias et al. 2015; Krishnan et al. 2015). Moreover, in the absence of truly pan-genotypic regimens, which will require the same treatment combination and duration for all genotypes, pre-treatment genotyping will still be necessary for the use of any regimen.

The pill burden of the ombitasvir/paritaprevir/r plus dasabuvir regimen is slightly greater than that of some other newly licensed regimens such as Harvoni™, the co-formulated ledipasvir/sofosbuvir tablet that only needs to be taken once daily (see Table 2). Despite this, the medication burden is considerably lower than that of Peg-IFN-based regimens which require weekly injections accompanied by daily tablets. The inconvenience is reflected in the marginally lower price of the regimen compared with other licensed treatments (see section 12.1) and is a small drawback given the high efficacy and barrier to resistance.

In total, over 3,000 GT1 patients and almost 200 non-GT1 from over 25 countries have completed Phase 2 or 3 clinical trial programmes to assess the efficacy and safety of ombitasvir/paritaprevir/r with or without dasabuvir. A number of other clinical trials are currently in progress or are anticipated to start to assess the regimen in a wider range of patient populations. Given that the regimen has only been recently licensed (December 2014 in the US and January 2015 in Europe), its use in patients outside of clinical trials has been limited; an unknown but small number of patients have received treatment as part of market use. The regimen was granted Breakthrough Therapy designation by the FDA, indicating a substantial improvement
over available therapies for HCV, and as such is likely to be rapidly included in international treatment guidelines, which will likely dramatically increase the demand for use (FDA 2014).

8.3) Target population

The ombitasvir/paritaprevir/r and dasabuvir regimen with or without ribavirin is suitable for the treatment of chronic HCV GT1 infection in a wide range of patient populations. The ombitasvir/paritaprevir/r and ribavirin regimen is suitable for use in GT4 infected patients. The regimens are indicated for use in patients over the age of 18, regardless of gender, race/ethnicity, HIV-1 status, or treatment history, and are suitable for use in liver transplant recipients. The safety in paediatric patients has not yet been established, and as such, the AbbVie regimens are currently contraindicated in children and adolescents. The safety and efficacy of the regimens have not yet been established in pregnant women or nursing mothers, and as such, should only be used if clearly needed and not in combination with the ribavirin. Both regimens are currently contraindicated in patients with decompensated cirrhosis; a study to evaluate the safety and efficacy of ombitasvir/paritaprevir/r and dasabuvir in this population is currently underway, and results are expected in 2016 (TURQUOISE-CPB).

At present, a Phase 3 study of the ombitasvir/paritaprevir/r and ribavirin regimen is being conducted in GT2 patients and co-administration of ombitasvir/paritaprevir/r with sofosbuvir and other new DAAs is being investigated in GT3. The scope of the regimen may be expanded dependent on the results of these studies.

9) Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

Ombitasvir/paritaprevir/r and dasabuvir is an all-oral regimen consisting of three DAAs each with a distinct mechanism of action and non-overlapping resistance profiles. For treatment of GT1, the regimen consists of two tablets: 1) a once-daily fixed-dose combination tablet consisting of co-formulated ombitasvir, a NSSA inhibitor, and the NS3/4A protease inhibitor paritaprevir, boosted by ritonavir and 2) a twice-daily tablet containing the non-nucleoside HCV NS5B polymerase inhibitor dasabuvir (AbbVie Inc. 2015). The combination of the DAAs interrupts the HCV replication process at three separate stages, with the aim of optimising sustained virologic response (SVR) rates across a variety of patient populations. Ritonavir has no activity against HCV, but as a potent CYP3A4 enzyme inhibitor, is used as a pharmacologic booster for paritaprevir. The regimen is used with or without ribavirin, dependent on the specific patient population. Dasabuvir has limited genotypic potency, and as such, for treatment of GT4-infection only the ombitasvir/paritaprevir/r tablet is required, in combination with ribavirin.
9.1) Indications and usage
Ombitasvir/paritaprevir/r and dasabuvir is currently EMA and FDA-approved for adult patients with HCV GT1, inclusive of those with compensated cirrhosis, and is the only approved regimen to target three separate stages of the HCV lifecycle (FDA 2014). The regimen is not recommended for use in patients with decompensated liver disease. The full three DAA regimen is currently not FDA-approved for use in any other genotype however a simplified regimen of ombitasvir/paritaprevir/r (Viekirax™) with ribavirin has received EMA approval for the treatment of HCV GT4.

9.2) Dosage regimen

9.2.1) Ombitasvir/paritaprevir/r and dasabuvir with or without ribavirin for treatment of genotype 1
The recommended oral dosage for GT1 is two ombitasvir, paritaprevir, ritonavir tablets (12.5/75/50 mg) once daily (in the morning) and one dasabuvir tablet (250 mg) twice daily (morning and evening). Tablets should be taken with food with no specific fat or calorie content (AbbVie Inc. 2015). Duration of treatment is 12 weeks for most patients; those with the harder-to-treat HCV subtype 1a and cirrhosis treated for 24 weeks (see Table 3). The regimen is taken in combination with weight-based ribavirin in patients with GT1a and those with cirrhosis in order to prevent relapse: 1000 mg/day for patients <75 kg and 1200 mg/day for patients ≥75 kg. Treatment dosage and duration is the same regardless of treatment history.

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype 1a, without cirrhosis</td>
<td>Ombitasvir/paritaprevir/ritonavir plus dasabuvir + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1a, with compensated cirrhosis</td>
<td>Ombitasvir/paritaprevir/ritonavir plus dasabuvir + ribavirin</td>
<td>24 weeks*</td>
</tr>
<tr>
<td>Genotype 1b, without cirrhosis</td>
<td>Ombitasvir/paritaprevir/ritonavir plus dasabuvir</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 1b, with compensated cirrhosis</td>
<td>Ombitasvir/paritaprevir/ritonavir plus dasabuvir + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 4, without cirrhosis</td>
<td>Ombitasvir/paritaprevir/ritonavir + ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Genotype 4, with compensated cirrhosis</td>
<td>Ombitasvir/paritaprevir/ritonavir + ribavirin</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

*12 week treatment may be considered for some patients based on prior treatment history
9.2.2) Ombitasvir/paritaprevir/r plus ribavirin for treatment of genotype 4

For patients infected with HCV GT4, the recommended treatment regimen consists of two oral ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg) tablets once daily with food in combination with weight-based ribavirin. For patients without cirrhosis, the treatment should be followed for 12 weeks; for those with compensated cirrhosis, treatment should be extended to 24 weeks (Table 3).

9.2.3) Special populations and contraindications

Dosage recommendations are the same for patients co-infected with HIV-1 however drug interactions need to be considered, particularly with HIV-1 protease inhibitors and other ritonavir boosted regimens. Liver transplant recipients with little or mild fibrosis (≤F2 Metavir) should be treated with ribavirin for 24 weeks, regardless of genotype subtype. No dosage adjustment is required in patients with mild hepatic impairment (Child-Pugh A) however the use of ombitasvir/paritaprevir/r and dasabuvir is not recommended in patients with mild impairment (Child-Pugh B) and is contraindicated in patients with severe impairment (Child-Pugh C; decompensated liver disease) due to risk of potential toxicity. No dosage adjustment is required for use in geriatric patients and the safety and effectiveness has not yet been established in patients under 18.

Co-administration with drugs highly dependent on CYP3A for clearance is contraindicated, as is administration with drugs that are strong inducers of CYP3A and CYP2C8, or strong inhibitors of CYP2C8. If administered with ribavirin, the contraindications to ribavirin also apply to the regimen, precluding its use in pregnant woman, those with haemoglobinopathies, and patients treated with didanosine.

9.2) WHO and other clinical guidelines

The current WHO HCV treatment guidelines do not include the use of the AbbVie regimens as they were released prior to approval of the regimen. They do however advocate the use of HCV DAAs approved at the time of publication (sofosbuvir and simeprevir) (WHO 2014). It is thus likely that the process of updating WHO guidelines will consider recommendations for all newly approved DAA regimens, including ombitasvir/paritaprevir/r with or without dasabuvir.

The regimens have been included in the AASLD/IDSA-IAS-USA guidance which was updated December 19th 2014 to reflect the new treatment options (AASLD/IDSA/IAS-USA 2015). The full ombitasvir/paritaprevir/r and dasabuvir regimen (with or without ribavirin) has been included as one of the strategies recommended for treatment-naïve and experienced patients with HCV GT1a or GT1b. Ombitasvir/paritaprevir/r with ribavirin has been listed as one of the preferred regimens for treatment of HCV GT4 infection. The regimens are not included on EASL recommendations as they had not received EMA approval before guideline release, but the regimens are expected to be included on updated versions (last updated April 2014). This wide-
spread international approval is expected to result in the update of guidelines from APASL and the World Gastroenterology Organisation (WGO), two associations representing the need of patients living in LMICs (last updated 2012 and 2013, respectively).

