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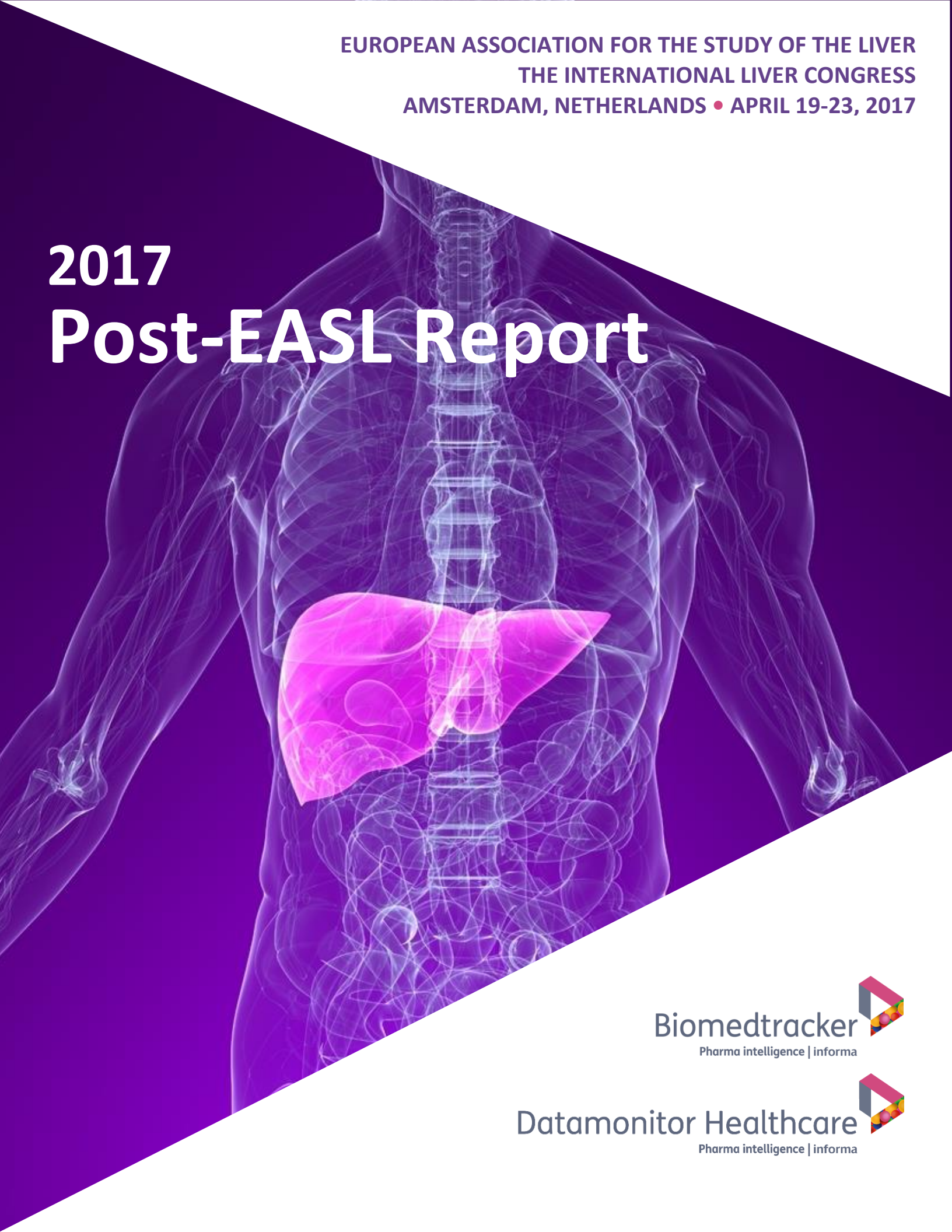
2017
Post-EASL Report



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Summary

As chronic hepatitis C virus (HCV) drug development approaches the end-game following the launch of the first pan-genotypic regimen, Epclusa (sofosbuvir/velpatasvir; Gilead), recent and upcoming advances in chronic hepatitis B virus (HBV) treatment emerged as an important focus of The International Liver Conference (ILC) 2017, the annual meeting of the European Association for the Study of the Liver (EASL), which took place in Amsterdam, the Netherlands, on 19–23 April 2017. Particular interest was paid to 96-week safety data from pivotal studies of Vemlidy (tenofovir alafenamide [TAF]; Gilead), which Gilead hopes will drive its uptake in the face of imminent competition from generic versions of Viread (tenofovir disoproxil fumarate [TDF]; Gilead). Updated EASL guidelines for the management and treatment of chronic HBV were also released, which included a novel recommendation for the use of Vemlidy as a first-line agent in select patients, as well as a revised nomenclature for classifying the stages of chronic HBV infection.

There was also considerable optimism regarding the potential of new modes of action in early-phase development for the treatment of HBV to improve upon the disappointingly low rates of hepatitis B surface antigen (HBsAg) loss observed after treatment with currently available therapies. While there are very limited efficacy data available for early-phase approaches, there was consensus during panel discussions of available data that combining currently approved nucleos(t)ide analogs (NAs) with novel agents, such as RNA interference, capsid assembly inhibitors, nucleic acid polymers, and immunostimulatory agents, represents a promising approach towards achieving “functional cure”.

Multiple abstracts for HCV therapies were also presented as AbbVie, Merck & Co, and Johnson & Johnson attempted to demonstrate differentiation in a highly-competitive market with few unmet needs remaining. AbbVie presented data from multiple Phase III studies which highlighted glecaprevir/pibrentasvir’s pan-genotypic efficacy in non-cirrhotic genotype 3 (GT-3) patients (ENDURANCE-3) and cirrhotic GT-1/2/4/5/6 patients (EXPEDITION-1), as well as its maintenance of competitive cure rates in direct-acting antiviral-experienced GT-1/4 patients (MAGELLAN-1) and post-transplant patients (MAGELLAN-2). Merck & Co presented data from the Phase II C-SURGE study in DAA-experienced patients which demonstrated that its triple combination of uprifosbuvir/grazoprevir/ruzasvir was an effective salvage regimen in DAA-experienced patients with resistance-associated substitutions, and future studies will investigate the regimen in both DAA-naïve and DAA-experienced patients. Finally, Johnson & Johnson suffered a setback as its triple combination of AL-335/odalasvir/simeprevir failed to demonstrate competitive efficacy in GT-3 patients, prompting the company to discontinue development for this subgroup and putting an end to the company’s hopes of marketing a pan-genotypic regimen. While AL-335/odalasvir/simeprevir is still being developed for the remaining GTs and could shorten treatment duration to just six weeks in non-cirrhotic GT-1 patients, it is likely that Johnson & Johnson will be forced to offer significant discounts to compensate for its late entry to the market.

In this report we summarize several notable highlights from this year’s EASL conference. Also included are key abstracts featuring commentary from Biomedtracker and Datamonitor Healthcare analysts including any changes in Likelihood of Approval (LOA), if applicable. At the end of the report we’ve provided a full list of Biomedtracker events from EASL and select large impact catalysts expected through 2018.

Highlights

- ENDURANCE-3 data position glecaprevir/pibrentasvir as an emerging gold standard for non-cirrhotic GT-3 patients – AbbVie's next-generation regimen demonstrated non-inferiority to sofosbuvir + daclatasvir in non-cirrhotic GT-3 patients, achieving competitive sustained virologic response (SVR) rates of 95% in both the eight- and 12-week arms. With non-cirrhotic (F0-F3) individuals comprising an increasing proportion of treated patients, glecaprevir/pibrentasvir eight-week duration poses a major threat to Gilead's Epclusa, which is currently approved as a 12-week regimen for all patients with compensated disease.

- MAGELLAN-1: glecaprevir/pibrentasvir suboptimal in DAA-experienced patients with multi-class resistance – Glecaprevir/pibrentasvir showed suboptimal SVR12 rates in DAA-experienced GT-1 patients of 89% and 91% after 12 and 16 weeks of treatment, respectively. While both 12- and 16-week regimens achieved 100% SVR12 in individuals with NS3 resistance-associated substitutions (RASs) only, such patients will be rare in the salvage setting given that all the first-generation regimens also select for NS5A resistance in virologic failures. SVR12 rates in patients with baseline NS3 and NS5A RASs were suboptimal in both the 12- and 16-week arms (79% and 81%, respectively), suggesting that a nucleotide NS5B-containing triple regimen is preferable in such cases.

