Trends-in-Medicine

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by Lynne Peterson

SUMMARY

Vertex's telaprevir for HCV appears to have a better overall profile than Schering-Plough's boceprevir now that doctors have learned to manage the rash. Yet, experts are not ruling boceprevir out despite a high rate of anemia and longer duration of therapy. The anemia is manageable with EPO and may be a marker for efficacy. ♦ The first positive data were presented on the combination of a protease inhibitor and a polymerase inhibitor for HCV, and numerous companies are investigating this area. ♦ There was disappointing news on several HCV drugs, including Anadys' ANA-598, Debiopharm's Debio-025, and Human Genome Sciences' Albuferon. ♦ There is still a big unmet need for HCV genotype 3. ♦ Two new therapies for hepatic encephalopathy look promising: Salex's Xifaxan and Ocera's AST-120.

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THE INTERNATIONAL LIVER CONGRESS OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

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The most exciting news out of EASL was new data on the two leading protease inhibitors plus the first data on the combination of a protease inhibitor and a polymerase inhibitor. So many drugs are on the horizon, that doctors were discussing whether patients should – or could – wait for some of these agents before starting therapy, but the general agreement was that patients willing to undergo therapy probably should not put off treatment – at least until regulatory approval is closer.

Dr. David Nelson of the University of Florida, Gainesville, summed up the general thinking: "I think we will be truncating therapy significantly, but we have some reality. Approval (for the first protease inhibitor) is unlikely until 2011, novel drugs will still require interferon plus ribavirin, and resistance will be a major barrier – a massive new hurdle – and we need to communicate this to patients. Adding a third drug means greater side effects. The continuing challenge for the next 2-3 years will be identifying who can wait for treatment and who needs treatment now."

The INFORM-1 trial offered the first look at the combination of a polymerase inhibitor (Roche/Pharmasset's R-7128) and a protease inhibitor (Roche/InterMune's ITMN-191 or R-7227). That isn't the only combination in development, though the others are further away in development.

Yet, combination STAT-C (specifically targeted antiviral therapy for HCV) agents are several years away from the U.S. market ***at best***. They face a difficult regulatory hurdle because the hope is that they will eliminate the need for interferon and ribavirin, but industry sources as well as researchers agreed that the FDA is unlikely to lift its ban on therapy longer than 2-3 days that does not include the current standard of care – pegylated interferon (pIFN) + ribavirin (RBV) or pIFN-R. Indeed, it is widely believed that the FDA will allow only three days of monotherapy with a new agent, but an expert said that one pharma was told it could only do two days.

Roche is attempting to change the FDA's mind about monotherapy with data obtained outside the U.S. – e.g., using the INFORM-1 trial data from Australia. However, experts warned – and Roche officials agreed – that more OUS data will be needed to even get the FDA thinking in monotherapy trial terms. And the consensus appears to be that the OUS data has to be done in New Zealand, Australia, or Western Europe to be convincing. In the meantime, the focus is on the new protease inhibitors on top of pIFN-R.

The other big news at EASL was the results of two Phase IIb protease inhibitor trials – the PROVE-3 trial of Vertex's telaprevir and the SPRINT-1 trial of Schering-Plough's boceprevir. At this point, it appears that telaprevir has the best overall profile – mainly because it probably has the shorter duration of therapy. However, hepatologists are not ruling boceprevir out yet despite the anemia, the consequent need for erythropoietin (EPO), and the likely longer duration of therapy, and Schering officials and investigators remain committed to boceprevir. "Wait for the Phase III data before drawing conclusions," they insisted. One expert commented, "You have to wait until the studies are finished. What we learned from the interim analyses of the PROVE-1 and -2 trials (of telaprevir) is that you have to wait for the final results."

While the idea of 24-week dosing with telaprevir is attractive, the drug has some drawbacks that open the door for competitors, including rash, pruritis, and every-8-hour dosing. On the other hand, though boceprevir is a true TID drug, it causes more anemia than telaprevir, requiring EPO in almost half the patients. Experts are divided on the short- vs. long-course therapy. Dr. Graham Foster of the U.K. said, "This is not a trivial little virus…I think we need prolonged courses of treatment. There are patients who will benefit with short-course therapy, but we don't know their characteristics yet… This virus has been a tough cookie to treat. I don't think it is ready to lie down and give up…I think we will need a long course of therapy – even with protease inhibitors." Dr. Stefan Zeuzem of Germany disagreed, "If you have eradicated the wild type, there is no reason to stay on a protease inhibitor... So, I think the duration of the protease inhibitor should be shorter than pIFN-R."