9.3) Diagnostics, treatment, and monitoring facilities

Diagnosis of HCV requires an initial HCV serologic test, HCV RNA viral load testing, and genotyping. Staging of liver fibrosis is also recommended by liver biopsy, or the less invasive liver ultrasound elastography or the use of indirect serarkers (MSF 2014). An assessment of potential drug-drug interactions with concomitant medications is recommended prior to starting antiviral therapy, particularly in the case of HIV-1 co-infected patients.

Treatment should be initiated and monitored by a physician experienced in the management of patients with chronic HCV. During therapy, HCV viral load testing is recommended after 4 weeks of therapy and at 12 weeks following completion of treatment; additional tests can be considered at the end of treatment and 24 weeks following completion (AASLD/IDSA/IAS-USA 2015). Baseline labs and monitoring should include full blood count, creatinine, and ALT measurements during the first 4 weeks and as clinically indicated thereafter. The WHO and other groups are in the process of determining the minimum number of diagnostic and monitoring tests required to start and monitor HCV treatment using different regimens.

The monitoring regimen for the AbbVie regimens is less specialised than for regimens containing Peg-IFN, inclusive of some new DAA regimens such as simeprevir plus Peg-IFN/ribavirin. Furthermore, the regimens are shorter than that of Peg-IFN/RBV. Combined these factors mean that total monitoring costs are likely to be lower and the simplified monitoring is facilitative of widespread scale-up in resource-limited settings.

10) Summary of comparative effectiveness in a variety of clinical settings:

A literature search was performed using PudMed (2005-February 2015) and EMBASE (2005-February 2015) databases with the following search terms used as either a keyword or in the title: ombitasvir, paritaprevir, dasabuvir, ABT-267, ABT-450, ABT-333, Viekira Pak, Viekirax, and Exviera. To supplement the search, abstracts and oral or poster presentations were extracted from the following conferences (2012-2014): AASLD, EASL, CROI, and AASLD/EASL Special Conference on Hepatitis C. The reference lists of articles were used to identify any further references. Lastly, clinical trial registries (clinicaltrials.gov) were review to identify any clinical trials currently in progress.
Data regarding efficacy and safety was extracted from the identified studies. Efficacy was measured by the attainment of a SVR12, defined as achieving undetectable HCV RNA 12 weeks post-treatment. For those patients without treatment success, reason for failure was investigated (on-treatment virological failure, relapse after treatment, treatment discontinuation [adverse events or other], or loss to follow-up).

10.1) Genotype 1

10.1.1) Phase 2

A number of Phase 2 studies have been carried out evaluating various combinations of ombitasvir, paritaprevir/r, and dasabuvir with or without ribavirin for treatment of HCV GT1. The studies include CO-PILOT (NCT01306617), PEARL-I (NCT01685203), NAVIGATOR (NCT01458535), AVIATOR (NCT01464827), NCT01672983, and NCT01563536 (Table 4).

Table 4. Completed Phase 2 clinical trials in genotype 1 infected patients (intent-to-treat analyses)

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Country</th>
<th>Study design</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>SVR12, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO-PILOT (Poordad et al. 2013)</td>
<td>US</td>
<td>Non-randomised, open-label</td>
<td>TN/TE, non-cirrhotic, GT1 (n=50)</td>
<td>Paritaprevir/r + dasabuvir + RBV (12 weeks)</td>
<td>TN: 31/33 (93.9%), TE: 8/17 (47.1%)</td>
</tr>
<tr>
<td>PEARL-I (Lawitz et al. 2013)</td>
<td>US, Puerto Rico, Europe</td>
<td>Randomised, open-label</td>
<td>TN/TE, non-cirrhotic, GT1b (n=82)</td>
<td>Ombitasvir/paritaprevir/r + dasabuvir (12 weeks)</td>
<td>TN: 40/42 (95.2%), TE: 36/40 (90.0%)</td>
</tr>
<tr>
<td>NAVIGATOR (Lawitz et al. 2015)</td>
<td>US, Puerto Rico</td>
<td>Non-randomised, open-label</td>
<td>TN, non-cirrhotic, GT1 (n=20)</td>
<td>Ombitasvir/paritaprevir/r ± RBV (12 weeks)</td>
<td>RBV: 10/10 (100%), No RBV: 6/10 (60.0%)</td>
</tr>
<tr>
<td>AVIATOR (Kowdley et al. 2014)</td>
<td>US, Canada, Australia, NZ, Europe</td>
<td>Randomised, open-label</td>
<td>TN/TE, non-cirrhotic, GT1 (n=571)</td>
<td>Paritaprevir/r ± ombitasvir ± dasabuvir ± RBV (8/12/24 weeks)</td>
<td>TN: 3D,8wks: 70/80 (88%), 2D,12wks: 70/79 (89%), 3D,12wks: 70/79 (89%), 3D+RBV,12wks: 76/79 (96%), 3D+RBV,24wks: 73/80 (91%), TE: 2D+RBV,12wks: 40/45 (89%), 3D+RBV,12wks: 42/45 (93%), 3D+RBV,24wks: 41/43 (95%)</td>
</tr>
<tr>
<td>NCT01563536 (Epstein et al. 2013)</td>
<td>US</td>
<td>Non-randomised, open-label</td>
<td>TN, non-cirrhotic, GT1 (n=12)</td>
<td>Ombitasvir/paritaprevir/r + dasabuvir + RBV (12 weeks)</td>
<td>10/12 (83%)</td>
</tr>
<tr>
<td>NCT01672983 (Chayama et al. 2015)</td>
<td>Japan</td>
<td>Randomised, open-label</td>
<td>TE, non-cirrhotic, GT1b (n=73)</td>
<td>Ombitasvir/paritaprevir/r (12 or 24 weeks)</td>
<td>12wks: 34/36 (94.4%), 24wks: 37/37 (100%)</td>
</tr>
</tbody>
</table>

Abbreviations: TN, treatment-naïve, TE, treatment-experienced; GT, genotype; RBV, ribavirin; 3D, ombitasvir/paritaprevir/r + dasabuvir; 2D, ombitasvir/paritaprevir/r
In treatment-naïve non-cirrhotic patients, SVR12 rates for GT1 patients ranged from 80-96% when paritaprevir/r was used in combination with or without ombitasvir, dasabuvir, and ribavirin. For patients with prior treatment-experience, SVR12 rates ranged from 47-100%. The highest SVR12 rates were obtained when treatment consisted of ombitasvir/paritaprevir/r and dasabuvir with or without ribavirin, for both the treatment naïve (88-96%) and treatment-experienced (90-95%) populations. Despite this, evidence from a Japanese study suggests that ombitasvir/paritaprevir/r treatment is highly efficacious in the Japanese GT1b population with prior treatment-experience (Chayama et al. 2015). The results of the AVIATOR study suggest that treatment duration should be extended from 8 weeks to 12 weeks; 24 weeks treatment did not provide a significant benefit in terms of treatment response, and led to a higher incidence of adverse events which could compromise treatment (Kowdley et al. 2014). The available evidence suggests that the predictors of treatment success with Peg-IFN/ribavirin therapy, including sex, race, gender, and IL28B subtype, do not affect the efficacy of ombitasvir/paritaprevir/r and dasabuvir treatment.

10.1.2) Phase 3

The efficacy and safety of ombitasvir/paritaprevir/r and dasabuvir in GT1 patients has been evaluated in six large multicentre, Phase 3, randomised trials enrolling almost 2,000 participants from over 25 countries. These trials included both treatment-naïve and treatment-experienced patients and patients with cirrhosis. In each trial, patients received ombitasvir/paritaprevir/r 25/150/100 mg once daily co-administered with dasabuvir 250 mg twice daily. In trials examining the addition of ribavirin, ribavirin was dosed based on the patients' weight as follows: 1000 mg daily if <75 kg and 1200 mg daily if ≥75 kg. The primary efficacy end point for all trials was SVR12. The six trials are summarised in Table 5.

SAPPHIRE-I

SAPPHIRE-I (NCT01716585) was a placebo controlled multicentre study of ombitasvir/paritaprevir/r and dasabuvir in combination with ribavirin for 12 weeks in treatment-naïve non-cirrhotic patients (Feld et al. 2014). In total 631 patients were enrolled from sites in North America, Europe, and Australia, and received at least one dose of the study drug (active regimen: n=473; placebo: n=158). In the intent-to-treat analysis, the rate of SVR12 was 96.2% (95%CI 94.5-97.9) in the active treatment group (455/473 patients). In genotype subtype analysis, SVR12 was reached in 95.3% (95%CI 93.0-97.6) of patients with GT1a infection (307/322) and 98.0% (95%CI 95.8-100) of patients with GT1b (148/151). Rates were consistently high in all patient subgroups, including those defined by IL28B genotype, race, fibrosis score at baseline, and baseline HCV RNA level. Among those patients undergoing ribavirin dose reduction, SVR12 was attained in 93.5% (29/31) compared with 96.4% of those without (426/442). Of the 18 patients not achieving SVR12, eight
experienced virologic failure during treatment or relapse (1 patient on-treatment vs. 7 relapse). Of the remaining ten patients, three discontinued for adverse events, three patients withdrew consent, and four were lost to follow-up.