- C-SURGE confirms potential of uprifosbuvir/grazoprevir/ruzasvir in DAA-experienced patients – Merck & Co's uprifosbuvir/grazoprevir/ruzasvir demonstrated excellent SVR12 rates of 98–100% after 16 weeks with ribavirin or 24 weeks without ribavirin in difficult-to-treat GT-1 patients who had previously failed treatment with Harvoni (sofosbuvir/ledipasvir) or Zepatier (grazoprevir/elbasvir). However, conservative treatment durations were utilized, and future studies will investigate shorter treatment durations with or without ribavirin to render the regimen more competitive with Gilead's 12-week salvage combination, sofosbuvir/velpatasvir/voxilaprevir.

- AL-335/odalasvir/simeprevir Phase II data disappoint – Johnson & Johnson's triple combination failed to show competitive efficacy in non-cirrhotic GT-3 patients, with SVR12 rates of 0% and 77% after eight and 12 weeks of treatment, respectively, putting an end to the company's hopes of marketing a pan-genotypic regimen. However, the regimen achieved 100% SVR12 in GT-1 patients after six weeks of treatment, suggesting that there is further leeway to reduce treatment durations in the easiest-to-treat patients.

- Updated EASL treatment guidelines for HBV – The new guidelines recommend Vemlidy as a first-line agent on par with Viread and Baraclude (entecavir; Bristol-Myers Squibb), providing a boost to Gilead's strategy of cannibalizing Viread's patient share before its anticipated loss of exclusivity in the EU in September 2017 and in the US in December 2017. The new guidelines also revised the nomenclature for the five stages of chronic HBV infection, but the indications for initiating treatment remain the same. Indeed, patients with hepatitis B e antigen (HBeAg)-positive infection (previously called "immune-tolerant" patients) remain unindicated for treatment because of the reduced efficacy of currently available treatments during this phase, as well as the possible occurrence of spontaneous HBeAg seroconversion and remission without treatment.

- 96-week comparisons confirm TAF's superior safety profile compared to TDF in HBV patients – Updated analysis from two pivotal switching studies in HBeAg-positive and HBeAg-negative patients showed that patients receiving TAF continued to display smaller declines from baseline in hip and spine bone mineral density (BMD) and in estimated creatinine clearance compared with patients taking TDF. However, the real-world significance of these minor improvements in bone/renal laboratory parameters is yet to be demonstrated and was met with some scepticism from the audience. TAF will also face pricing pressure from generic entecavir, which is also a recommended alternative to TDF in patients considered to be at elevated risk for bone/renal side effects on TDF treatment.

- SWAP study confirms that addition of pegylated interferon provides only modest improvements in HBsAg loss compared to NA therapy alone – Previous studies have suggested that switching to or adding on pegylated interferon to NA therapy can provide minor improvements in HBsAg loss compared to NA therapy alone. The SWAP study aimed to evaluate which strategy was superior in HBeAg-positive and HBeAg-negative patients who had achieved stable virologic suppression on NA therapy for at least one year. No significant differences were observed between the two strategies, and rates of HBsAg loss were once again a modest improvement (11-12%) compared to NA-treated controls (0%), highlighting the huge unmet need for combinations with agents possessing novel modes of action to improve rates of functional cure.

- Release of the World Health Organization's first-ever global hepatitis report – The report highlighted that poor diagnosis and linkage to care rates are the key steps of the HBV and HCV treatment cascades which pharmaceutical companies and national governments must aim to improve. In 2015, only 9% and 20% of HBV- and HCV-infected individuals globally were aware of their infection, and only 8% and 7% received appropriate antiviral treatment, respectively. Without substantial increases in these rates, it is clear that the ambitious WHO goals of a 90% reduction in the incidence of viral hepatitis and a 65% reduction in mortality will not be achieved. In a bid to improve detection of infection and treatment access for difficult-to-reach risk groups such as migrants, prisoners, and people who inject drugs, the report encouraged the deployment of targeted screening programs and the provision of DAA-treatment at the primary care level via knowledge-sharing initiatives with specialists.

- Reduced liver fat as evaluated by imaging technology rather than invasive liver biopsy as a key feature of mid-stage non-alcoholic steatohepatitis (NASH) drugs – Bristol-Myers Squibb, Gilead and NGM Biopharmaceuticals presented promising liver fat results for their respective Phase II NASH candidates ARX618, GS-0976 and NGM282. Phase II data on Bristol-Myers Squibb's ARX618 (pegylated human fibroblast growth factor 21) showed 10 mg daily and 20 mg weekly subcutaneous doses resulted in absolute changes in liver fat of -6.8% and -5.2%, respectively, compared to -1.3% for placebo, as assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF). Gilead's oral acetyl-CoA carboxylase inhibitor GS-0976 also resulted in a -6.7% change in liver fat as measured by MRI-PDFF in an open-label proof-of-concept Phase I trial. Finally, and most impressively, Phase II data on NGM Biopharmaceutical's NGM282 (non-tumorigenic human fibroblast growth factor 19) showed 3 mg and 6 mg daily subcutaneous doses resulted in absolute changes in liver fat of -9.7% and -11.9%, respectively, compared to -0.9% for placebo, as assessed by MRI-PDFF.

About the Author

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Contents

Hepatitis B (HBV)

Vemlidy (Gilead, Approved)

Phase III - vs. Tenofovir Disoproxil Fumarate (Antigen-Positive)
Phase III - vs. Tenofovir Disoproxil Fumarate (Antigen-Negative)
Trial Data - Updated Results

Change to LOA: 0%

Abstract PS-041: Improved bone and renal safety of switching from tenofovir disoproxil fumarate to tenofovir alafenamide: Preliminary results from 2 phase 3 studies in HBeAg-positive and HBeAg-negative patients with chronic hepatitis B

Abstract PS-042: A phase 3 study comparing tenofovir alafenamide to tenofovir disoproxil fumarate in patients with HBeAg-negative, chronic hepatitis B: Efficacy and safety results at week 96

Data from these studies were previously seen in April 2016.

Improved bone and renal safety of switching from tenofovir disoproxil fumarate to tenofovir alafenamide: Preliminary results from 2 phase 3 studies in HBeAg-positive and HBeAg-negative patients with chronic hepatitis B (Abstract PS-041)

Design
In two identically-designed Phase III studies, immune active chronic hepatitis B (CHB) patients who were HBeAg negative (GS-US-320-0108; N = 425) or HBeAg positive (GS-US-320-0110; N = 873) were randomized to and treated with TAF 25 mg QD or TDF 300 mg QD. A subset of patients (N = 200 in Study 0108 and N = 340 in Study 0110) in these ongoing 8 year studies had completed 96 weeks of double-blind (DB) treatment with TAF or TDF and switched to open-label (OL) TAF 25 mg QD at the time of the Week 96 analysis. Dual energy X-ray absorptiometry (DXA) scans were evaluated every 24 weeks as were serial assessments of creatinine clearance and viral suppression. Analyses included subjects with values at Week 96 and Week 120 for creatinine clearance (n = 362), spine BMD (n = 228) or hip BMD (n = 222).

Results
A total of 540 subjects had entered the OL TAF phase after 96 weeks of blinded therapy across both studies. Creatinine clearance improved significantly in patients switched from DB TDF to OL TAF at Week 120 compared to Week 96 (N = 117, mean (SD) change = +2.43 (12.81) ml/min, p = 0.04); and remained stable in those previously receiving TAF. BMD also showed improvement at Week 120 from Week 96 among patients switched from DB TDF to OL TAF (hip: N = 58, mean (SD) % change = +0.71% (1.43), p = 0.0004; spine: N = 60, mean (SD) % change = +1.41% (2.30), p <.0001). BMD changes in hip and spine for DB TAF patients entering the OL TAF period were relatively stable. Compared to results at Week 96, high rates of virologic control were maintained across subjects in both studies during the OL period (97-99% and 80-83% in Studies 0108 and 0110, respectively).

Conclusion
Patients switching from Viread to Vemlidy after Week 96 demonstrated maintenance of viral suppression,

improvement in serum alanine aminotransferase (ALT) normalization rates, and improvement in bone and renal parameters 24 weeks after switching to Vemlidy.