Asked how they would choose between telaprevir and boceprevir if both were approved, doctors generally said it is too early to say; most see a role for both. Dr. Fabio Mara, a hepatologist from Florence, Italy, said, "I want to see the final results and the side effects for both." Dr. Nelson said, "Boceprevir may be effective…It probably will have to be used longer…Six months is not an optimal duration…and lead-in is becoming a mess…Understanding lead-in is important…with these drugs…We need well-randomized data on each molecule." Dr. Thomas Berg of Germany said, "I favor short-term therapy, and I would favor a 12-week regimen, which is not possible with boceprevir but it could be possible with telaprevir in some patients."

Dr. Nelson offered two reasons that lead-in "complicates the landscape" but is important:

1. Patients might be able to be identified who may not need the addition of a STAT-C – which would prevent additional adverse events, save money, and limit the risk of resistance. However, he called this a "debatable strategy."
2. Viral resistance might be decreased at the time of protease inhibitor introduction. This could overcome an unfavorable IFN pharmacokinetic profile, allow a steady state of IFN and/or ribavirin to occur, and decrease viral load."

There was disappointing news at EASL on several HCV drugs, though none of the companies confirmed that any of them are formally dead. Among the agents with negative data were:

- **Anadys' ANA-598**, a non-nucleoside polymerase inhibitor. The company announced, in a press release (not at EASL), that three cases of rash occurred in a healthy volunteer trial, and it does not appear that the rash is only related to dose peaks or QD dosing since two cases occurred with 800 mg QD and one case occurred with 600 mg BID.
- **Debiopharm's Debio-025,** a cyclophilin inhibitor. In an open-label, Phase IIa study Debio-025 showed efficacy but elevated bilirubin was a concern, even though ALT declined on treatment.
- **No protease inhibitors so far have been shown to work in HCV genotype 3.** About 40% of HCV patients in Western Europe have genotype 3, so the new agents only address slightly more than half the HCV market. Vertex presented data on telaprevir that showed no or minimal efficacy in either genotype 3 or 4, and experts do not believe any others will be effective in those subgroups either.
- **Human Genome Sciences' Albuferon (albinterferon alfa-2b).** The hope was that this would be effective with once-monthly dosing, but it appears every-other-week dosing will be necessary.

THE HEPATITIS C (HCV) MARKET

Hepatitis C is a serious and potentially life-threatening disease. It is the most common blood-borne infection in America and Europe, and the most common form of liver disease, affecting some 200 million people worldwide. HCV is the leading cause of cirrhosis and liver cancer and the No. 1 reason for liver transplants in the United States and Europe.

HCV Incidence Worldwide

Region	Number infected	% of population
Americas	13.1 million	1.7%
Europe	8.9 million	1.0%
SE Asia	32.3 million	2.15%
Africa	31.9 million	5.3%

Type of HCV by Country

Country	HCV Genotype 1	HCV Genotype 2-3	HCV - other
Australia	55%	41%	4%
France	57%	30%	13%
India	63%	34%	3%
U.S.	73%	22%	5%
Germany	81%	18%	1%

The number of ***diagnosed patients not on treatment*** varies from 5% in some countries to 50% in others. The annual incidence also varies, but in France it is ~6,000-7,000 per year and in Italy about 4.2%.

Dr. Mara estimated that 25% of Italian patients who are eligible for treatment are not treated. He also estimated that <50% of genotype 1 patients who have been treated either relapsed or were non-responders.