**SAPPHIRE-II**

SAPPHIRE-II (NCT01715415) was a randomised, placebo-controlled study to evaluate the safety and efficacy of ombitasvir/paritaprevir/r and dasabuvir plus ribavirin in treatment-experienced, non-cirrhotic, GT1-infected patients (Zeuzem et al. 2014). Patients (n=394) were enrolled from North America, Europe, Australia, and New Zealand, and were randomised to either the active regimen (n=297) or placebo (n=97) for 12 weeks. A total of 286/297 patients in the active regimen group had a SVR12, for a rate of 96.3% (95% CI 94.2-98.4). By genotype subtype, 166/173 with GT1a infection (96.0%, 95% CI 93.0-98.9) achieved SVR12 compared with 119/123 patients with GT1b infection (96.7%, 95% CI 93.6-99.9). No patient experienced virologic failure on treatment, however seven (2.4%) experienced relapse. Of these 6 were prior null responders and one patient had a prior treatment relapse. Of the remaining four patients, three discontinued owing to adverse events and one discontinued for other reasons.

**PEARL-III**

PEARL-III (NCT01767116) was a randomised controlled trial to evaluate 12 weeks treatment with ombitasvir/paritaprevir/r and dasabuvir with ribavirin versus the regimen without ribavirin (Ferenci et al. 2014). Participants were treatment-naïve with no evidence of liver cirrhosis and were infected with chronic HCV GT1b-infection and were mainly of European origin. Overall, 419 patients were randomised and treated with at least one study dose (active regimen with ribavirin: n=210; active regimen without ribavirin: n=209). In the ribavirin included arm 209/210 patients achieved SVR12 for a rate of 99.5% (95% CI 98.6-100); 207/209 patients who received the regimen without ribavirin had an SVR12 (99.0%, 95% CI 97.7-100). Thus both regimens were superior to the historical rate of telaprevir plus peg-IFN/ribavirin therapy and were non-inferior with respect to each other. Of the three patients not achieving SVR12, only one had virologic failure during treatment; this patient was receiving concomitant ribavirin. The remaining two patients completed therapy however did not attend the follow-up testing 12 weeks post-treatment (both in non-ribavirin arm). No patients experienced relapse or discontinued therapy as a result of adverse events.

**PEARL-IV**

PEARL-IV (NCT01833533) was the sister study of PEARL-III, evaluating 12 weeks treatment with ombitasvir/paritaprevir/r and dasabuvir with or without ribavirin in GT1a-infected treatment-naïve, non-cirrhotic patients (Ferenci et al. 2014). In total 305 patients were randomised, including 100 patients in the active regimen with ribavirin arm and 205 patients in the active regimen without ribavirin arm. Patients were
predominantly from North America. After 12 weeks treatment, 97/100 patients who received the regimen with ribavirin had a SVR12 (97.0%, 95%CI 93.7-100) and 185/205 patients who received the regimen without ribavirin had a SVR12 (90.2%, 95%CI 86.2-94.3). Thus, the regimen without ribavirin was found to be inferior to the regimen inclusive of ribavirin (difference -6.8%, 95% -12.0 to -1.5). Of the 3 patients not achieving SVR12 in the ribavirin arm, one patient experienced virologic failure during treatment, one patient experience relapse, and one had missing data at the post-treatment Week 12 time-point. Of the 20 patients not achieving SVR12 in the regimen with ribavirin arm, sixteen experienced virologic failure (6 on-treatment vs. 10 relapse). Considering the remaining four patients, two discontinued treatment early due to adverse events, one discontinued early for other reasons, and one patient completed treatment but did not have data at the SVR12 time-point.

TURQUOISE-II

TURQUOISE-II (NCT01704755) is the only Phase 3 study to date to include patients with cirrhosis (Poordad et al. 2014). The study enrolled GT1-infected patients who were either treatment-naïve or experienced and had compensated cirrhosis at screening (Metavir score >3 or Ishak score >4 and ≤6). Participants were randomised to ombitasvir/paritaprevir/r and dasabuvir plus ribavirin for either 12 weeks or 24 weeks. Of the 380 patients that were enrolled and received at least one dose of study treatment, 208 were randomised to the 12 week group, and 172 were randomised to the 24 week group. Distribution of GT1a and GT1b subtypes was not significantly different between the two arms. A total of 191/208 patients who received 12 weeks treatment had a SVR12 (91.8%, 95%CI 87.6-96.1) compared with 165/172 patients who received 24 weeks (95.9%, 95%CI 92.6-99.3). The difference in rate of SVR12 between the two arms was not significant (p=0.09). Response rates did not differ according to race, body-mass index, IL28B genotype, history of diabetes, depression, or bipolar disorder, or baseline HCV RNA level, platelet count, or serum albumin level. Virologic failure during treatment or relapse occurred in 13/208 (6.2%) patients in the 12 week group (1 on-treatment vs 12 relapse) and 4/172 (2.3%) in the 24 week group (3 on-treatment vs 1 relapse). Significantly more patients in the 12 week group had relapse after treatment.

For patients with GT1a infection treated for 12 weeks, SVR12 rates were 92.2% (59/64) for treatment-naïve patients and 80.0% (40/50), 100% (11/11), and 93.3% (14/15) for patients with prior null response, partial response, and relapse, respectively. For GT1a infected patients treated for 24 weeks, response rates were 92.9% (52/56) for treatment-naïve patients, and 92.9% (39/42), 100% (10/10), and 100% (13/13) for prior null response, partial response, and relapse, respectively. For patients with GT1b infection, 100% of treatment-naïve patients (40/40) achieved an SVR12. For treatment-experienced GT1b patients treated for 12 weeks response rates were 100% (25/25), 85.7% (6/7), and 100% (14/14) for prior null response, partial response, and relapse, respectively. For those treated for 24 weeks, all patients achieved SVR12 (20 prior
null, 3 partial, and 10 relapse). Multivariate logistic-regression showed that prior null response and HCV GT1a infection were associated with a lower chance of SVR12.

PEARL-II

PEARL-II (NCT01674725) was an open-label, randomised, multicentre study to evaluate the safety and efficacy of 12 weeks ombitasvir/paritaprevir/r and dasabuvir treatment with or without ribavirin in treatment-experienced, non-cirrhotic GT1b-infected patients (Andreone et al. 2014). In total, 186 patients, predominantly from Europe, were randomised and treated with at least one dose of the study drug (active regimen plus ribavirin: n=91; active regimen without ribavirin: n=95). After 12 weeks of treatment 85/88 patients in the ribavirin group achieved SVR12, equating to a rate of 96.6% (95% CI 92.8-100); 100% (91/91) of participants in the group receiving treatment without ribavirin achieved SVR12 (95% CI 95.9-100). Thus, the regimen without ribavirin was found to be non-inferior to the ribavirin inclusive regimen. No patient from either group experienced on-treatment virologic failure or post-treatment relapse. Of the three patients not achieving SVR12 in the ribavirin group, two patients discontinued due to adverse events and one was lost to follow-up after completion of therapy.

Summary

Results from the Phase 3 studies suggest that ombitasvir/paritaprevir/r and dasabuvir, with or without ribavirin, is a highly efficacious regimen for treatment of chronic HCV GT1 infection, regardless of treatment history or the presence of cirrhosis. For patients with subtype GT1a and patients with GT1b and cirrhosis, concurrent administration with ribavirin is recommended to maximise response rate. A longer treatment duration of 24 weeks is beneficial in cirrhotic patients with HCV GT1a-infection. Given the consistently high SVR12 rates observed, baseline characteristics, such as age, gender, race, and IL28B subtype, do not seem to impact response rate.
Table 5. Phase 3 clinical trials in genotype 1 infected patients with ombitasvir/paritaprevir/r and dasabuvir, with or without ribavirin (intent-to-treat analyses)