A phase 3 study comparing tenofovir alafenamide to tenofovir disoproxil fumarate in patients with HBeAg-negative, chronic hepatitis B: Efficacy and safety results at week 96 (Abstract PS-042)

Design

425 patients were randomized to receive TAF 25 mg QD (n = 285) or TDF 300 mg QD (n = 140) and treated for 144 weeks. After Week 144, patients receive open label TAF through 8 years. Viral resistance was evaluated by deep sequencing or population sequencing in all patients with HBV DNA ≥ 69 IU/mL at Week 96 or time of discontinuation. Baseline characteristics included: mean age 46 years, 61% males, 72% Asians, genotypes A through D (5%, 24%, 38%, 31%); 19% had HBV DNA ≥ 7 log10 IU/mL, and 21% were previously treated with nucleos(t)ides.

Endpoints

Efficacy analyses at Week 96 included virologic (HBV DNA <29 IU/mL), and biochemical (ALT normalization) responses; key secondary safety endpoints were changes in hip and spine bone mineral density (BMD), and changes in serum creatinine and estimated GFR by Cockcroft-Gault method (eGFRCG). Serum markers of bone turnover and urine markers of renal tubular function were also assessed.

Results

Results demonstrate continued advantages of treatment with Vemlidy over Viread between Week 48 and Week 96. Virologic response rates at Week 96 were 90 percent (n=257/285) and 91 percent (n=127/140) in HBeAg-negative patients (Study 108) receiving Vemlidy and Viread, respectively. In HBeAg-positive patients (Study 110), virologic response rates at Week 96 were 73 percent (n=423/581) and 75 percent (n=218/292) in the Vemlidy and Viread groups, respectively. In both studies, a greater percentage of patients taking Vemlidy achieved normalization of ALT levels relative to patients taking Viread as measured by both central laboratory criteria, and by the American Association for the Study of Liver Diseases (AASLD) criteria. Patients receiving Vemlidy also demonstrated ongoing benefits at Week 96 in bone and renal safety parameters, including smaller declines from baseline in hip and spine bone mineral density (BMD) and smaller declines from baseline in estimated creatinine clearance compared with patients taking Viread in both studies. Viral resistance analyses showed no resistance to Vemlidy or Viread at Week 96.

Most Common Adverse Events

The rates of treatment discontinuations for adverse events (<2%) and serious adverse events were (≤11%) were similar in the two arms.

Conclusion

Analyses conducted at Week 96 of treatment demonstrate continued benefits of Vemlidy including high rates of viral suppression, with no evidence of resistance, and less impact on renal and bone safety parameters as compared to Viread.

Comment

The long-term bone and renal safety of nucleotide analogs is coming under increasing scrutiny given the aging of the chronic HBV-infected population, as well as the older mean age of HBeAg-negative patients compared to their HBeAg-positive counterparts. 48-week data from this study in HBeAg-negative individuals were previously announced in January 2016, and the 96-week data further support TAF's

improved bone and renal safety profile compared to TDF, with TAF continuing to show lesser declines in BMD and eGFR parameters compared to TDF. Gilead hopes that these data will encourage physicians to swap patients from TDF to TAF before Viread's (TDF) EU and US patent expiries in September 2017 and December 2017 respectively, however, members of the audience expressed doubts over the real-world clinical significance of the improvement in surrogate markers as comparative data on the incidence of bone fractures and renal disorders are unlikely to be available for several years. Additionally, given the widespread availability of generic entecavir, it was noted by the audience that entecavir was also a recommended alternative to TDF for patients at risk of renal or bone disease, and would likely be more cost-effective for widespread use than TAF. While other members of the audience noted that the higher rates of ALT normalization observed in patients who switched to TAF could provide additional incentive for swapping patients, the consensus was that this approach may be premature given that the mechanism behind this trend is still unclear and is being investigated further during long-term follow-up.

Source:
Press Release 04/20/2017
European Association for the Study of the Liver (EASL) (Abstract PS-041)
European Association for the Study of the Liver (EASL) (Abstract PS-042)
Sagient Analysis

Hepatitis C (HCV)

Glecaprevir/Pibrentasvir (AbbVie, NDA)

Phase III – EXPEDITION-1 (GT 1-6)
Trial Data - Top-Line Results

Change to LOA: 0%

Abstract GS-006: EXPEDITION-I: Efficacy and safety of glecaprevir/pibrentasvir in adults with chronic hepatitis C virus genotype 1, 2, 4, 5 or 6 infection and compensated cirrhosis

	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment
Treatment Description	Glecaprevir/ Pibrentasvir (300 mg/120 mg) HCV GT1 Patients	Glecaprevir/ Pibrentasvir (300 mg/120 mg) HCV GT2 Patients	Glecaprevir/ Pibrentasvir (300 mg/120 mg) HCV GT4 Patients	Glecaprevir/ Pibrentasvir (300 mg/120 mg) HCV GT5 Patients	Glecaprevir/ Pibrentasvir (300 mg/120 mg) HCV GT6 Patients	Glecaprevir/ Pibrentasvir (300 mg/120 mg) All Patients
Number of Patients	N/A	N/A	N/A	N/A	N/A	146
Number of Evaluable Patients	90	31	16	2	7	146
Sustained Virologic Response at 12 Weeks Post-Treatment (SVR12) (Endpoint=Primary)	99 %	100 %	100 %	100 %	100 %	99.3 %

Context

AbbVie is presenting additional data at ILC in patients with specific treatment challenges, including in those with chronic kidney disease (SAT-273), HIV-1 co-infection (LBP-522), post liver and renal transplant patients (LBO-03) and in patients who did not achieve SVR12 with previous direct-acting antiviral (DAA) treatment (PS-156).

Authorization applications for G/P are currently under review by regulatory authorities around the world. G/P has been granted accelerated assessment by the European Medicines Agency (EMA), and priority review designations by the U.S. Food and Drug Administration (FDA) and Japanese Ministry of Health, Labour and Welfare (MHLW).

Design

EXPEDITION-1 is a Phase III single arm, multicenter, open-label study evaluating the efficacy and safety of 12 weeks of G/P in adults with GT1, 2, 4, 5 or 6 chronic HCV infection and compensated cirrhosis (Child-Pugh A). The study enrolled 146 patients, including those new to treatment or had prior treatment experience with IFN-based treatments (IFN/pegIFN ± RBV, or sofosbuvir + RBV ± pegIFN). 25% had prior treatment experience. Patients had either HCV GT1 (59.6%), GT2 (23.3%), GT4 (11.0%), GT5 (1.4%) or GT6 (4.8%) infection. Patients received G/P (300 mg/120 mg) once daily for 12 weeks.

Endpoints

The primary endpoint was the percentage of patients achieving SVR12. Safety was assessed in all patients who received at least 1 dose of study drug.

Results

99 percent (n=145/146) of chronic hepatitis C virus (HCV) infected patients with genotype 1, 2, 4, 5 or 6 and compensated cirrhosis (Child-Pugh A) achieved sustained virologic response at 12 weeks post-treatment (SVR12) with the investigational, pan-genotypic regimen of glecaprevir/pibrentasvir (G/P). One GT1a-infected patient experienced relapse at post-treatment week 8. These high SVR12 rates were seen following 12 weeks of G/P treatment without ribavirin. Patients with specific virus strains associated with resistance or with a high quantity of the virus in their bloodstream before treatment initiation were not excluded from the study.

Most Common Adverse Events

In the EXPEDITION-1 study, the majority of adverse events (AEs) were mild (65%) and no patients discontinued treatment due to an AE. The most common AEs (≥10 percent) were fatigue and headache. Of the 11 patients (7.5 percent) who experienced serious AEs, none were considered treatment-related.

One patient died post-treatment due to an AE not related to study drug (cerebral hemorrhage). One patient with a previous history of esophageal varices experienced esophageal variceal bleeding on Day 22 without worsening of hepatic function. No discontinuations of study drug due to adverse events occurred and no subject had ≥ Grade 3 ALT elevations.

Conclusion

SVR12 was achieved by 99.3% of patients with GT1, 2, 4, 5 or 6 HCV infection and compensated cirrhosis treated with G/P for 12 weeks, supporting the pangenotypic efficacy of the regimen. The regimen was well tolerated, with mostly mild AEs reported, and no serious AEs were considered study-drug related.