If the new antivirals in development help improve both diagnosis and treatment, there could be a shortage of hepatologists to treat HCV patients. The Secretary General of EASL, Dr. Jean-Michel Pawlotsky of France said, "I think there will be a shortage of doctors…but it is highly specialized treatment, so you have to see many of these patients and treat them well. There are not enough hepatologists…so other specialties will have to be involved – gastroenterologists and infectious disease specialists, but I personally am not in favor of having these patients taken care of by primary care doctors. HCV therapy is complicated, difficult. You have to be good in liver diagnosis." Dr. Mara was a little more optimistic, "Maybe you could change the composition of your clinic. A shortage of doctors is not the main problem…HCV patients can be seen by internal medicine, gastroenterologists, and infectious disease doctors, so I don't think there will be a shortage."

Yet, as therapies get more complicated – closer to the HIV model – hepatologists may need to change the way they practice, approaching HCV the way infectious disease specialists approach HIV. There will need to be more genotyping, more combination therapy, perhaps even using boosters like Abbott's Norvir (ritonavir). A speaker said, "There has been an explosion of new drugs in development to treat HCV, making this an exciting time for hepatologists."

Who will not benefit from STAT-C therapy in 2012? A speaker suggested the following patients might not benefit:

- Non-genotype 1 patients.
- Patients intolerant to INF-based therapy.
- Patients who cannot or will not be compliant with potentially more challenging regimens.
- Patients who can't afford the new drugs.

What is the most likely standard therapy in 2012? Dr. Berg said it will be different for naïve and treatment-experienced patients, "Monotherapy (with a protease inhibitor) will not be the way to cure infection because of the very rapid resistance developed within days…The reason for the resistance is that there is a marginal amount of resistant mutants at baseline, and if you can't eradicate them, they may initially have low viral fitness, but there may be compensatory changes to where they get more fit…So, it is clear you need rapid response to prevent resistance. The good news from *in vitro* studies is that resistance to protease inhibitors does not confer resistance to interferon. Interferon is critical for optimal response to telaprevir, but it has also been clearly shown that ribavirin is critical for optimal response."

PROTEASE INHIBITORS

Protease Inhibitors for HCV

Company	Drug	Status
Abbott/Enanta	(EA-058 and EA-063)	N/A
Boehringer Ingelheim	BI-201335	N/A
Boehringer Ingelheim	Celurevir (BILN-2061)	On hold
Gilead/Achillion	GS-912	N/A
InterMune/Roche	ITMN-191 (R-7227)	Phase II
Johnson & Johnson/ Tibotec/Medivir	TMC-435350	Phase I
Merck	MK-7009	N/A
Phenomix	PHX-1766	Phase I
Schering-Plough	Boceprevir	Phase III
Schering-Plough	SCH-900518	Phase II
Vertex/J&J/Tibotec	Telaprevir (VX-950)	Phase IIb

ABBOTT/ENANTA PHARMACEUTICALS

Dr. L. J. Jian of Enanta discussed two compounds her company has in development with Abbott – EA-058 and EA-063, suggesting these agents may have an advantage over other HCV drugs in development, "The Enanta drugs are highly potent, with broad genotype coverage, and are more potent than ITMN-191, MK-7009, and TMC-435350 against genotypes 2 and 3a. They are also active against genotype 1a and 1b R155K mutants. EA-063 is superior to the other agents against the most important resistant mutation…People believe viral rebound is caused by mutations…so EA may have an advantage over other agents in the clinic in preventing viral rebound…The Enanta drugs also are stable in human liver microsomes…and ITMN-191 and MK-7009 are not." She said the company will provide data on the resistance profiles of EA-058 and EA-063 at future meetings.

BOEHRINGER INGELHEIM's BI-201335

There were not much new data on this at EASL. However, a poster looking at resistance didn't find any unusual problems.

INTERMUNE/ROCHE's ITMN-191 (R-7227)

Dr. Zeuzem said the 900 mg BID dose has shown the most profound viral load decline, but the resistance with that dosing regimen still needs to be determined. Dr. Nelson said, "What you see is convincing antiviral activity…But it looks like all the doses are equivalent to me…but approach a 6 log drop at end of treatment…There was no virologic breakthrough with R-7227 + IFN-R…(With the ongoing Phase II) we will understand how best to use it."

