EASL 2017 - Presentation Notes Day 1

As part of our ongoing coverage of the 2017 annual meeting of the European Association for the Study of the Liver (EASL), we attended multiple oral presentations on April 20th and our notes are below. Affected companies include Arrowhead Pharmaceuticals (NasdaqGS: ARWR), Bristol-Myers Squibb (NYSE: BMY), ContraVir Pharmaceuticals (NasdaqCM: CTRV), Eiger BioPharmaceuticals (NasdaqGM: EIGR), Gilead (NasdaqGS: GILD), and Metacrine (private).

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Hepatitis B and D: Emerging Treatment Options

PS-039: A phase 2 dose-escalation study of lonafarnib plus ritonavir in patients with chronic hepatitis D: final results from the Lonafarnib with ritonavir in HDV-4 (LOWR HDV-4) study

Heiner Wedemeyer, Germany

Affected companies: Eiger BioPharmaceuticals

- Final results of LOWR-4 study
- HDV is a defective virus; needs HBsAg
- 10-20 million are anti-HDV positive
- Causes most severe form of chronic viral hepatitis
- Treatment options
  - IFN-a for 48 weeks: 25-30% clear the virus
    - Some may have late relapses
    - HDV suppression is a good thing that improves clinical outcomes
- Prenylation is the last step in HDV replication; this step is targeted by lonafarnib
- Licensed from Merck originally
- LOWR-4 studied dose escalation as well as safety an tolerability of lonafarnib boosted with ritonavir
  - In the trial, 13 made it to 75 mg dose; 10 made it to 100 mg dose; 5 patients were able to maintain the high dose for 24 weeks; GI tolerability issues can affect some patients.
  - Mean decline in viral load of 1.7
  - 2 patients who reached 100 mg reached HDV negativity
  - 53% had ALT normalization
  - At week 48 follow-up, 1/15 was RNA negative
  - GI AEs mostly grade 1-2
  - 8/15 required dose reduction
- Also studying long-term control in patients.
- Relationship between dose and viral load reduction. This was seen in LOWR-3, run by NIH; some level of correlation

For analyst certification and disclosures please see page 8

PS-040: Pharmacokinetics, safety and antiviral activity of CMX157, a novel prodrug of tenofovir, administered as ascending multiple doses to healthy volunteers and Hepatitis B virus-infected subjects

Tawesak Tanwandee, Thailand

Affected companies: ContraVir

- Tenofovir exalidex (TXL), prodrug of tenofovir; for HBV
- 97 fold more potent in HBV than TFV
  - Could reduce exposure of drug, side effects
- Tested 5, 10, 25, 50, 100 mg of TXL vs Viread in 52 subjects
- Approximately dose proportional
- No accumulation between doses
- All side effects were mild, no clustering
- No SAEs or early discontinuation
- Doses did not differ in AUC
- All doses reduced viral load; saw rebound after treatment stopped
- Lower circulating levels may reduce risk of bone and kidney toxicities
- First generation prototype formulation; potential to reduce dosing/pricing

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

Henry Chan, Hong Kong, China

Affected companies: Gilead

- TAF is a new prodrug of tenofovir; week 48 data showed non-inferiority
- Two Phase III trials comparing TAF to tenofovir
- 2:1 randomization; stratified by disease severity
- At week 96, TAF was associated with higher rates of ALT normalization
- Minimal change in EGFR in TAF vs TDF suggesting minimal effect on kidney
  - Saw significant improvement once patients switched to TAF
- Decreased bone mineral density for TDF; minimal change in the TAF patients;
  - Patients who switched from TDF to TAF showed an improvement
- High rates of viral suppression; maintained through week 120;
- Chronic HBV patients showed improvements in renal and bone minseral density.
- Evaluating switching to TAF in a Phase IIb study