Comment
These positive results are unsurprising given the excellent data in non-cirrhotic patients from the pivotal ENDURANCE-1-4 studies, which were previously presented at the 2016 annual meeting of the American Association for the Study of Liver Diseases (AASLD). In contrast to the ENDURANCE studies which enrolled non-cirrhotic patients, the EXPEDITION-1 study exclusively enrolled cirrhotic patients who are considered harder to treat. The sustained virologic response rate of 99% is identical to that achieved by Epclusa in cirrhotic patients enrolled in the ASTRAL-1 study, confirming glecaprevir/pibrentasvir's competitive efficacy and tolerability profile in a market with an extremely high bar to entry. Notably, the only GT-1 patient who experienced relapse possessed the Y93N resistance-associated substitution at baseline; a polymorphism which is known to confer high-level resistance against other first- and second-generation inhibitors in the NS5A class.

Source:
Press Release 04/20/2017 (ABBV)
Press Release 04/20/2017 (ENTA)
European Association for the Study of the Liver (EASL) 04/20/2017 (Abstract GS-006)
European Association for the Study of the Liver (EASL) 04/20/2017 (Presentation Slides)
Sagient Analysis

Glecaprevir/Pibrentasvir (AbbVie, NDA)

Phase II – MAGELLAN-1
Trial Data – Updated Results

Change to LOA: 0%

Abstract PS-156: MAGELLAN-1, Part 2: Glecaprevir and Pibrentasvir for 12 or 16 weeks in Patients with Chronic Hepatitis C Virus Genotype 1 or 4 and Prior Direct-Acting Antiviral Treatment Failure

Abstract SAT-204: Resistance Analysis in the MAGELLAN-1 Study (Part 2): Glecaprevir/Pibrentasvir Therapy in HCV-infected Patients who had Failed Prior DAA Regimens Containing NS3/4A protease and/or NS5A Inhibitors

Data from this study were previously seen in January 2017.

MAGELLAN-1, Part 2: Glecaprevir and Pibrentasvir for 12 or 16 weeks in Patients with Chronic Hepatitis C Virus Genotype 1 or 4 and Prior Direct-Acting Antiviral Treatment Failure (Abstract PS-156)

Design
Part 2 of MAGELLAN-1 is a randomized, open-label study. Patients with chronic HCV GT1 or GT4 infection and prior direct-acting antiviral (DAA) treatment failure to NS5A and/or NS3/4A protease inhibitors, with or without compensated cirrhosis, were randomized 1:1, stratified by HCV GT and prior DAA experience, to receive 12 or 16 weeks of coformulated GLE/PIB (G/P; 300/120 mg). A total of 91 patients were enrolled: 44 received 12 weeks of G/P and 47 received 16 weeks. The majority of patients were male (70%), with a mean BMI of 29.3 kg/m2, and mean baseline HCV RNA of 6.1 log10 IU/ml. In total, 74% of

patients had HCV GT1a, 21% had GT1b, and 4% had GT4 infection. Thirty percent of patients had compensated cirrhosis, and baseline demographics were well distributed between study arms.

Endpoints
The primary endpoints were safety (including all patients receiving ≥1 dose of study drug) and the percentage of patients achieving sustained virologic response (HCV RNA <15 IU/ml) at post-treatment week 12 (SVR12).

Results
Overall, SVR12 was achieved by 89% (39/44) and 91% (43/47) of patients who received 12 and 16 weeks of G/P, respectively.

Most Common Adverse Events
The majority of adverse events (AEs) were mild in severity, and no patient discontinued due to AEs. No patients had serious AEs considered related to study drug. Headache was the only AE that occurred in ≥10% of patients. No treatment emergent grade 3+ elevations in alanine/aspartate aminotransferases or bilirubin were observed.

Conclusion
G/P retreatment of HCV GT1 or GT4 infected patients, with or without compensated cirrhosis, who experienced prior DAA therapy failure resulted in high overall SVR12 rates. The regimen was well tolerated with no relevant laboratory abnormalities and no discontinuations due to adverse events.

Resistance Analysis in the MAGELLAN-1 Study (Part 2): Glecaprevir/Pibrentasvir Therapy in HCV-infected Patients who had Failed Prior DAA Regimens Containing NS3/4A protease and/or NS5A Inhibitors (Abstract SAT-204)

Design
Part 2 of MAGELLAN-1 enrolled 91 patients who had previously failed 1 or more regimens containing an NS3/4A protease inhibitor (PI) and/or an NS5A inhibitor (NS5Ai). Patients were treated for 12 or 16 weeks with glecaprevir (NS3/4A PI identified by AbbVie and Enanta) and pibrentasvir (NS5Ai). Next generation sequencing was conducted using Illumina MiSeq on all available baseline (BL) and virologic failure (VF) samples. The prevalence and impact on SVR12 rates of BL polymorphisms (BP) at amino acid positions 155, 156, 168 in NS3, and 24, 28, 30, 31, 58, 92, 93 in NS5A were determined based on prior treatment category (PI,experienced [NS5Ai naïve], NS5Ai experienced [PI naïve], or PI+NS5Ai experienced) using a 15% detection threshold. Treatment-emergent substitutions were analyzed for the 9 patients experiencing VF.

Results
NS3 and NS5A sequences were generated from 88/91 BL samples: 67 GT1a (73.6%), 18 GT1b (19.8%), and 3 GT4r (3.3%). The prevalence of BPs was 6.8% (6/88) in NS3 only, 53.4% (47/88) in NS5A only, and 10.2% (9/88) in NS3+NS5A.

Among PI-only experienced patients, neither presence of BPs nor treatment duration had an impact on outcome; all achieved SVR12. NS5A BPs were prevalent (80.6%; 50/62) among NS5Ai-experienced patients with or without PI exposure; all patients without NS5A BPs achieved SVR12. Among NS5Ai-only experienced patients who had NS5A BPs, SVR12 rates were 86.7% (13/15) and 91.7% (11/12) in the 12 and 16 week arms, respectively. Among PI+NS5Ai-experienced patients with BPs in only in NS5A, SVR12

rates were 71.4% (5/7) and 100% (8/8) in the 12 and 16 week arms, respectively, whereas SVR12 rates were 75% (3/4) and 25% (1/4) in those with BPs in both targets in the 12 and 16 week arms, respectively.

Four of 9 VFs had BPs in NS3, and additional treatment-emergent NS3 substitutions were observed in 6 patients at VF. All 9 VF patients had 1 or more NS5A BPs, and additional NS5A substitutions emerged at VF in 6 patients. All VF patients had 2 or more NS5A substitutions at failure.

Conclusion

PI-only experienced patients had an SVR12 rate of 100% irrespective of the presence of BPs or treatment duration. In NS5Ai experienced patients receiving 16 weeks of treatment, the presence of NS5A BPs (without NS3 BPs) did not impact efficacy; the SVR12 rate was 95% (19/20). The minority of PI+NS5Ai experienced patients who had BPs in both NS3 and NS5A had a higher rate of VF than those with BPs in only 1 target.

Comment

These were mixed results for glecaprevir/pibrentasvir which highlighted the regimen's ability to achieve high cure rates in difficult-to-treat patients with baseline resistance-associated substitutions, but only if treatment was extended to 16 weeks. Patients who possessed NS3 RASs only at baseline performed equally well in the 12- and 16-week arms, but such individuals are likely to form a small proportion of DAA-experienced patients going forwards given that the leading protease inhibitors (paritaprevir and grazoprevir) are both co-formulated with NS5A inhibitors. In patients with baseline NS5A RASs, 16 weeks of treatment was numerically superior to the shorter treatment course, and in both arms, cure rates were suboptimal in patients with both protease inhibitor and NS5A inhibitor experience. It is therefore likely that nuc-containing triple regimens will be preferred options for patients with RASs to multiple classes. An alternative option would be to explore the potential benefit of adding ribavirin to a 16-week course, but this approach would be unattractive in an era aiming to dispense with ribavirin and its associated side effects and patient monitoring requirements.