A randomized, double-blind, placebo-controlled, inpatient, Phase Ib multiple ascending dose study was presented at EASL. Doses tested were: 100 mg Q8H, 200 mg Q8H,

400 mg Q12H, 300 mg Q8H, 600 mg Q12H, and 900 mg Q12H. All doses showed a median change in HCV RNA of ~5.3 log at Day 14. No dose showed rebound, but the dosing was short. The most rapid declines in HCV RNA occurred with 900 mg Q12H. Adverse events included headache, myalgia, and fatigue.

A Phase IIb trial of both the 600 mg Q12H and 900 mg Q12H doses as well as the 300 mg Q8H dose is expected to start this summer (2009).

The FDA really wants 48-week regimens of pIFN-R. While shorter regimens may be allowed later, initially, it wants to see this data.

JOHNSON & JOHNSON/TIBOTEC/MEDIVIR's TMC-435350

A speaker presented the results of OPERA-1, a Phase IIa, double-blind, placebo-controlled, proof-of-concept trial in treatment-naïve and treatment-experienced genotype 1 patients. Three doses were tested – 25 mg QD, 75 mg QD, and 200 mg QD – and there was a clear dose response. Patients at the 75 and 200 mg doses – but not the 25 mg dose – achieved HCV RNA levels <25 IU/mL, and 8 of 9 and 7 of 10, respectively, were undetectable at the end of 4-week triple therapy. However, bilirubin increases – and other side effects – at the 200 mg dose raise questions about the feasibility of that dose going forward.

MERCK's MK-7009

With Merck's acquisition of Schering-Plough, the question is: Which programs will Merck continue once the acquisition of Schering-Plough is finalized? Sources generally agreed that Schering's boceprevir would be commercialized. Beyond that, the Merck researchers seemed to think their internal Merck program is best, but the Schering officials were optimistic that SCH-900518 would be continued. It is likely to take time for Merck to sort this out. Meanwhile, a Phase IIb trial is recruiting in treatment-experienced patients.

A poster presented at EASL looked at a variety of doses, and the results were good for all, with the 600 mg QD having the least benefit, suggesting that either this will be a BID drug or the QD dose has to be higher. However, as the dose increased above 600 mg total dose, so did the side effects.

MK-7009 + pIFN-R in Genotype 1 Patients

Measurement	MK-7009 300 mg BID n=18	MK-7009 600 mg BID n=20	MK-7009 600 mg QD n=18	MK-7009 800 mg QD n=19	Placebo n=19
RVR per protocol	75.0%	78.9%	68.8%	82.4%	56%
RVR by ITT	70.6%	80.0%	70.6%	83.3%	5.3%
Virologic failure	With known mutations	N/A	N/A	With known mutations	N/A
Adverse events					
Headache	27.8%	45.0%	44.4%	15.8%	36.8%
Nausea	27.8%	40.0%	38.9%	31.6%	26.3%
Fatigue	16.7%	35.0%	16.7%	5.3%	31.6%
Flu-like illness	22.2%	20.0%	22.2%	26.3%	15.8%
Vomiting	0	40.0%	16.7%	15.8%	5.3%

SCHERING-PLOUGH's boceprevir

The final results of the randomized, multicenter, 48-week, Phase II SPRINT-1 trial in 595 genotype 1 HCV patients (in Europe, the U.S., and Canada, including 7% cirrhotics) showed very good efficacy with triple therapy (boceprevir + PegIntron + Rebetol), using a four-week lead-in of pIFN-R. The sustained virologic response (SVR) was almost double control.

The results also suggest that up to three-quarters of boceprevir patients may need only 28 weeks of therapy rather than 48 weeks. Dr. Paul Kwo, director of liver transplantation at Indiana University School of Medicine and the SPRINT-1 principal investigator, said, "The Boceprevir Phase III clinical program individualizes treatment based on response, utilizing rapid virologic response (RVR) criteria at Week 4 of boceprevir treatment to determine overall duration of therapy. Based on the RVR rate seen in this Phase II study, we are hopeful that the majority of patients can be treated with 28 weeks of therapy."