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Study design</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>SVR12, n(%)</th>
<th>VF or relapse, n(%)</th>
<th>D/C due to AE, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPPHIRE-I</td>
<td>Multicentre, randomised, double-blind, placebo-controlled, Phase 3</td>
<td>TN (GT1a and GT1b), no cirrhosis (n=631)</td>
<td>3D + RBV 12wks (n=473)</td>
<td>GT1a: 307/322 (95.3%)</td>
<td>GT1b: 148/151 (98.0%)</td>
<td>3/473 (0.6%)</td>
</tr>
<tr>
<td>(Feld et al. 2014)</td>
<td></td>
<td></td>
<td></td>
<td>GT1a: 7/322 (2.2%)</td>
<td>GT1b: 1/151 (0.7%)</td>
<td></td>
</tr>
<tr>
<td>PEARL-III</td>
<td>Multicentre, randomised, double-blind, placebo-controlled, Phase 3</td>
<td>TN (GT1b), no cirrhosis (n=419)</td>
<td>3D + RBV 12wks (n=210)</td>
<td>209/210 (99.5%)</td>
<td>1/210 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>(Ferenci et al. 2014)</td>
<td></td>
<td></td>
<td></td>
<td>3D alone 12wks (n=209)</td>
<td>207/209 (99.0%)</td>
<td>0</td>
</tr>
<tr>
<td>PEARL-IV</td>
<td>Multicentre, randomised, double-blind, placebo-controlled, Phase 3</td>
<td>TN (GT1a), no cirrhosis (n=305)</td>
<td>3D + RBV 12wks (n=100)</td>
<td>97/100 (97.0%)</td>
<td>2/100 (2.0%)</td>
<td>0</td>
</tr>
<tr>
<td>(Ferenci et al. 2014)</td>
<td></td>
<td></td>
<td></td>
<td>3D alone 12wks (n=205)</td>
<td>185/205 (90.2%)</td>
<td>16/205 (7.8%)</td>
</tr>
<tr>
<td>TURQUOISE-II</td>
<td>Multicentre, randomised, open-label, Phase 3</td>
<td>TN &amp; TE (GT1), cirrhotic (TN: n=160; TE: n=220)</td>
<td>3D + RBV 12wks (TN: n=86; TE: n=122)</td>
<td>TN: GT1a: 59/64 (92.2%)</td>
<td>GT1b: 22/22 (100.0%)</td>
<td>13/208 (6.2%)</td>
</tr>
<tr>
<td>(Poordad et al. 2014)</td>
<td></td>
<td></td>
<td></td>
<td>TE: GT1a: 65/76 (85.5%)</td>
<td>GT1b: 45/46 (97.8%)</td>
<td>4/208 (1.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3D + RBV 24wks (TN: n=74; TE: n=98)</td>
<td>TN: GT1a: 52/56 (92.9%)</td>
<td>GT1b: 18/18 (100.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TE: GT1a: 62/65 (95.4%)</td>
<td>GT1b: 33/33 (100.0%)</td>
</tr>
<tr>
<td>SAPPHIRE-II</td>
<td>Multicentre, randomised, double-blind, placebo-controlled, Phase 3</td>
<td>TE (GT1a and GT1b), no cirrhosis (n=394)</td>
<td>3D + RBV 12wks (n=297)</td>
<td>GT1a: 166/173 (96.0%)</td>
<td>GT1b: 119/123 (96.7%)</td>
<td>3/297 (1.0%)</td>
</tr>
<tr>
<td>(Zeuzem et al. 2014)</td>
<td></td>
<td></td>
<td></td>
<td>GT1a: 5/173 (2.9%)</td>
<td>GT1b: 2/123 (1.6%)</td>
<td>All PT-relapse</td>
</tr>
<tr>
<td>PEARL-II</td>
<td>Multicentre, open-label, Phase 3</td>
<td>TE (GT1b), no cirrhosis (n=179)</td>
<td>3D + RBV 12wks (n=88)</td>
<td>85/88 (96.6%)</td>
<td>0</td>
<td>2/88 (2.3%)</td>
</tr>
<tr>
<td>(Andreone et al. 2014)</td>
<td></td>
<td></td>
<td></td>
<td>3D alone 12wks (n=91)</td>
<td>91/91 (100.0%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: TN. Treatment-naive; TE, treatment-experienced; GT, genotype; 3D, ombitasvir/paritaprevir/ritonavir and dasabuvir; RBV, ribavirin; VF, virologic failure; D/C, discontinued; AE, adverse events
10.1.3) Special populations

HIV-1/HCV co-infected patients

Chronic HCV patients co-infected with HIV-1 have traditionally presented a treatment challenge due to considerably lower response rates, coupled with ineligibility to treatments due to the potential for drug-drug interactions with ART. In HIV-1/HCV GT1-infected patients, SVR rates were as low as 14-29% in patients treated with Peg-IFN and ribavirin, and have increased to 60-74% with the addition of telaprevir or boceprevir, two first generation HCV NS3/4A protease inhibitors (Kilbanov, Gale & Santevecchi 2015). Treatment with sofosbuvir and ribavirin has led to 76% of co-infected patients achieving SVR12, and recent results from the ION-4 trial, evaluating sofosbuvir/ledipasvir, have shown a further increased SVR12 rate of 96% (321/335; 98% of participants GT1) (Naggie et al. 2015).

TURQUOISE-I

TURQUOISE-I (NCT01939197) is an ongoing Phase 2/3 open-label study to evaluate the efficacy and safety of ombitasvir/paritaprevir/r and dasabuvir plus ribavirin treatment in patients with GT1-infection co-infected with HIV-1 (Table 6) (Wyles et al. 2014; Sulkowski et al. 2015). Patients were receiving atazanavir or raltegravir-inclusive regimens and were enrolled regardless of treatment history or fibrosis stage (excluding patients with liver decompensation). Participants were randomised to receive treatment for 12 weeks (n=31) or 24 weeks (n=32). SVR12 rates were 93.5% (29/31; 95%CI 79.3-98.2) in the 12-week treatment group and 90.6% (29/32; 95%CI 75.8-96.8) in the 24-week group. Of the two patients not achieving SVR12 in the 12-week group, one withdrew consent and one experienced post-treatment relapse. Of the three patients not achieving SVR12 in the 24-week group, one experienced on-treatment viral breakthrough, and the remaining two patients appeared to have achieved SVR followed by re-infection with a different GT1a isolate from their original infection. By genotype subtype, SVR12 was achieved by 51/56 (91.1%) patients with GT1a infection and 7/7 (100%) with GT1b infection. The regimen was well tolerated, with no patients discontinuing treatment owing to adverse events. Safety and efficacy of the regimen is currently being evaluated in patients taking stable darunavir-containing HIV-1 ART regimens in the ongoing second part of the study.

Liver-transplant recipients

The safety and efficacy of DAA treatment in recipients of liver transplants is of high importance given that HCV re-infection post-transplantation is frequent and can significantly impair patient and graft survival (Roche & Samuel 2012). Chronic HCV infection develops in 75-90% of liver transplant recipients, and ultimately leads to cirrhosis in 5-30% within 5 years (Berenguer 2008). Studies have shown the treatment of established HCV infection post-transplantation with Peg-IFN/ribavirin leads to an SVR rate of approximately 30% (Berenguer 2008). The addition of telaprevir or boceprevir to therapy increased SVR12 rates to
approximately 50% (Verna et al. 2015), and sofosbuvir/simeprevir therapy has further augmented response rates to 90% (Pungapong et al. 2015).

**CORAL-I**

CORAL-I (NCT01782495) is a Phase 2, open-label study recruiting adult transplant recipients with recurrent GT1 chronic HCV infection (Table 6) (Kwo et al. 2014). All patients (n=34) were on stable cyclosporine or tacrolimus therapy, had mild or no fibrosis, and were treated for ombitasvir/paritaprevir/r, dasabuvir, and ribavirin for 24 weeks. In total 33 of 34 patients had a SVR12 for a rate of 97.1% (95%CI 85-100). The one patient that did not achieve SVR12 experienced very early relapse post-treatment (day 3) and showed emergent resistant variants. By genotype, 5/5 patients (100%) infected with GT1b and 28/29 (96.6%) GT1a-infected patients reached SVR12.

**Other special populations**

Two pooled analyses have been conducted to assess the efficacy and safety of the ombitasvir/paritaprevir/r and dasabuvir regimen with or without ribavirin in: i) patients with history of depression or bipolar disorder and ii) patients receiving stable opioid substitution treatment (OST). In the pooled Phase 3 analysis, similarly high SVR12 rates were observed in GT1 patients with and without history of depression or bipolar (Nelson et al. 2014). Similarly, the rates of on-treatment virologic breakthrough and post-treatment relapse for patients with depression or bipolar disorder history did not differ from the overall rates. Rate of treatment discontinuation was similar, although a slightly high percentage of patients in the depression/bipolar disorder group discontinued due to adverse events (2.5% vs 1.9%). Patients with depression or bipolar disorder history had a higher incidence of adverse events, however, in general adverse events were mild and the regimen was well tolerated.

Given the high prevalence of HCV in IDUs, and since IDUs represent the majority of new cases of HCV infection, it is important that there is information to guide clinical management in this population. One Phase 2 study (NCT01911845) was conducted to evaluate the efficacy and safety of the regimen in GT1 patients on stable OST with either methadone or buprenorphine. A pooled analysis of all patients on OST in Phase 2/3 studies was conducted (Puoti et al. 2014). Across the eight trials, 54/56 patients receiving OST achieved SVR12 (96.4%, 95%CI 91.6-96.4), which is consistent with the high response rates observed overall. No patient receiving OST experienced virologic failure. Of the two patients not achieving SVR12, both discontinued treatment early; one patient discontinued due to adverse events, and one because of noncompliance for reasons other than virologic failure. The regimen was well tolerated and no patient required a dose adjustment of OST during the treatment period.
Table 6. Phase 2/3 clinical trials in genotype 1 infected special populations (intent-to-treat analyses)