Source:
European Association for the Study of the Liver (EASL) 04/22/2017 (Abstract PS-156)
European Association for the Study of the Liver (EASL) 04/22/2017 (Abstract SAT-204)
Sagient Analysis

JNJ-4178 (Johnson & Johnson, Phase IIb)

Phase IIa - w/AL-335/Simeprevir (Treatment-Naive, GT1)
Trial Data - Updated Results

Change to LOA: -2%

Abstract PS-153: Short duration treatment with AL-335 and odalasvir, with or without simeprevir, in treatment-naïve patients with hepatitis C virus (HCV) genotype 1 infectio

	Comparator	Treatment	Treatment
Treatment Description	AL-335 + Odalasvir Patients with HCV Genotype 1 Infection Without Cirrhosis	JNJ-4178 Patients with HCV Genotype 1 Infection Without Cirrhosis	JNJ-4178 Patients with HCV Genotype 3 Infection Without Cirrhosis
SVR24 After 6 Weeks of Treatment	N/A	100 %	N/A
SVR24 After 8 Weeks of Treatment	84 %	100 %	N/A
SVR12 After 12 Weeks of Treatment	N/A	N/A	77 %

Data from this study were previously seen in September 2016.

Context

Janssen has initiated a multi-center, randomized, open-label Phase IIb study of JNJ-4178, the triple combination of once-daily odalasvir 25mg, AL-335 800mg, and simeprevir 75mg for treatment durations of six and eight weeks. Designated OMEGA-1, this trial has now completed enrollment of more than 365 treatment-naïve and treatment-experienced, non-cirrhotic patients chronically infected with HCV genotype 1,2,4,5 and 6. Results from this trial are anticipated during the second half of 2017. In addition, the '604 Study' is ongoing and will assess the triple combination JNJ-4178 in patients with compensated cirrhosis.

In addition to the OMEGA-1 and '604 Study,' a number of supplemental clinical trials are being conducted by Janssen including those assessing special populations, certain drug-drug interactions, the bioavailability of a fixed dose combination, and providing for long-term follow-up of patients, all supporting the global development of JNJ-4178.

Design

This is an ongoing open-label study evaluating various dosing regimens of AL-335 + odalasvir ± simeprevir for ≤12 weeks in treatment-naïve, HCV genotype (GT) 1–3 infected patients with or without compensated cirrhosis.

Results

Data from this study demonstrate that JNJ-4178, the three-drug combination of simeprevir, odalasvir and AL-335, was highly effective in treatment naïve patients with HCV genotype 1 infection without cirrhosis, achieving 100% SVR24 for treatment durations of both 6 and 8 weeks. The two-drug regimen of odalasvir and AL-335, a combination regimen not anticipated to move forward, achieved 84% SVR24 for treatment duration of 8 weeks in patients with HCV genotype 1 without cirrhosis. The three-drug regimen of simeprevir, odalasvir and AL-335 in HCV genotype 3 patients without cirrhosis achieved an SVR12 of 77% following 12 weeks of therapy, and is also not anticipated to move forward. Genomic sequencing results indicate that despite the presence of multiple NS5A mutations observed at baseline there was no apparent impact on SVR rates.

Most Common Adverse Events

The all-oral combination regimens containing odalasvir and AL-335, with or without simeprevir, were generally safe and well tolerated.

Per the abstract, the majority of adverse events (AEs) were mild, most commonly headache, fatigue, upper respiratory tract infection, and bruising. There were 2 serious AEs: urethral transition cell carcinoma (unrelated; Cohort 2) and Mobitz Type 1 2nd degree atrioventricular block (probably related; Cohort 1), which was not associated with clinical/echocardiographic abnormalities and resolved after treatment discontinuation. No other AE resulted in discontinuation. No significant laboratory abnormalities were observed.

Conclusion

These results demonstrate that the triple combination of simeprevir, odalasvir and AL-335 has the ability to shorten treatment duration, offer high efficacy and be generally well tolerated in those whose disease is caused by hepatitis C virus (HCV) genotype 1 (GT1).

Comment

Despite the positive SVR data in GT-1 patients, these results are negative overall for Johnson & Johnson, which had hoped to market a "one-size-fits-all" pan-genotypic regimen. While the triple regimen has displayed an impressive 100% cure rate after an ambitious course of just six weeks of treatment in easier-to-treat GT-1 patients, it is unlikely that this duration will be sufficient for cirrhotic patients. In addition, it is unclear if a further two-week shortening of treatment duration will be considered a key differentiator from Harvoni and glecaprevir/pibrentasvir, which have already displayed competitive efficacy after eight weeks in non-cirrhotic GT-1 patients. The 77% cure rate in GT-3 patients is particularly disappointing, as this group is now considered the most difficult to treat, and rival triple pan-genotypic regimens have already demonstrated competitive efficacy in this subset. As a result Johnson & Johnson/Achillion are not expected to pursue approval for GT-3 in future studies. The observation of a serious treatment emergent cardiac adverse event (Type I second-degree atrioventricular block) is also a potential cause for concern given the history of cardiac toxicity with the nucleotide NS5B class, although in this case the event was not clinically significant. Nevertheless, future safety data should be scrutinized for evidence of cardiac toxicity. Based on these data, we are lowering the LOA by 2%.

Source:
Press Release 04/22/2017 (ACHN)
European Association for the Study of the Liver (EASL) (Abstract PS-153)
Press Release 04/24/2017 (Medivir)
Sagient Analysis

MK-3682 (Merck & Co., Phase II)

Phase II – C-SURGE
Trial Data - Updated Results

Change to LOA: +1%

Abstract PS-159: Safety and efficacy of the fixed-dose combination regimen of MK-3682/grazoprevir/ruzasvir in cirrhotic or non-cirrhotic patients with chronic HCV GT1 infection who previously failed a direct-acting antiviral regimen (C-SURGE)

	Treatment	Treatment
Treatment Description	MK-3682B w/RBV **16 weeks**	MK-3682B **24 weeks**
Number of Patients	45	49
SVR12 *Full Analysis Set*	98 %	100 %
SVR12 *Modified Full Analysis Set*	100 %	100 %

Data from this study were previously seen in November 2016.

Design

The Phase II C-SURGE study enrolled 94 patients who were randomized to receive a once-daily regimen of MK-3682B for either 16 weeks with RBV (n=45) or 24 weeks without RBV (n=49); one patient in the 16-week arm withdrew prior to starting treatment. Of the 93 patients who received treatment (full analysis set), 57 had previously received a regimen of ledipasvir/sofosbuvir (LDV/SOF) for 12 to 24 weeks, 14 had previously received LDV/SOF for 8 weeks and 22 had previously received ZEPATIER (elbasvir and grazoprevir) for 12 weeks. Seventy-eight patients who received treatment had at least one baseline NS5A resistance-associated substitution (RAS) at positions 28, 30, 31 or 93. Eighty patients who received treatment in C-SURGE had GT1a infection, and 40 patients had compensated cirrhosis.

Results

In the full analysis set, 98 percent of patients who received MK-3682B for 16 weeks with RBV (43/44) and 100 percent of patients who received MK-3682B for 24 weeks without RBV (49/49) achieved SVR12. Results from the modified full analysis set, which excludes one patient in the 16-week arm who withdrew after three doses of treatment, show that 100 percent of patients receiving treatment with MK-3682B for 16 weeks with RBV (43/43) and 100 percent of patients receiving treatment with MK-3682B for 24 weeks without RBV (49/49) achieved SVR12.

Most Common Adverse Events

Across the combined treatment arms, the most common adverse events (AEs) reported in the full analysis set were fatigue (35%), headache (13%), diarrhea (9%), rash (9%) and pruritus (5%). There were no drug-related serious AEs, and no patients discontinued treatment due to a drug-related AE.

Conclusion

Per the abstract, the regimen of MK-3682/GZR/RZR was highly efficacious and well-tolerated in cirrhotic and non-cirrhotic GT1 patients who previously failed an NS5A-containing direct-acting antiviral regimen and in whom a majority had NS5A RASs.

Comment

These efficacy data are very impressive in a difficult-to-treat population who had failed previous treatment with either Harvoni or Zepatier; the majority of whom possessed at least one baseline NS3 or NS5A resistance-associated substitution. During the discussion, the panel noted that the high cure rates were largely expected given the inclusion of three potent DAA classes (with or without RBV) and the conservative treatment durations employed compared to the 12-week duration in the pivotal POLARIS-1 study of SOF/VEL/VOX. Future studies should therefore investigate shorter treatment durations with or without ribavirin to optimize the triple combination's dosing schedule, as well as to reduce the cost of treatment. Based on these results, we are raising the LOA by 1%.