A new side effect has emerged – dysgeusia (change in taste) – but the main problem is anemia. Overall, 45% of patients in SPRINT-1 needed EPO for low hemoglobin (<10 g/dL), but >75% of patients with anemia got EPO. Ribavirin lowers hemoglobin, but boceprevir lowers it about an additional 1 g/dL. Boceprevir researchers and Schering officials argued that the anemia is a marker for response to boceprevir, and patients with anemia did have higher response rates. And treatment with EPO appeared to reduce patient discontinuation of therapy. A U.K. doctor commented, "Most patients tolerate the anemia without too many problems." A German doctor said, "Anemia is more or less a killer for boceprevir, especially on top of the need for one-year therapy."

Dr. Mark Sulkowski, medical director of the Viral Hepatitis Center at Johns Hopkins University in Baltimore MD, said, "It appears that the more hemoglobin one loses, the better the end-of-treatment response and SVR are with pIFN-R. The SVR was higher in patients who lost more hemoglobin. EPO did not increase ribavirin delivery. The real impact of EPO in this trial was treatment adherence. 94% of patients completed ≥12 weeks of therapy if they had no anemia, but only 92% completed if they had anemia without EPO, and 99% completed if they got anemia and received EPO…The effect of EPO is to prevent dropouts. The point is about preventing dropouts. The role of EPO is not to manipulate the ribavirin dose."

Other messages from this trial:

- **Full-dose ribavirin is needed**; low-dose ribavirin was associated with a high rate of viral breakthrough.
- **A 4-week lead-in period with pIFN-R is necessary.** However, not all experts are convinced this is a good idea. Dr. Graham Foster of the U.K. said, "I don't like lead-ins. I'm not convinced it is the right strategy. My concern is what do you do with a patient with RVR at 4 weeks?...Do you continue on p-IFN-R or add boceprevir? And how long do you go?...Lead-in is an innovative approach…but I'm not convinced it is the right way to go…We have a long way to go to understand the lead-in phase…I want to see simplified therapy – a pill handed out by primary care doctors. Complicated regimens are not the way forward."
- **4-week pIFN-R response, RVR, and EVR all appear to be good for guiding therapy.**
- **Anemia management with EPO is important** and leads to improved compliance and higher trial completion rates.

Ribavirin. Asked if the message is that the more ribavirin a patient can handle the better, Dr. Sulkowski said, "The issue with ribavirin is that for the last 10 years we said ribavirin dose reduction is a problem. That is simply not true. The issue is the ribavirin dose ingested is not the parameter we should be focused on. It is true that when you start therapy, you want to deliver enough ribavirin (13 mg/kg/day), but the amount ingested and the amount excreted (are not the same)…Anemia patients are holding on to ribavirin. Their exposure to ribavirin is higher, so the anemia is a marker for the fact that the patient is adequately loaded with ribavirin…So, you are just adjusting the ribavirin to their own level...We saw no detriment to decreasing the ribavirin dose."

However, Dr. Sulkowski said that testing serum ribavirin levels is not feasible, "I don't think we will be doing (measuring) ribavirin levels. The real key is that losing more the 3 g of hemoglobin is associated with a higher likelihood of response (to boceprevir)…You start with an accurate dose, and then monitor. If someone hasn't lost enough hemoglobin at Week 4, should you increase the ribavirin? That is a trial that needs to be done." He added that the role of EPO is not to manipulate the ribavirin dose.

Anemia. Dr. Kwo called the anemia problem a class effect but admitted it is probably worse with boceprevir than telaprevir, though it also occurs with telaprevir, "There is also an anemia signal with telaprevir. It may not be as much anemia, but there is a signal. One of the reasons it doesn't come out as much (with telaprevir) is that telaprevir is given for 12 weeks, and we give boceprevir for 48 weeks. Having said that, it is entirely possible there is a higher signal with boceprevir than telaprevir, but it does appear to be a class