<table>
<thead>
<tr>
<th>Study reference</th>
<th>Study design</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>SVR12, n(%)</th>
<th>VF or relapse, n(%)</th>
<th>D/C due to AE, n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TURQUOISE-I (Sulkowski et al. 2015)</td>
<td>Multicentre, randomised, open-label, Phase 2/3</td>
<td>HIV-1/HCV co-infection (GT1), 33% TE, 19% cirrhosis (n=63)</td>
<td>3D + RBV 12wks (n=31)</td>
<td>29/31 (93.5%)</td>
<td>1/31 (3.2%)</td>
<td>0</td>
</tr>
<tr>
<td>CORAL-I (Kwo et al. 2014)</td>
<td>Open-label, Phase 2</td>
<td>Liver transplant with recurrent HCV (GT1), TN after transplant, mild-moderate fibrosis</td>
<td>3D + RBV 24wks (n=34)</td>
<td>33/34 (97.1%)</td>
<td>1/34 (2.9%)</td>
<td>0</td>
</tr>
<tr>
<td>OST substitution (Puoti et al. 2014)</td>
<td>Pooled analysis, Phase 2/3</td>
<td>On stable OST (GT1), TN/TE, non-cirrhotic</td>
<td>3D + RBV 12wks (n=56)</td>
<td>54/56 (96.4%)</td>
<td>0</td>
<td>1/56 (1.8%)</td>
</tr>
</tbody>
</table>

Abbreviations: TN, treatment-naive; TE, treatment-experienced; GT, genotype; 3D, ombitasvir/paritaprevir/r + dasabuvir; RBV, ribavirin; VF, virologic failure; AE, adverse event; OST, opioid substitution therapy

10.2) Non-genotype 1

While the complete regimen consisting of three active antivirals (ombitasvir/paritaprevir/r and dasabuvir) with or without ribavirin is only licensed for the treatment of GT1 infection, the less drug regimen, consisting of ombitasvir/paritaprevir/r with or without ribavirin has been investigated in HCV GT4 and in a limited number of patients with GT2 and GT3. Following these studies, ombitasvir/paritaprevir/r with ribavirin has been licensed in Europe for the treatment of HCV GT4 infection. Furthermore, although the FDA has not approved ombitasvir/paritaprevir/r plus ribavirin for the treatment of GT4, the regimen is included in the latest AASLD guidelines.

PEARL-I (GT4)

PEARL-I (NCT01685203) was a Phase 2 randomised open-label study to evaluate ombitasvir/paritaprevir/r with or without ribavirin in non-cirrhotic GT1b and GT4 patients (Hezode et al. 2014). Treatment-naïve patients with GT4 were randomised to receive either 12 weeks treatment with the active regimen alone (n=44) or in combination with ribavirin (n=42). Treatment-experienced patients received 12 weeks treatment with ombitasvir/paritaprevir/r plus ribavirin for 12 weeks (n=49). Of the treatment-naïve patients, 40/44 (90.9%) receiving the active regimen without ribavirin achieved SVR12 compared with 42/42 (100%) of patients taking the regimen in combination with ribavirin. Of the four patients not achieving SVR12 (all without ribavirin), one experienced on-treatment breakthrough, two had relapse, and one was lost to follow up. With regard to the 49 treatment-experienced patients, 37 had the potential to reach the SVR12 time-
point by the cut-off for analysis; 37/37 (100%) achieved SVR12. The regimen was well tolerated; only one patient experienced a serious adverse event not related to treatment (motor vehicle accident) and no patients discontinued owing to adverse events.

The results of the PEARL-I study suggest that 12 weeks treatment with ombitasvir/paritaprevir/r and ribavirin is highly effective in the GT4 population. Furthermore, the response rates observed in the GT4 population in the PEARL-I study are higher than those of 12 weeks of sofosbuvir/ribavirin treatment (79-84% in treatment-naïve and 59-70% in treatment-experience) and similar to that of sofosbuvir/ledipasvir (19/20; 95.0%) (Abdel-Razek & Waked 2015).

**Japanese study (GT2)**

This AbbVie study (NCT01672983) was a randomised Phase 2, dose- and duration-finding study evaluating the ombitasvir/paritaprevir/r regimen in GT1b and GT2 infected Japanese patients (Chayama et al. 2015). GT2 patients were non-cirrhotic, treatment-experienced, and were treated with either ombitasvir/paritaprevir/r (25/100/100 mg) for 12 weeks (n=19) or ombitasvir/paritaprevir/r (25/150/100 mg) for 12 weeks (n=18). In the 100 mg low-dose paritaprevir arm, 11/19 (57.9%) patients achieved SVR12. Of the 8 patients not achieving SVR12, seven (36.8%) experienced on-treatment failure, and one (5.3%) post-treatment relapse. In the 150 mg high-dose paritaprevir arm 13/18 (72.2%) achieved SVR12. Of the 5 patients not achieving SVR12, three (16.7%) had on-treatment failure and two (11.1%) relapsed after treatment. By prior response, all patients with a prior partial response achieved SVR12 (3/3); in relapsers the response was 62% (21/34) and no prior null responders were recruited. Response rate was significantly higher in patients infected with GT2a (18/20; 90.0%) compared with GT2b (4/15; 26.7%). In terms of safety, the regimen was well tolerated and no patients discontinued for adverse events.

These preliminary data in GT2 patients show lower efficacy than the majority of studies in GT2 treatment-experienced patients treated with sofosbuvir and ribavirin which have shown 86-95% response rates (Bourlière et al. 2015). Treatment of GT2 with ombitasvir/paritaprevir/r in combination with ribavirin is being evaluated in further studies.

**NAVIGATOR (GT2 and GT3)**

Navigator (NCT01458535) was a Phase 2 study to assess the efficacy of ombitasvir/paritaprevir/r with or without ribavirin in treatment-naïve, non-cirrhotic patients with GT1, GT2, or GT3 (Lawitz et al. 2015). The study enrolled twenty GT2 patients (regimen with ribavirin: n=10; regimen without ribavirin: n=10) and twenty-one GT3 patients (regimen with ribavirin: n=10; regimen without ribavirin: n=11).
Of the GT2 patients, 8/10 (80%, 95%CI 44-97) of those receiving ribavirin, and 6/10 (60%, 95%CI 26-88) not receiving ribavirin achieved SVR12. Of the two patients taking ribavirin and not achieving SVR12, one experienced virological breakthrough, and one was lost to follow-up. Of the four treatment failures not taking ribavirin, one experienced breakthrough, two relapse, and one was lost to follow-up.

Of the GT3 patients, 5/10 (50%, 95%CI 19-81) taking ribavirin and 1/11 (9%, 95%CI 0-41) not taking ribavirin achieved SVR12. The majority of patients not achieving SVR12 experienced breakthrough or relapse (4/5 in the ribavirin arm and 9/10 in the non-ribavirin arm). These results suggest that the regimen is not acceptable for use in the GT3 population. Ombitasvir/paritaprevir/r is currently being evaluated in combination with other DAAs for the treatment of GT3 infection.

10.3) Additional ongoing or planned studies

A review of the clinicaltrials.gov database revealed a number of additional ongoing studies of both the ombitasvir/paritaprevir/r and dasabuvir with or without ribavirin regimen and the ombitasvir/paritaprevir/r with or without ribavirin regimen in further patient populations. The results of this search are shown in Table 7. Populations studied include patients with GT1, GT2, and GT4 infection, patients with decompensated cirrhosis, renal impairment, liver or renal transplant recipients, DAA treatment-experience, and patients with HIV-1 co-infection. Studies are being conducted in a variety of locations, including North America, Egypt, Japan, Russia, Australasia, and Europe. These trials include those to assess the role of ribavirin in the treatment of patients with GT1b HCV/HIV-1 co-infection given that the addition of ribavirin to the active regimen is not associated with an increase in SVR in patients with GT1b mono-infection.