Source:
Press Release 04/22/2017
European Association for the Study of the Liver (EASL) 04/22/2017 (Abstract PS-159)
Sagient Analysis

Non-Alcoholic Steatohepatitis (NASH)

ARX618 (Bristol-Myers Squibb, Phase II)

Phase II – MB130-045
Trial Data – Top-Line Results

Change to LOA: +2%

Abstract LBO-02: BMS-986036 (pegylated FGF21) in patients with non-alcoholic steatohepatitis: a phase 2 study

	Placebo	Treatment	Treatment
Treatment Description	Placebo	BMS-986036 10 mg Daily	BMS-986036 20 mg Weekly
Number of Evaluable Patients	24	23	21
Absolute Change in MRI-PDFF at Week 16 *P-value vs. Placebo* (Endpoint=Primary)	-1.3 %	-6.8 % (P=0.0004)	-5.2 % (P=0.008)
Patients Reaching > 30% Relative Risk Reduction	25 %	57 %	52 %

Context
Bristol-Myers Squibb exclusively licensed the rights to research, develop and commercialize BMS-986036 from Ambrx.

Design
This was a multicenter, randomized (1:1:1), double-blind, placebo-controlled study in adults with body mass index ≥25 kg/m2, biopsy-confirmed NASH (F1-F3), and hepatic fat fraction ≥10%, assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF), a noninvasive measurement of liver fat. Randomization was stratified by diabetes status. Patients received subcutaneous injections of BMS-986036 10 mg daily (n=25), BMS-986036 20 mg weekly (n=23), or placebo (n=26) daily for 16 weeks. Among the 74 patients treated, 68 were assessed by MRI-PDFF at both Baseline and Week 16. Liver biopsy was conducted to confirm NASH at Baseline.

Endpoints
The primary efficacy endpoint was absolute change in MRI-PDFF at Week 16. Exploratory endpoints included serum Pro-C3 (N-terminal type III collagen propeptide, a fibrosis biomarker), enzymes alanine

aminotransferase (ALT) and aspartate aminotransferase (AST), and, in a subset of patients, liver stiffness, assessed by MR elastography (MRE).

Results

At Week 16, both dosing regimens of BMS-986036 (10 mg daily or 20 mg weekly) significantly reduced liver fat as measured by MRI-PDFF versus placebo (6.8% and 5.2%, respectively, vs. 1.3%, p=0.0004 and p=0.008). The 10 mg daily dose resulted in 57% of patients (13/23) reaching ≥30% relative risk reduction. The 20 mg weekly dose resulted in 52% of patients (11/21) reaching ≥30% relative risk reduction. Both dosing regimens also improved Pro-C3 (a serum biomarker of fibrosis), magnetic resonance elastography (MRE, a measure of liver stiffness), as well as adiponectin, ALT and AST (markers of liver injury). Improvements in triglycerides, low density lipoprotein (LDL), and high density lipoprotein (HDL) were also observed in the treatment groups.

Most Common Adverse Events

Overall, BMS-986036 had a favorable safety profile, with no deaths or serious adverse events related to treatment, and no discontinuations due to adverse events. The most frequent adverse events were diarrhea (13% and 22%, respectively, vs. 8% in placebo), nausea (16% and 13%, respectively, vs. 8%), and frequent bowel movements (20% and 0%, respectively, vs. 0%), none of which were severe.

Conclusion

The study achieved its primary endpoint of significant reduction in liver fat versus placebo. Statistically significant improvements were also seen in prespecified exploratory endpoints including biomarkers of fibrosis, metabolic parameters and markers of liver injury.

Comment

These encouraging early data on liver fat reduction for ARX618, a long-acting variant of FGF21, are comparable to those recently reported for Gilead's oral acetyl-CoA carboxylase inhibitor GS-0976 and we are raising the LOA by 2%.

Source:
Press Release 04/22/2017 (BMY)
European Association for the Study of the Liver (EASL) 04/22/2017 (Abstract LBO-02)
Sagient Analysis

GS-0976 (Gilead, Phase II)

Phase I – NASH (POC)

Trial Data – Top-Line Results

Change to LOA: +2%

Abstract GS-009: Acetyl-CoA carboxylase (ACC) inhibitor GS-0976 leads to suppression of hepatic de novo lipogenesis and significant improvements in MRI-PDFF, MRE, and markers of fibrosis after 12 weeks of therapy in patients with NASH

Context

A separate Phase II, randomized, double-blind, placebo-controlled trial evaluating GS-0976 in 125 patients with NASH is ongoing.

Preclinical data from a mouse model of NASH were also being presented at The International Liver Congress demonstrating that GS-0976 reduces hepatic steatosis, liver biochemistry and the expression of pro-fibrotic and pro-inflammatory genes in the liver.

Design

Per the abstract, 10 subjects with NASH diagnosed noninvasively by a hepatic proton density fat fraction (PDFF) >10% by MRI and liver stiffness >2.88 kPa by MR elastography (MRE) received GS- 0976 20 mg orally QD for 12 weeks (W12). Centrally-read MRIPDFF and MRE, and serum markers of fibrosis were measured at baseline, W4, and W12. Heavy water (2 H2O, 35 mL) was administered three times daily for one-week cycles prior to baseline, W4, and W12. Deuterium incorporation into palmitate in very-low-density lipoprotein (VLDL) particles was measured in fasting plasma samples by gas chromatography mass spectrometry with kinetic modeling to calculate hepatic DNL and its inhibition by GS-0976.

Results

Based on a novel approach involving the labeling of newly synthesized palmitate by deuterated water administration, patients receiving GS-0976 experienced a median decrease of 29 percent in hepatic DNL from baseline after 12 weeks. At week 12, patients receiving GS-0976 experienced a 43 percent median relative decrease in liver fat content, from 15.7 percent to 9.0 percent (p=0.006), as measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF). Median liver stiffness, a noninvasive marker of fibrosis, declined from 3.4 to 3.1 kPa at week 12 (p=0.049), as assessed by magnetic resonance elastography (MRE). In addition, patients with reductions in hepatic fat demonstrated improvements in liver biochemistry and serum markers of fibrosis and apoptosis, supporting the biological activity of GS-0976.

Per the abstract, at W4 GS-0976 resulted in a median decrease of 34% (IQR 9-53) in hepatic DNL (P = 0.002). Compared with baseline, reductions at W12 were observed in TIMP-1 (275 vs. 244 ng/mL; P = 0.049) and serum ALT (101 vs. 57 U/L; P = 0.23) in GS-0976 treated subjects. At W12, a ≥30% decline in hepatic PDFF was observed in 7 subjects (70%) and 3 subjects (30%) had a ≥15% decrease in MRE-stiffness. Decreases in PDFF and/or MRE-stiffness correlated with changes in ALT, GGT, ELF score, and its components.

Most Common Adverse Events

GS-0976 was well-tolerated. All adverse events were Grade 1 or 2 in severity. No patients prematurely discontinued study medication.

Conclusion

The data, from ten patients treated with GS-0976 20 mg taken orally once daily for 12 weeks, indicated that treatment was associated with statistically significant improvements in liver fat content and noninvasive markers of fibrosis, via inhibition of hepatic de novo lipogenesis (DNL).

Comment

These are impressive early efficacy results albeit from a small number of patients and we are raising the LOA by 2%. The 43% median reduction in liver fat content as measured by MRI-PDFF at week 12 in particular compares favorably to that observed with Gilead's apoptosis signal-regulating kinase 1 inhibitor

selonsertib. In an open-label Phase II trial of selonsertib alone or in combination with simtuzumab (SIM) in NASH patients with moderate to severe liver fibrosis (fibrosis stages F2 or F3), selonsertib 18 mg +/- simtuzumab lead to ≥30% reduction in liver fat content as measured by MRI-PDFF in 26% of patients.

GS-0976 is the only drug in clinical development in the US that targets acetyl-CoA carboxylase. This enzyme catalyzes the first step in DNL. We await with interest the results of the placebo-controlled Phase II trial of GS-0976 in NASH patients anticipated in the second quarter of 2017.