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

Maurizia Brunetto, Italy

Affected companies: Gilead

- New tenofovir prodrug, tenofovir alafenamide

- Double blind, placebo controlled Phase III study for 96 weeks
- 93% of TAF treatment remained on drug; 91% for TDF
- HDV DNA < 29 IU/mL: 94% with TAF; 93% for TDF
- 1 patient had loss of HBsAg
- 81% ALT normalization for TAF vs 71% for TDF
- TEAEs were similar between the two groups
- 6% SAE for TAF vs 11% in TDF
- Less effect of TAF on bone mineral density
  - Minimal changes in bone turnover markers with TAF

PS-044: A phase1 study evaluating anti-PD-1 treatment with or without GS-4774 in HBeAg negative chronic hepatitis B patients

Ed Gane*, New Zealand*

Affected companies: Bristol-Myers Squibb

- Checkpoint inhibitor in chronic HDV, nivolumab
- HBV insufficient T cell reponse to HBV antigens
- Current approaches to boost T cell responses through vaccination have been unsuccessful
- Nivolumab can rescue T cell response
- Evaluate efficacy of PD-1 blockade in virally suppressed patients
- Monoclonal antibody
- Receptor occupancy studies have shown that 0.1 mg/kg dose achieved near full receptor occupancy
- Some patients also received a therapeutic vaccine, GS-4774; contains surface X and core antigens
- Primary endpoint 12 weeks post nivolumab change in HBV DNA
- A few patients had elevated ALT at baseline
- With 0.3, within 1 week, patients achieved a ~80% occupancy; similar with 0.1
- At 12 weeks, 0.3 log reduction in HBV DNA, no benefit from vaccine addition
  - At 24 weeks, nearly 0.5 log reduction
- Seem to be ALT flares in some patients, leading to surface antigen los
  - 1 patient remained off treatment for 8 months with sustained surface antigen loss.
- Safety:
  - Safe and well-tolerated doses of nivo
  - ALT elevation: 2 grade 1, 1 grade 3; these were transien
  - No patient developed any autoimmune manifestation
- Modest reduction in HBV DNA, but may be useful in an eventual future functional core.
- Q: Why no autoimmune?...because this is seen in other clinical studies?
  - A: think this was at much higher doses

PS-045: Prolonged RNA interference therapy with ARC-520 Injection in treatment naïve, HBeAg positive and negative patients with chronic HBV results in significant reductions of HBs antigen

Man-Fung Yuen, Hong Kong, China

Affected companies: Arrowhead

- Single center study, funded with grant from Arrowhead
- Approach: silence entire HBV genome; reduce surface antigen production; reversal of immune suppression;
- ARC-520: composed of two main molecules
- Toxicity issue related to delivery platform, not the actual drug
- Differential HBsAg reduction also observed in untreated chimps
  - HBeAg positive responded better than negative chimps
  - For neg: 0.5-0.9; for pos: 1.5-1.7 log reduction
- Majority of E negative patients produce altered S transcripts; lack target sites for ARC-520; limits efficacy in E negative patients
- Extension study from Heparc-2001
- 8 CHB patients were enrolled to receive 4 mg/kg ARC-520 once every 4 weeks with daily entecavir
- 7/8 patients reported at least one mild AE
- None were rated as serious or caused withdrawal from trial
- High levels of knockdown achieved with ARC-520; log reduction was max seen; mean was 0.7 log reduction;
  - E negative patients showed a delayed response;

Fatty Liver Disease: From Pathophysiology to Drug Discovery

PS-025: The soluble guanylate cyclase stimulator IW-1973 prevents inflammation and fibrosis in experimental non-alcoholic steatohepatitis