Additionally, there are a number of ongoing studies to investigate the regimen in combination with other DAAs for treatment of GT1 or GT3 infection. These DAAs include sofosbuvir, and two new AbbVie DAAs in development, ABT-530 and ABT-493. ABT-450 has demonstrated potent pan-genotypic activity and exhibits a high genetic barrier to resistance, while ABT-493 displays potent and broad genotype activity (Ng et al. 2014a; Ng et al. 2014b).
<table>
<thead>
<tr>
<th>Trial identifier</th>
<th>Location</th>
<th>Population</th>
<th>Genotype</th>
<th>Treatment regimen (duration)</th>
<th>Expected completion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CORAL-I (NCT01782495)</td>
<td>US, Australia, Europe</td>
<td>TN, liver or renal transplant recipient, with or without cirrhosis (on immunosuppressant regimen)</td>
<td>GT1</td>
<td>Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12/24 weeks)</td>
<td>Mar 2017</td>
</tr>
<tr>
<td>NIAD (NCT02194998)</td>
<td>US, Puerto Rico</td>
<td>TN, with or without cirrhosis, with HIV-1 co-infection</td>
<td>GT1</td>
<td>Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12/24 weeks)</td>
<td>Jan 2016</td>
</tr>
<tr>
<td><strong>Phase 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIFT-I (NCT02023099)</td>
<td>Japan</td>
<td>TN/TE with or without compensated cirrhosis</td>
<td>GT1b</td>
<td>Ombitasvir/paritaprevir/r (12 weeks)</td>
<td>Oct 2015</td>
</tr>
<tr>
<td>GIFT-II (NCT02023112)</td>
<td>Japan</td>
<td>TN/TE with or without compensated cirrhosis</td>
<td>GT2</td>
<td>Ombitasvir/paritaprevir/r + RBV (12/16 weeks)</td>
<td>Sept 2015</td>
</tr>
<tr>
<td>QAQISH (NCT02247401)</td>
<td>Egypt</td>
<td>TN/TE, with or without cirrhosis</td>
<td>GT4</td>
<td>Ombitasvir/paritaprevir/r + RBV (12/24 weeks)</td>
<td>Aug 2016</td>
</tr>
<tr>
<td>TURQUOISE-III (NCT02219503)</td>
<td>US, Canada, Belgium</td>
<td>Compensated cirrhosis</td>
<td>GT1b</td>
<td>Ombitasvir/paritaprevir/r + dasabuvir (12 weeks)</td>
<td>Nov 2015</td>
</tr>
<tr>
<td>TURQUOISE-IV (NCT02216422)</td>
<td>Russia, Belarus</td>
<td>Compensated cirrhosis</td>
<td>GT1b</td>
<td>Ombitasvir/paritaprevir/r + dasabuvir + RBV (12 weeks)</td>
<td>Dec 2015</td>
</tr>
<tr>
<td>TURQUOISE-CPB (NCT02219477)</td>
<td>US, Canada, Germany</td>
<td>TN/TE with or without compensated cirrhosis</td>
<td>GT1</td>
<td>Ombitasvir/paritaprevir/r + dasabuvir + RBV (12/24 weeks)</td>
<td>Oct 2016</td>
</tr>
<tr>
<td>RUBY-I (NCT02207088)</td>
<td>US</td>
<td>TN with renal impairment, with or without cirrhosis</td>
<td>GT1</td>
<td>Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12/24 weeks)</td>
<td>Mar 2016</td>
</tr>
<tr>
<td>AGATE-I (NCT02265237)</td>
<td>US, Canada, Europe</td>
<td>TN/TE with compensated cirrhosis (inc. DAA experienced)</td>
<td>GT4</td>
<td>Ombitasvir/paritaprevir/r + RBV (12/16/24 weeks)</td>
<td>Jan 2017</td>
</tr>
<tr>
<td>TOPAZ-I (NCT02219490)</td>
<td>Canada, Europe, Israel</td>
<td>TN/TE, with or without cirrhosis; long-term outcomes</td>
<td>GT1</td>
<td>Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12/24 weeks)</td>
<td>Dec 2020</td>
</tr>
<tr>
<td>TOPAZ-II (NCT02167945)</td>
<td>US</td>
<td>TN/TE, with or without cirrhosis; long-term outcomes</td>
<td>GT1</td>
<td>Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12/24 weeks)</td>
<td>Mar 2020</td>
</tr>
<tr>
<td>MALACHITE-I (NCT01854697)</td>
<td>Canada, Europe, Australia, South America</td>
<td>TN, non-cirrhotic; randomised against telaprevir-based therapy</td>
<td>GT1</td>
<td>Ombitasvir/paritaprevir/r + dasabuvir ± RBV (12 weeks)</td>
<td>Jul 2015</td>
</tr>
<tr>
<td>MALACHITE-II (NCT01854528)</td>
<td>South America, Europe</td>
<td>TE; randomised against telaprevir-based therapy</td>
<td>GT1</td>
<td>Ombitasvir/paritaprevir/r + dasabuvir + RBV (12 weeks)</td>
<td>Jul 2015</td>
</tr>
<tr>
<td>Follow-up (NCT01773070)</td>
<td>US, Canada, Europe, Australia, NZ, Puerto Rico,</td>
<td>Follow-up study of prior AbbVie Phase 2/3 studies</td>
<td>Mainly GT1</td>
<td>Follow-up only</td>
<td>Oct 2016</td>
</tr>
</tbody>
</table>
11) Summary of comparative evidence of safety:

11.1) Adverse events

Available data from clinical trials has shown excellent tolerance with the ombitasvir/paritaprevir/r and dasabuvir regimen with or without ribavirin (Table 8). In a pooled analysis of 2,887 patients from Phase 2/3 trials (regimen with ribavirin: n=2044; regimen without ribavirin: n=588; placebo: n=255) adverse events occurring in >20% of patients were fatigue (32.3%, 25.7%, and 26.3%) and headache (28.9%, 24.5%, and 29.8%) (Fried et al. 2014). The overall rate of study drug discontinuation as a result of adverse events was low in the active treatment arms (27/2632, 1.0%). Rates of adverse events and laboratory abnormalities were higher in the ribavirin inclusive arms compared with ombitasvir/paritaprevir/r and dasabuvir alone (Table 8).

11.1.1) Bilirubin elevations

Paritaprevir is an inhibitor of the OATP1B1 bilirubin transporter and as such may increase indirect bilirubin. In the pooled analysis, 4.5% of patients treated with the regimen with ribavirin and 0.3% of those treated without the addition of ribavirin experienced bilirubin levels at least three times the upper limit of normal (ULN) after starting treatment (Fried et al. 2014). The transient bilirubin elevations tended to peak by Week 1 of the study, and were usually resolved with ongoing therapy. Elevated bilirubin was not associated with elevated serum alanine aminotransferase (ALT).
11.1.2) Serum ALT elevations

Elevation in ALT levels were also rare with only 1% of patients treated with ombitasvir/paritaprevir/ritonavir and dasabuvir experiencing transient ALT levels greater than 5 x ULN. The majority of ALT elevations were considered drug-related liver injury; cirrhosis was not a risk factor for ALT elevations. Concurrent systemic oestrogen use was the main risk factor for ALT elevations, and as such, is not recommend for use with the regimen.

11.1.3) Ribavirin and haemoglobin levels

The use of ribavirin can result in significant adverse events, including haemolytic anaemia. Overall, in all Phase 3 studies, the mean change in haemoglobin levels in patients treated with the regimen with and without ribavirin were -2.4 g/dL and -0.5 g/dL, respectively (AbbVie Inc. 2015). In the pooled analysis, only nine patients experienced haemoglobin levels <8.0 g/dL; all patients were receiving concomitant ribavirin and only one discontinued therapy due to anaemia (Fried et al. 2014). One patient (0.2%) treated with ombitasvir/paritaprevir/r plus dasabuvir alone had a haemoglobin level less than 10 g/dL, compared with 132 (6.4%) in the ribavirin arms. Ribavirin dose reductions were used to manage anaemia in 159 patients (6.0%); less than 0.5% of patients received erythropoietin or required a red blood cell transfusion. Of concern, there is evidence of ribavirin teratogenic and embryocidal activity and thus it should not be administered to pregnant women, and pregnancy should be avoided for up to six months after treatment completion. The avoidance pertains both to treatment of women receiving ribavirin treatment and women whose male partners are undergoing ribavirin therapy.

Table 8. Adverse events associated with ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ombitasvir/paritaprevir/ritonavir and dasabuvir WITH ribavirin (n=2044)</th>
<th>Ombitasvir/paritaprevir/ritonavir and dasabuvir WITHOUT ribavirin (n=588)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>1794 (87.8%)</td>
<td>451 (76.7%)</td>
</tr>
<tr>
<td>Any AE leading to study drug discontinuation</td>
<td>25 (1.2%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>56 (2.7%)</td>
<td>9 (1.5%)</td>
</tr>
<tr>
<td>Any AE leading to RBV/placebo dose modification</td>
<td>158 (7.7%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Haemoglobin (g/dL) &lt;10-8 / &lt;8</td>
<td>123 (6.0%) / 9 (0.4%)</td>
<td>1 (0.2%) / 0</td>
</tr>
<tr>
<td>Total bilirubin &gt;3xULN</td>
<td>91 (4.5%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>ALT &gt;5xULN</td>
<td>25 (1.2%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; RBV, ribavirin; ULN, upper limit of normal; ALT, alanine aminotransferase
11.1.4) Patients co-infected with HIV-1, suppressed on antiretroviral treatment (n=63)
Sixty-three patients with HIV-1 co-infection were enrolled on to the TURQUOISE-1 study and the safety of
the regimen was evaluated in this population (Sulkowski et al. 2015). The most common adverse events
included fatigue (48%), insomnia (19%), nausea (17%), and headache. No treatment-emergent serious
adverse events were reported, and no patient discontinued HCV therapy as a result of an adverse event.
Seventeen patients experienced an increase in bilirubin >3 x ULN; one patient experience an increase above
10 x ULN (13.0 mg/dL) that improved upon further testing. Fifteen of the seventeen patients (88%) with
bilirubin elevations were receiving atazanavir-inclusive ART. No patients experience ALT elevations. Seven
patients (11%) experienced haemoglobin <10 g/dL and no patient experience haemoglobin <8 g/dL. Ribavirin
dose reduction was used in six patients (10%), all of which achieved SVR; no subject required a blood
transfusion or erythropoietin. The mean absolute CD4+ cell count declined during treatment but returned to
baseline by post-treatment Week 4; no patient required a switch of their HIV-1 ART regimen due to loss of
plasma HIV-1 RNA suppression (Sulkowski et al. 2015).