Source:
Press Release 04/21/2017
European Association for the Study of the Liver (EASL) 04/21/2017 (Abstract GS-009)
Sagient Analysis

NGM282 (NGM, Phase II)

Phase II – 15-0105
Trial Data – Top-Line Results

Change to LOA: +3%

Abstract LBO-07: NGM282, a novel variant of FGF19, significantly reduces hepatic steatosis and key biomarkers of NASH: results of a Phase 2, multicenter, randomized, double-blinded, placebo controlled trial in biopsy-confirmed NASH patients

	Placebo	Treatment	Treatment
Treatment Description	Placebo	NGM282 3 mg	NGM282 6 mg
Number of Evaluable Patients	27	27	26
Mean Change in MRI-PDFF (Absolute) (Endpoint=Primary)	-0.9 %	-9.7 % (P<0.001)	-11.9 % (P<0.001)
Mean Change in MRI-PDFF (Absolute) in Patients w/MRI-PDFF >20% at Baseline	-0.3 %	-12.9 % (P<0.001)	-18.9 % (P<0.001)
Mean Change in MRI-PDFF (Relative) (Endpoint=Secondary)	-1 %	-47 % (P<0.001)	-61 % (P<0.001)
Patients w/ >30% Relative Change in MRI-PDF	7 %	85 % (P<0.001)	92 % (P<0.001)
Response Rate	7 %	74 % (P<0.001)	85 % (P<0.001)
Mean Change in Alanine Transaminase (ALT) Levels (Absolute)	-2 U/L	-35 U/L (P<0.001)	-33 U/L (P<0.001)
Mean Change in ALT Levels (Absolute) in Patients w/ ALT >60 U/L at Baseline	-10 U/L	-63 U/L (P<0.001)	-55 U/L (P<0.001)
Mean Change in ALT Levels (Relative)	-1 %	-43 % (P<0.001)	-45 % (P<0.001)
Mean Change in Triglycerides Levels	N/A	-39 mg/dL	-44 mg/dL
Mean Change in LDL Cholesterol (LDL-C) Levels	N/A	52 mg/dL	38 mg/dL

Design

This Phase II trial evaluated the activity, safety and tolerability of 3 and 6 mg daily subcutaneous injections of NGM282 over 12 weeks of treatment compared to placebo. Eighty-two patients with biopsy-confirmed nonalcoholic steatohepatitis (NASH) were enrolled, all of whom had a minimum NAFLD activity score (NAS) ≥ 4 (with at least one point in each component), Stage 1-3 fibrosis and ≥8% absolute liver fat content by magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF).

Endpoints

The primary endpoint was an absolute decrease in liver fat content by a minimum of 5% as measured by MRI-PDFF. Secondary endpoints included relative decreases in liver fat content as well as biomarkers of liver function and lipid metabolism. Biomarkers of fibrosis were examined as exploratory endpoints.

Results

NGM282 met the primary endpoint and key secondary endpoints. NGM282 demonstrated a significant reduction in liver fat content and improvement of biomarkers associated with the resolution of NASH.

Patients treated with NGM282 for 12 weeks showed statistically significant and clinically meaningful reductions in both absolute and relative MRI-PDFF measures of liver fat content, with the 3 mg and 6 mg dose groups demonstrating a reduction in absolute liver fat content of 9.7% and 11.9%, respectively (both $p<0.001$ versus placebo). Of the patients treated with NGM282, 34% reached a normal liver fat content. The greatest magnitude of effect was observed in patients with the highest baseline liver fat content (i.e., >20% by MRI-PDFF) and most active disease (i.e., alanine transaminase (ALT) levels greater than 60 U/l). Significant improvements in other serum biomarkers of liver function, lipid metabolism and fibrosis were observed.

Notable treatment effects included a decrease in triglycerides of 39 and 44 mg/dl for the 3 and 6 mg doses, respectively, consistent with FGFR1c activity. Patients on NGM282 also experienced LDL cholesterol (LDL-C) increases of 52 and 38 mg/dl for the 3 and 6 mg doses, respectively, at 12 weeks, reflecting potent FGFR4-mediated CYP7A1 inhibition.

Most Common Adverse Events

The most common adverse events reported in this study were lower gastrointestinal symptoms, nausea and injection site erythema, the majority of which were mild and dose-dependent. There was a single serious adverse event (acute pancreatitis) in the 3 mg dose group. The safety and tolerability of NGM282 has been consistent across more than 275 healthy volunteers and patients treated to date in multiple clinical studies.

Conclusion

Per the abstract, treatment of NASH patients with NGM282 for 12 weeks showed rapid and highly significant reductions in LFC, serum aminotransferases and other biomarkers suggestive of improvements in NASH. Targeting the FGF19 pathway with pharmacologic doses of NGM282 appears to affect multiple relevant biologic pathways and supports further development in NASH.

Comment

These are quite impressive efficacy data in NASH patients with early-stage fibrosis and we are raising the LOA by 3%. The absolute reductions in liver fat content for the 3 mg and 6 mg doses compare favorably to those also reported at EASL 2017 for the other subcutaneous human FGF variant in Phase II clinical development in the US for NASH, Bristol-Myers Squibb's ARX618.

Source:
Press Release 04/22/2017
European Association for the Study of the Liver (EASL) 04/22/2017 (Abstract LBO-07)
Sagient Analysis