Roger Flores-Costa, Spain

- Soluble guanylate cyclase (sGC) is involved with cGMP signaling
- sGC stimulators being assessed in studies of the lung, heart, kidney, and immune system
- Objective: investigate the effects of the sGH stimulator IW-1973 in choline-deficient, L-aminoacid-defined high-fat diet (CDAAH)-fed mice
- Effects of IW-I973 showed increases in cGMP signaling
- IW-I973 in CDAAH-fed mice showed significant reductions in oil-red-O, reductions in hepatic inflammation, and decreases in NAFLD Activity Score (NAS)
- IW-I973 also significantly reduced inflammatory cytokines
- Mice demonstrated fibrosis in study, and IW-I973 treated animals showed reductions in Masson's trichrome, Sirius red, and alpha-SMA, among other markers of fibrosis
- White adipose tissue (WAT) has a direct influence on NASH
- IW-I973 in HFD-fed mice showed increased macrophage infiltration, though a more striking finding was reduction in adipocyte area
- Conclusions: IW-I973 reduced hepatic steatosis, inflammation, and fibrosis, along with amelioration of WAT dysfunction and decreases in adipocyte area, with increases in autophagy

PS-026: Small ubiquitin-like modifier protein-specific protease 3 de-SUMOylates NR4A2 protein and controls lipid metabolism in non-alcoholic fatty liver disease

Yuhan Liu, China

- NAFLD: high energy food intake, lack of exercise, appearance of metabolic syndrome and NAFLD appears
- Prevalent in US, EU, as well as Asia
- SUM0ylation is a dynamic process modulated by several enzymes, regulates spectrum of biological responses
- SENP3 is sensitive to cell stress, and a role in NAFLD is due to the "multiple hits" of lipid accumulation and inflammation causing a state of cellular stress
- SENP3 was found to be upregulated in livers of NAFLD patients, as well as in HFD-fed rats
- Significant correlation between hepatic SENP3 and hepatic TG in NAFLD rat model, invites speculation that SENP3 is a player in steatosis development
- SENP3 was also upregulated in hepatocytes treated with free fatty acids (FFA)
- SENP3 was silenced with various techniques, leading to decreases in hepatic lipids, while overexpression of SENP3 led to increases in hepatic lipids
- Gene expression related to SENP3 was detected via RNA-seq, with 11 identified as lipid metabolic disorder related genes
- Assessed top 3 genes to confirm, finding levels of *Apoe, a2m,* and *tnfrsf11b* were regulated by SENP3 with FFA treatment *in vitro*
- Levels of APOE, A2M, and TNFRSF11B were detected in NAFLD patients and showed increases in intrahepatic levels
- Liver-specific SENP3 knockout mice are needed to investigate role in NAFLD

PS-027: FXR agonists with sustained systemic rather than transient intestinal exposure are more efficacious in a diet-induced obese non-alcoholic steatohepatitis mouse model

Brandee Wagner, US

Affected Companies: Metacrine

- FXR regulates lipogenesis, lipoprotein catabolism, and clearance
- Obeticholic acid (Oca) is an FXR agonist and has shown reductions in NASH and fibrosis
- Fexaramine is a novel FXR scaffold with GI "selective" activity due to rapid compound metabolism
- Main expression is in the ileum, as opposed to the liver
- Utilized a diet-induced obese NASH model (40% trans-fat, 18% fructose, and 2% cholesterol)
- Continue NASH diet during 8 week treatment period: OCA (30 mg/kg) and fexaramine (100 mg/kg)
- Fexaramine decreased body weight and fat mass, with no improvement in steatosis or NAS
- Gene expression at study termination confirms GI activity of fexaramine and systemic activity of OCA
- No regulation of direct target genes in liver with fexaramine, but do see them with Oca
- To optimize related compounds, the Company modified fexaramine to maintain scaffold but alter targeting of ileum and liver and thus levels of activity
- Drug activity ranged from GI selective (low/no systemic exposure) all the way to high systemic exposure with high GI and liver activity.
- Increasing systemic FXR activity correlated with improvements in diet-induced obese mouse NASH model.
- All generated compounds decreased body weight and fat mass, with decreases in liver transaminases at 4 weeks of treatment
- Greatest effects with compounds with high systemic (liver) exposure
- Liver transaminase normalized by M450 (most potent and systemic compound generated)
- Liver TG decrease with increasing activity in liver and intestine
- M450 also showed the highest magnitude of significant reductions in NAS
- All liver parameters improved with systemic FXR agonists: steatosis, inflammation, ballooning
- Fibrosis improved only with systemic FXR agonist, significance with M450
- NASH model efficacy correlates with systemic FXR engagements