11.1.5) Liver transplant recipients (n=34)
Adverse events affecting >20% of the population included fatigue (50%), headache (44%), cough (32%),
diarrhoea (26%), insomnia (26%), asthenia (24%), nausea (24%), muscle spasms (21%), and rash (21%). Ten
subjects (29%) had a decrease in haemoglobin below 10 g/dL. Of these all ten dose reduced ribavirin and one
patient had an interruption of ribavirin; five subjects received erythropoietin and none received a blood
transfusion. No episodes of graft rejection were observed and there were no deaths during the study (Kwo
et al. 2014).

11.1.6) Summary
The ombitasvir/paritaprevir/r and dasabuvir regimen appears to be well tolerated, with few patients
discontinuing treatment owing to adverse events. The addition of ribavirin to the regimen led to a marginally
higher rate of adverse events and higher rate of treatment discontinuation as a result of adverse events;
despite this, adverse effects can be well managed through ribavirin dose reductions, without compromising
treatment efficacy. Furthermore, the regimen seems to be well tolerated in patients with HIV-1/HCV co-
infection and those who have undergone liver transplantation.

11.2) Drug-drug interactions
The drug-drug interactions between ombitasvir/paritaprevir/r and dasabuvir and other common agents have
been evaluated in over 200 healthy volunteers and a number of significant interactions have been identified
(Menon et al. 2014; Menon et al. 2014; Khatri et al. 2014). The majority of drug-drug interactions occur as
a result of the potent ritonavir inhibition of CYP3A4 enzyme. Other key enzymes/transporters inhibited by the regimen include UGT1A1, OATP1B1, OATP1B3, and BCRP. Thus co-administration with drugs that are substrates of these enzymes may result in increased plasma concentrations, and as such, dose reductions of these drugs are recommended (see Table 9).
Many currently used HIV-1 regimens already include ritonavir to enhance the pharmacokinetics of HIV-1 protease inhibitors, and as such careful consideration is necessary when deciding whether to concomitantly prescribe ombitasvir/paritaprevir/ritonavir and dasabuvir. For patients receiving atazanavir/ritonavir, no dosage adjustment is required, however the ritonavir 100 mg should not be given whilst receiving the HCV regimen. Co-administration with lopinavir/ritonavir led to an increased paritaprevir concentration and increased gastrointestinal adverse events, while co-administration with darunavir/ritonavir led to a sub-therapeutic level of darunavir. Accordingly, co-administration with lopinavir/ritonavir or darunavir/ritonavir is contraindicated in patients receiving ombitasvir/paritaprevir/ritonavir and dasabuvir (Table 9).

Data from healthy volunteers suggests that co-administration with the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) emtricitabine or tenofovir does not require dose adjustments (Khatri et al. 2014). Similarly, no dose adjustments are necessary with the integrase strand transfer inhibitor, raltegravir. Rilpivirine and efavirenz are not recommended due to increased drug exposure and a high rate of adverse events, respectively (Table 9). Data regarding other NRTIs, integrase inhibitors, and non-NRTIs have not yet been reported.

11.3) Resistance

The mutation rate of HCV is very high at approximately 1 nucleotide per virion (Pawlotsky 2003). Given the estimated production rate of $10^{12}$ virions/day, this means that single- and double-nucleotide-mutant viruses are present in the majority of patients prior to therapy (Rong et al. 2010). While the majority of variants are unfit, selective drug pressure may lead to replacement of these variants with drug-resistant variants, which ultimately may lead to treatment failure (Rong et al. 2010; Bartels et al. 2008).

In vitro, the most common amino acid variants selected by paritaprevir in GT1 were located in NS3 at positions 155, 156, and 168, resulting in decreased antiviral activity by up to 337-fold (Pilot-Matias et al. 2015). In vitro, the use of ritonavir prevented or delayed the emergence of these variants. After three days treatment with paritaprevir/ritonavir (n=24), the most common resistance variants were R155K and D168V. Both R155K and D168V display cross-resistance to second-generation NS3 protease inhibitors, including simeprevir, faldaprevir, asunaprevir, and vaniprevir (Wyles & Gutierrez 2014).

For ombitasvir, in vitro, the variants that conferred resistance in the HCV NS5A gene were at amino acid positions 28, 30, 31, 58, and 93 in GT1-6 (Krishnan et al. 2015). After three day monotherapy in treatment-naïve GT1 patients (n=12), resistance-associated variants (RAVs) were observed at positions 28, 30, 58 and 93 in NS5A in patients with GT1a and were associated with high-level resistance. In GT1b-infected patients,
only the Y93H mutation was observed. A similar resistance pattern was observed with ledipasvir and daclatasvir monotherapy (Wyles & Gutierrez 2014).

For dasabuvir, sequencing of the NS5B coding region revealed the presence of C316Y, M414T, Y448C/H, and S556G variants (Kati et al. 2015). Of these, only the C316Y mutation conferred a high level of resistance. These variants differ to those known to confer resistance to other polymerase inhibitors, including mericitabine and sofosbuvir, suggest a high barrier to resistance and cross-resistance (Wyles & Gutierrez 2014).

The resistance profile of the regimen in clinical studies has been evaluated in a pooled analysis of over 2,500 subjects treated with ombitasvir/paritaprevir/r and dasabuvir with or without ribavirin in Phase 2b and Phase 3 clinical trials (Krishnan et al. 2014). The presence of RAVs at baseline was evaluated in a subset of 700 GT1a and GT1b infected patients. At baseline, NS3 variants were rare (<1%), NS5A variants were observed in 12.5% of GT1a and 7.5% of GT1b samples, and NS5B variants were seen in 5.2% of GT1a and 28.6% of GT1b samples. No patient had baseline variants in all three targets.

In total, 74 patients experienced virological failure and were evaluated for the presence of resistance-associated variants (Table 10). Of the 67 GT1a patients, 18 patients experienced on-treatment breakthrough and 49 relapsed after treatment, and of the 7 GT1b-infected patients experiencing virological failure, 2 experienced on-treatment breakthrough and 5 relapsed. In resistance analysis, the predominant RAVs observed in GT1a-infected patients were R155K and D168V in NS3, M28T and Q30R in NS5A, and S556G in NS5B. The predominant RAVs in GT1b were Y56H+D168V in NS3, Y93H in NS5A, and S556G in NS5B. Among those patients experiencing virological failure, 58.1% had RAVs in all 3 targets (39 GT1a and 4 GT1b); 14.9% had no RAVs in any target (9 GT1a and 2 GT1b) (Krishnan et al. 2014).

<table>
<thead>
<tr>
<th>Table 10. Proportion with treatment-emergent RAVs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of RAVs</strong></td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>RAVs in all three targets</td>
</tr>
<tr>
<td>RAVs in any two targets</td>
</tr>
<tr>
<td>RAVs in one target</td>
</tr>
<tr>
<td>No RAVs</td>
</tr>
</tbody>
</table>

Abbreviations: RAV, resistance-associated variants
The clinical relevance of baseline and treatment-related RAVs in patients experiencing virological failure to DAA regimens has not yet been determined. In the pooled analysis, the presence of baseline RAVs was found to have no impact on treatment outcome (Krishnan et al. 2014). Studies evaluating treatment in DAA-experienced patients are necessary and three studies are currently underway.

In patients co-infected with HIV, resistance to HIV protease inhibitors is a concern given the inclusion of ritonavir in the HCV regimen. As such, all patients with HIV should be fully suppressed on an antiretroviral drug regimen prior to and throughout treatment to reduce the risk of HIV-1 protease inhibitor drug resistance (AbbVie Inc. 2015).

11.4) Translation of clinical data to practice

There is currently no data evaluating the safety and efficacy of the ombitasvir/paritaprevir/ritonavir and dasabuvir regimen in real-life settings, including from patients living in LMICs. Despite this, the magnitude of the effect size and consistency of the safety and efficacy data across a broad range of patient populations, combined with the simplified monitoring and treatment schedule suitable for use in resource-limited settings, highlight the importance of the regimen in treating HCV.

12) Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group (range of costs of the proposed medicine; resource use and comparative cost-effectiveness presented as range of cost per routine outcome):

12.1) Costs of proposed medicines

Due to patent restrictions, the ombitasvir/paritaprevir/r and dasabuvir regimen is currently only produced by the originator manufacturer, AbbVie Inc. The US launch price for a 12-week treatment course with Viekira PakTM is US$83,319. For those regimens that require ribavirin, the additional cost is more difficult to determine given the variety of manufacturers and the variability in daily dosing. The approximate cost of generic ribavirin is US$700 for 12-weeks, giving a total 12-week cost in the region of US$84,000. In the US, AbbVie Inc. have launched a financial assistance program, ProCeeldTM, aimed at providing Viekira PakTM free of charge to eligible patients not covered by medical insurance and without access to other funding sources.