2017 Biomedtracker EASL Events

Lead Company	Ticker	Product	Trial Name	Event Type	Link
Biliary Tract Cancer					
PCI Biotech AS	PCIB:NO	Amphinex/Gemcitabine	Phase I/II - A202/12 (Cholangiocarcinoma)	Trial Data - Updated Results	258926
Diabetes Mellitus, Type II					
NGM Biopharmaceuticals, Inc.		NGM282	Preclinical Studies	Trial Data - Preclinical Results	259091
Hepatic Encephalopathy (HE)					
Asarina Pharma		GR3027	Phase Ia - First-in-Human	Trial Data - Updated Results	258922
Hepatitis B (HBV) Treatment (Antiviral)					
Arbutus Biopharma Corporation	ABUS	ARB-1467	Phase II - Non Cirrhotic	Trial Data - Updated Results	259400
Arrowhead Pharmaceuticals, Inc.	ARWR	ARC-521	Phase I/II - ARC5211001	Trial Data - Top-Line Results	258767
Arrowhead Pharmaceuticals, Inc.	ARWR	ARC-520	Phase IIb - Heparc-2002 (HBeAg Negative; Ex. US)	Trial Data - Top-Line Results	258778
Chimerix, Inc.	CMRX	Tenofovir Exalidex	Phase Ib/IIa - 201	Trial Data - Updated Results	258477
ContraVir Pharmaceuticals, Inc.	CTRV	CRV431	Preclinical Studies	Trial Data - Preclinical Results	259331
Gilead Sciences, Inc.	GILD	Vemlidy	Phase III - vs. Tenofovir Disoproxil Fumarate (Antigen-Positive), Phase III - vs. Tenofovir Disoproxil Fumarate (Antigen-Negative)	Trial Data - Updated Results	258777
REPLICor Inc.		REP 2055	Phase II - REP 301	Trial Data - Updated Results	258785
REPLICor Inc.		REP 2139-Mg	Phase II - w/REP 2165-mg	Trial Data - Updated Results	258795
Hepatitis C (HCV) (Antiviral)					
AbbVie Inc.	ABBV	Glecaprevir/Pibrentasvir	Phase III - EXPEDITION-1 (GT 1-6)	Trial Data - Top-Line Results	258467
AbbVie Inc.	ABBV	Glecaprevir/Pibrentasvir	Phase III - EXPEDITION-2 (GT 1-6, HIV)	Trial Data - Top-Line Results	259374
AbbVie Inc.	ABBV	Glecaprevir/Pibrentasvir	Phase III - ENDURANCE-3 (GT-3)	Trial Data - Updated Results	258906
AbbVie Inc.	ABBV	Glecaprevir/Pibrentasvir	Phase III - CERTAIN-1 (GT-1) (Japan)	Trial Data - Updated Results	259110
AbbVie Inc.	ABBV	Glecaprevir/Pibrentasvir	Phase III - MAGELLAN-2	Trial Data - Top-Line Results	259397
AbbVie Inc.	ABBV	Glecaprevir/Pibrentasvir	Phase II - MAGELLAN-1	Trial Data - Updated Results	259412
Gilead Sciences, Inc.	GILD	Harvoni	Phase II - Pediatric (+/-Ribavirin), Phase IIIb - Taiwan	Trial Data - Updated Results	259102
Johnson & Johnson	JNJ	JNJ-4178	Phase IIa - w/AL-335/Simeprevir (Treatment-Naive, GT1)	Trial Data - Updated Results	259191
Merck & Co., Inc.	MRK	MK-3682	Phase II - C-CREST 011 (w/Grazoprevir + Elbasvir or MK-8408), Phase II - C-CREST 012 (w/Grazoprevir + Elbasvir or MK-8408)	Trial Data - Updated Results	258806
Merck & Co., Inc.	MRK	Zepatier		Trial Data - Retrospective Analysis	259087
Merck & Co., Inc.	MRK	Zepatier	Phase II - C-ISLE	Trial Data - Top-Line Results	259127
Merck & Co., Inc.	MRK	Zepatier	Phase III - C-EDGE IBLD	Trial Data - Updated Results	259128
Merck & Co., Inc.	MRK	MK-3682	Phase II - C-SURGE	Trial Data - Updated Results	259188
Hepatitis D (HDV) (Antiviral)					
Eiger BioPharmaceuticals, Inc.	EIGR	Sarasar	Phase II - LOWR 4	Trial Data - Final Results	258793
Eiger BioPharmaceuticals, Inc.	EIGR	Sarasar	Phase II - LOWR-1, Phase II - LOWR-2	Trial Data - Updated Results	259441
Eiger BioPharmaceuticals, Inc.	EIGR	Sarasar	Phase II - LOWR-3	Trial Data - Final Results	259459
Eiger BioPharmaceuticals, Inc.	EIGR	Sarasar	Phase II - LOWR-2	Trial Data - Updated Results	259429
REPLICor Inc.		REP 2055		Trial Data - Updated Results	259180
Hepatocellular (Liver) Cancer (HCC) (Including Secondary Metastases)					
Medivir AB	MVIRB:SS	MIV-818	Preclinical Studies	Trial Data - Preclinical Results	259422
NGM Biopharmaceuticals, Inc.		NGM282		Trial Data - Preclinical Results	259327
Liver Failure / Cirrhosis					
Arrowhead Pharmaceuticals, Inc.	ARWR	ARC-AAT	Phase I - Healthy Volunteers	Trial Data - Updated Results	259334
Promethera Biosciences		H2Stem	Preclinical Studies	Trial Data - Preclinical Results	258975
Non-Alcoholic Steatohepatitis (NASH)					
3-V Biosciences, Inc.		TVB-2640	Preclinical Studies	Trial Data - Preclinical Results	261382
Bristol-Myers Squibb Company	BMY	ARX618	Phase II - MB130-045	Trial Data - Top-Line Results	259366
DURECT Corporation	DRRX	DUR-928	Phase Ib - SAD (Australia)	Trial Data - Updated Results	259215
Enanta Pharmaceuticals, Inc.	ENTA	EDP-305	Preclinical Studies	Trial Data - Preclinical Results	258298
Galmed Pharmaceuticals Ltd.	GLMD	Aramchol	Preclinical Studies	Trial Data - Preclinical Results	259123
Galmed Pharmaceuticals Ltd.	GLMD	Aramchol	Preclinical Studies	Trial Data - Preclinical Results	259426
Gilead Sciences, Inc.	GILD	GS-0976	Phase I - NASH (POC)	Trial Data - Top-Line Results	258903
Gilead Sciences, Inc.	GILD	GS-0976	Preclinical Studies	Trial Data - Preclinical Results	258910
NeuroVive Pharmaceutical AB	NVP:SS	NV556		Trial Data - Preclinical Results	258475
NGM Biopharmaceuticals, Inc.		NGM282	Phase II - 15-0105	Trial Data - Top-Line Results	259199
Ocera Therapeutics Inc.	OCRX	OCR-002	Preclinical Studies	Trial Data - Preclinical Results	257467
ProMetic Life Sciences Inc.	PLI:CN	PBI-4050	Preclinical Studies	Trial Data - Preclinical Results	258499
Primary Biliary Cholangitis (PBC) and Hepatic Fibrosis					
Enanta Pharmaceuticals, Inc.	ENTA	EDP-305	Preclinical Studies	Trial Data - Preclinical Results	258306
Albireo Pharma, Inc.	ALBO	A4250	Phase II - Pediatric	Trial Data - Top-Line Results	259465
CymaBay Therapeutics, Inc.	CBAY	Seladelpar	Phase II - 50 or 200 mg	Trial Data - Updated Results	259420
Wilson's Disease					
Wilson Therapeutics AB	WTX:SS	WTX101	Phase II - Study 201	Trial Data - Final Results	259468

Biomedtracker Large Impact Catalysts

Expected Date Range	Lead Company	Ticker	Product	Expected Catalyst	Trial Name	Link
Hepatitis B (HBV) Treatment (Antiviral)						
07/01/2017-12/31/2017	Arbutus Biopharma Corporation	ABUS	ARB-1740	Trial Data - Top-Line Results	Phase II - Multi-Dose	128377
Now-05/31/2017	Gilead Sciences, Inc.	GILD	GS-9620	Trial Data - Top-Line Results	Phase II - Virally-Suppressed	108503
Hepatitis C (HCV) (Antiviral)						
Now-05/31/2017	GlaxoSmithKline plc	GSK	GSK2878175	Trial Data - Top-Line Results	Phase II - w/RG-101 (Non-US)	122777
Now-12/31/2017	Biotron Limited	BIT:AU	BIT225	Partnership - New		90619
8/8/2017	Gilead Sciences, Inc.	GILD	Sofosbuvir/Velpatasvir/Voxilaprevir FDC	Regulatory - PDUFA/Approval Decision (US)		128297
8/18/2017	AbbVie Inc.	ABBV	Glecaprevir/Pibrentasvir	Regulatory - PDUFA/Approval Decision (US)		128523
07/01/2017-09/30/2017	AbbVie Inc.	ABBV	Glecaprevir/Pibrentasvir	Regulatory - CHMP (European Panel) Results		130108
07/01/2017-09/30/2017	Gilead Sciences, Inc.	GILD	Sofosbuvir/Velpatasvir/Voxilaprevir FDC	Regulatory - CHMP (European Panel) Results		129914
07/01/2017-12/31/2017	GlaxoSmithKline plc	GSK	GSK2878175 LAP	Trial Data - Top-Line Results	Phase II - w/RG-101 (Single-Visit Cure)	122847
07/01/2017-12/31/2017	Johnson & Johnson	JNJ	JNJ-4178	Trial Data - Top-Line Results	Phase IIb - OMEGA-1	132593
10/01/2017-12/31/2017	Regulus Therapeutics Inc.	RGLS	RG-101	Trial Data - Top-Line Results	Phase II - w/GSK2878175 (Non-US)	118607
01/01/2018-06/30/2018	Novartis AG	NVS	Emricasan	Trial Data - Top-Line Results	Phase IIb - POLT-HCV-SVR	104001
01/01/2018-06/30/2018	Regulus Therapeutics Inc.	RGLS	RG-101	Trial Data - Top-Line Results	Phase II - w/GSK2878175 LAP (Single-Visit Cure)	122830
01/01/2018-12/31/2018	Roche Holding AG	RHHBF	Pegasys	Patent - Expiration		113185
Non-Alcoholic Steatohepatitis (NASH)						
Now-06/30/2017	Gilead Sciences, Inc.	GILD	GS-0976	Trial Data - Top-Line Results	Phase II - GS-US-426-3989	130602
Now-06/30/2017	Viking Therapeutics, Inc.	VKTX	VK2809	Trial Data - Top-Line Results	Phase II - Elevated LDL-C (Safety and Tolerability)	126016
Now-09/30/2017	Intercept Pharmaceuticals, Inc.	ICPT	Ocaliva	Trial Data - Top-Line Results	Phase II - CONTROL (w/Statin Therapy)	127362
Now-12/31/2017	GRI Bio, Inc.		GRI-0621	Trial Data - Top-Line Results	Phase IIa - Chronic Liver Disease (201)	120356
07/01/2017-09/30/2017	Madrigal Pharmaceuticals, Inc.	MDGL	MGL-3196	Trial Data - Top-Line Results	Phase II - 05	121060
12/01/2017-12/15/2017	Galectin Therapeutics, Inc.	GALT	GR-MD-02	Trial Data - Top-Line Results	Phase IIb - NASH-CX	71846
01/01/2018-12/31/2018	Novartis AG	NVS	Emricasan	Trial Data - Top-Line Results	Phase IIb - ENCORE-PH	127108
04/01/2018-06/30/2018	Galmed Pharmaceuticals Ltd.	GLMD	Aramchol	Trial Data - Top-Line Results	Phase IIb - ARREST (Obesity and Insulin Resistance)	98077