- Strong regulation of liver Cyp8b1 and BSEP
- Increasing activity in both GI and liver, have increased efficacy in various components of NAFLD
- Conclusions: systemic FXR activity may be a key factor for drugs in clinical development, systemic FXR agonists are efficacious in improving NASH, GI "selective" agonists show greater activity in intestine than liver

PS-028: A2a receptor stimulation prevents the multiple processes that lead to hepatic "immuno-lipotoxicity" in mice fed with MCD diet and blocks non-alcoholic steatohepatitis development

Elisa Alchera, Italy

- Steatosis is benign but can progress to NASH in ~20% of patients.
- Lipotoxicity occurs in humans and in animal models
- Infiltrating immune response leads to NASH development
- A2aR stimulation exerts a cytoprotective effect, and reduces NASH in rats on a MCD diet
- A2aR stimulation mediates hepatoprotective effects of ischemic preconditioning
- Adenosine is also a modulator of immune-mediated reactions
- A2aR stikulation halts progression of liver injury induced by MCD diet in mice, including inflammation and fibrosis markers
- A2aR stimulation also reduces expression of inflammatory signals involved with recruitment of T cells
- Particular cell types reduced: Th17, Th22, Th1, and t regulatory cells showed an increased suppressive ability
- CGS21680 prevents immunolipotoxicity of hepatocytes in mice exposed to PA and IL-17, through activation of Akt and down regulation of PTEN
- Conclusion: A2aR stimulation prevents NASH development by inhibiting the signals leading to immunolipotoxicity

PS-029: Elucidation of non-alcoholic fatty liver disease immunopathogenesis in humanized mice

Qingfeng Chen, Singapore

- Objective: to create a novel humanized model for diet-induced fatty liver disease, as there is a gap in knowledge pertaining to NAFLD pathogenesis moving from animals to humans
- Would like the model to incorporate weight increase, steatosis, inflammation, ballooning, and fibrosis
- Used the Surwit diet, and key NAFLD pathologies were recapitulated in humanized mice fed the HFHC diet.
- NSG mice on a HFHC diet (background without humanized immune system) showed weight increases, steatosis, intrahepatic lipid accumulation, but not fibrosis
- Evidence also supports role of human immune cells in inducing the HFHC diet associated pathologies
- Application of model: can be used to overcome difficulties between mice and human species drug testing

PS-030: Combination of an ASK1 inhibitor and FXR agonist increases efficacy in a mouse model of non-alcoholic steatohepatitis

John T. Liles, US

Affected Companies: Gilead

- ASK1 and FXR regulate independent pathways related to NASH
- When ASK is activated, it signals to p38 and JNK to a number of key cell types
- FXR is a regulator of bile acid metabolism, leads to production of FGF19
- These agents in combination have potential synergies

- Selonsertib is an ATP competitive inhibitor of ASK1, it is a widely expressed kinase activated by oxidative stress
- Selonsertib is currently in Phase 3 testing for patients with NASH
- GS-9674 is a potent and selective FXR agonist in the ileum, and has limited effects on the liver.
- GS-9674 is currently in Phase 2 trials for PBC, PSC, and NASH
- ASK1 inhibitor and FXR agonist in FFD mouse: animals fed diet high in fat, sugar, and cholesterol
- Primarily directed at steatosis, and fibrosis effects are limited
- Doses selected to mimic clinical doses being used
- ASK1 inhibitor with FXR agonist in combination increases reduction of steatosis, as compared to each agent along
- Hepatic TG content was also significantly reduced with agents used in combination
- Liver expression of fibrogenic genes (*Col1a1, Timp1,* and other) was also reduced by drug combo more than monotherapy
- ASK1 and FXR in combination also reduce hepatic stellate cell (HSC) more in combination than in monotherapy
- Conclusions: ASK1 and FXR agonists regulate independent pathways

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