The launch price for Viekira PakTM is only slightly lower than that of other all oral regimens such as Gilead’s SovaldiTM (sofosbuvir) and HarvoniTM (ledipasvir/sofosbuvir), marketed at US$84,000 (used in combination with ribavirin) and US$94,500, respectively for a 12-week course (Table 11). The lower cost possibly reflects the increased dosing inconvenience of the regimen (twice daily, multi-pill regimen).
Table 11. Wholesale acquisition costs and predicted minimum costs of 12 weeks treatment with various all-oral HCV regimens

<table>
<thead>
<tr>
<th>Regimen, 12 weeks</th>
<th>US Wholesale acquisition cost</th>
<th>Lowest emerging market acquisition cost</th>
<th>Predicted minimum cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ombitasvir/paritaprevir/r + dasabuvir ± ribavirin</td>
<td>Without RBV: US$83,319  With RBV: “…US$84,000”</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sofosbuvir + ribavirin</td>
<td>“…US$84,700”</td>
<td>“…US$1,050”</td>
<td>US$149</td>
</tr>
<tr>
<td>Sofosbuvir/ledipasvir</td>
<td>US$94,500</td>
<td>-</td>
<td>US$193</td>
</tr>
<tr>
<td>Sofosbuvir + simeprevir</td>
<td>US$150,000</td>
<td>-</td>
<td>US$231-US$371</td>
</tr>
<tr>
<td>Sofosbuvir + daclatasvir</td>
<td>-</td>
<td>-</td>
<td>US$121</td>
</tr>
<tr>
<td>MK-8742 + MK-5172</td>
<td>-</td>
<td>-</td>
<td>US$118</td>
</tr>
</tbody>
</table>

Minimum costs taken from (van de Ven et al. 2014) & (Hill et al. 2014)
*Based on approximate cost of ribavirin of US$700
†Based on US$900 cost of sofosbuvir in Egypt and assuming mass acquisition of generic ribavirin at a price of US$0.30/tablet (manufacturer: Zydus; full ribavirin regimen: “…US$150)

Evidence from two recent studies suggests that the manufacturing costs for a 12-week all-oral regimen could be a fraction of the current market prices (van de Ven et al. 2014; Hill et al. 2014). Specifically, the analyses suggest that 12-week regimens could cost as little as US$118 for the currently unapproved Merck combination, up to US$149 for treatment with sofosbuvir/ribavirin and US$193 for sofosbuvir/ledipasvir (Table 11). This cost analysis has not been conducted for the ombitasvir/paritaprevir/r and dasabuvir combination, but it is not unreasonable to suppose that similar price reductions could be feasible. Despite this assumption, the minimum costs of the regimen need to be validated with further economic evaluation.

No generic suppliers have been identified for ombitasvir/paritaprevir/r and dasabuvir, and to date, AbbVie have not announced any plans to provide a discount program for emerging markets. In contrast, Gilead have announced a significantly reduced price of US$900 for sofosbuvir in Egypt, Vietnam, and India, and are working with national governments to provide Sovaldi™ and Harvoni™ in LMICs at lower costs based on the country’s disease burden and economic means (Gilead Sciences 2014a). Furthermore, Gilead have agreed licensing agreements with generic pharmaceutical manufacturers in India; these companies have begun to produce generic treatment for approximately the same price as Gilead’s US$900 access price for use in 91 of the poorest countries. Other generic suppliers not covered by the Gilead’s license, such as Incepta Pharmaceuticals Ltd. in Bangladesh and a number of suppliers in Egypt, have begun producing generic versions of sofosbuvir for sale in countries such as Thailand, Malaysia, and Morocco, where the drug is currently not patented (Gokhale & Kitamura 2015). Promisingly, the WHO is in communication with a number of generic manufacturers regarding pre-qualification of Sovaldi™ generics.
In terms of costs associated with monitoring, the simplified monitoring regimen and shorter treatment duration, combined with the aversion of the need of weekly injections necessary with traditional regimens, will likely decrease both direct and indirect healthcare costs. One UK analysis suggests that the direct monitoring costs for GT1 non-cirrhotic treatment-naive patients would be cut be over half for 12-weeks treatment with sofosbuvir/ledipasvir compared with the recommended 48-weeks treatment with Peg-IFN/ribavirin (US$1,122 compared with US$2,575; 56% reduction) (Gilead Sciences 2014b). The difference was even more pronounced in cirrhotic patients (US$1,367 compared with US$3,719; 63% reduction).

Whilst the minimal diagnostic and monitoring algorithm is still to be validated by the WHO, the favourable safety profile of DAA regimens suggests that monitoring could be significantly reduced. The minimum costs study determined that monitoring could be limited to two full blood counts plus simple clinical chemistry tests, once pre-treatment and once during treatment, costing US$22 in total (van de Ven et al. 2014). In addition, compared with HCV RNA viral load testing, HCV antigen testing could be a cheaper and more appropriate for resource-limited settings and could be carried out once prior to treatment to establish infection, and 6 months post-treatment completion to determine treatment success (US$34). Diagnostic testing is still reasonably expensive at US$90, but could be redundant if treatment becomes pan-genotypic. Thus, the minimum costs of diagnostic monitoring with or without genotyping could be US$146 or US$56, respectively, and it is reasonable to suggest that the complete treatment and monitoring package could cost under US$500 per person per 12-week course (van de Ven et al. 2014).

12.2) Resource use

The development of complications associated with HCV, such as decompensated cirrhosis, HCC, and the need for liver transplantation pose a high economic burden in high-income and LMICs alike. In a US analysis, the yearly per-person all-cause health care costs were shown to be significantly higher for patients with HCV compared with a matched comparison group (McAdam-Marx et al. 2011). For patients with HCC, annual costs were US$48,190 higher, and for liver transplant recipients, in the year immediately succeeding transplantation, costs were US$210,758 higher than control (costs converted to 2014 US$). Similar results were observed in a European study which showed higher direct and indirect costs in patients with HCV compared with matched controls (Vietri, Prajapati & El Khoury 2013). There is limited data regarding resource use and costs originating from LMICs. One study from Thailand showed an increasing annual cost associated with procedures, medications aside from antiviral medications, and hospitalisations as the severity of HCV disease progressed (Thongsawat et al. 2014).

According to a large analysis of 16 countries, despite a projected decrease in the total number of HCV infections between 2013 and 2030, if current HCV treatment practices continue, the number of patients with
HCV-related cirrhosis, decompensated cirrhosis, and HCC, can be expected to increase in the same time period (Razavi et al. 2014). This increased resource utilisation will impose a high economic burden on healthcare systems, individuals, and society. In a simulation study, the total annual HCV-associated medical costs was predicted to more than double from US$30 billion in 2009 up to US$85 billion in 2028 in the US alone (Pyenson, Fitch & Iwasaki 2009). Given the superior SVR rates compared with traditional therapy, the om下班avir/paritaprevir/r with or without dasabuvir regimens, along with other all-oral treatments for HCV, have the potential to significantly decrease future complication rates and dramatically mitigate the long-term economic burden. In treated patients, failure to achieve an SVR was associated with a 13-fold increase in 5-year post-treatment costs compared with non-SVR in a UK study (Backx et al. 2014); given the slow rate of disease progression, greater savings would be expected over a longer time frame. Similar findings were reported in a US study (Manos et al. 2013), highlighting the potential economic impact of improved efficacy.

12.3) Comparative cost-effectiveness

Despite the aversion of HCV related complications and the associated costs, the cost-effectiveness of the regimen will be largely dependent on the cost of treatment. To date, no analyses have been conducted to examine the cost-effectiveness of the AbbVie regimen, however, other all-oral regimens have demonstrated cost-effectiveness for GT1 infection in high-income countries at current costs (Petta et al. 2014; Hagan et al. 2013; Younossi et al. 2015). Again, there is limited evidence relating to the cost-effectiveness of treatment in LMICs. Results from the UK’s critical appraisal and cost-effectiveness analysis of om下班avir/paritaprevir/r and dasabuvir (conducted by NICE) are expected in September 2015.

Affordability and budget impact need to be considered before widespread treatment access can become a reality. It is only at low prices, such as those proposed in the abovementioned studies, that widespread access to HCV treatment in LMICs could become a realistic goal. Inclusion on the EML would provide the impetus for price negotiations and generic manufacture of the AbbVie regimen and other all-oral regimens.

13) Summary of regulatory status of the medicine (in various countries)

- United States of America – approved on December 19th 2014 (Trade name: Viekira PakTM)
- Canada – approved on December 23rd 2014 (Trade name: Holkira PakTM)
- European Union – approved on January 16th 2015 (Trade name: ViekiraxTM and ExvieraTM)
- Also approved in Switzerland, Iceland, Liechtenstein, and Norway
- Japan – submitted for approval on February 12th 2015
14) Availability of pharmacopoeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia)

Not yet included in these British, International, United States, or European pharmacopoeias.

15) Proposed new text that could be included in a revised WHO Model Formulary

**Treatment of Hepatitis C**

Ombitasvir, paritaprevir, ribavirin (12.5/75/50 mg) tablet PLUS dasabuvir (250 mg) tablet for treatment of HCV genotype 1*

Ombitasvir, paritaprevir, ribavirin (12.5/75/50 mg) tablet for treatment of HCV genotype 4*

*To be used in adults in combination with ribavirin in certain patient populations
References


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Wyles, D & Gutierrez, J 2014, 'Importance of HCV genotype 1 subtypes for drug resistance and response to therapy', *J Viral Hepat*, vol 21, no. 4, pp. 229-40.