48-Week Results of Phase II SPRINT-1 Trial of Boceprevir in HCV

Measurement	Part 1					Part 2	
	CONTROL: pIFN-R alone for 48 weeks n=104	Triple therapy (boceprevir + pIFN-R) for 28 weeks n=107	LEAD-IN: pIFN-R 4 weeks, then triple therapy for 24 weeks n=103	Triple therapy for 48 weeks n=104	LEAD-IN: pIFN-R 4 weeks, then triple therapy for 48 weeks n=103	Triple therapy 48 weeks n=16	Triple therapy with low-dose ribavirin for 48 weeks n=59
SVR							
Overall	38% *	54% *	56% *	67% *	75% *	50%	36%
Patients with RVR	100%	74%	82%	84%	94%	86%	75%
Patients with EVR	86%	68%	68%	84%	91%	73%	60%
Patients ***with*** anemia	48%	---	67%	---	88%	---	58%
Patients ***without*** anemia	35%	---	47%	---	64%	---	30%
Other results							
EPO use in patients with anemia	19/25	---	41/51	---	42/48	---	9/12
Relapse rate	24%	30%	24%	7%	3%	11%	22%
Relapse rate in RVR patients	0	21%	11%	5%	2%	0	14%
Adverse events							
Anemia (Hb <10 g/dL)	34%	56%	53%	52%	56%	63%	24%
Dysgeusia	9%	21%	26%	32%	27%	44%	31%
Alopecia	26%	34%	29%	29%	34%	31%	32%
Dizziness	15%	18%	16%	20%	14%	44%	19%
Vomiting	5%	22%	15%	24%	17%	44%	19%
Discontinuations							
Patients with EPO	7%	---	14%	---	15%	---	11%
Patients with no EPO	18%	---	38%	---	38%	---	60%

* statistically significant

effect…In 2012, if I'm treating with telaprevir with pIFN-R and the patient becomes anemic, I promise you I will give EPO."

Yet, the willingness of doctors to give a drug where they are likely to have to give quadruple therapy (boceprevir + pIFN-R + EPO) is uncertain. European doctors did not consider EPO use a big negative to boceprevir use, noting that they already use it for ribavirin-induced anemia. For American doctors, it may be more problematic.

Thus, Dr. Kwo was urging that "rational guidelines" for EPO use in HCV be established, "It will be important to come up with reasonable, rational guidelines for the use of EPO in patients on pIFN-R plus a protease inhibitor…It is likely that to some degree EPO may be over-used in some people, so the point is because of the expense and rare side effects – but not zero – I think it is important we judiciously use EPO…I think moving forward we probably should develop guidelines for a variety of supportive agents to maintain hemoglobin…My analogy is: We use antidepressants for IFN-related depression routinely…Are antidepressants indicated? No. We use acetaminophen and sedative hypnotics. Are they indicated for IFN treatment? No. This is a temporary use of EPO, presumably the longest you would use it is 10-11 months, and then you would stop. If the Phase II data are replicated in Phase III, I think that one could make a cogent argument that, in some individuals, using EPO to preserve high response rates would be a perfectly reasonable approach."

Boceprevir vs. telaprevir. The bottom line is that there is probably a role for both boceprevir and telaprevir, though telaprevir is likely to take the biggest market share. For example, Dr. Kwo said that cirrhotic patients won't get telaprevir, and sickle cell anemia patients won't get boceprevir.

Why choose one or the other? Boceprevir is as – or slightly more – effective than telaprevir, but patients may have to take it longer. If Phase III data indicate a substantial number of boceprevir patients can take a shorter course, like telaprevir, that would help balance the scales. Boceprevir doesn't have the patient discomfort side effects (rash/pruritis) that telaprevir does, but it has its own problem – anemia. Boceprevir also may have a slight dosing advantage (true TID). Neither boceprevir nor telaprevir can be boosted with ritonavir into a QD drug.

A Schering official emphasized that the length of boceprevir therapy is not a disadvantage, "Two-thirds of SPRINT-1 patients got RVR quickly. If a patient is negative at Week 4, you can go for short-term therapy. If not, go long term (24 or 48 weeks)…In RVR patients, telaprevir and boceprevir are both 24 weeks, and two-thirds of boceprevir patients will be this. For the remaining one-third, we think we will have less relapse."

Ongoing boceprevir studies include:

- A **Phase IIIb study** of boceprevir + Roche's Pegasys (peginterferon alpha-2a) in non-responders is actively enrolling patients, and that data may be at EASL 2010.
- **SPRINT-2** is a randomized, double-blind, placebo-controlled Phase III trial evaluating 28- and 48-week regimens of boceprevir (600 mg TID) + pIFN-R (with a 4-week pIFN-R lead-in) vs. pIFN-R alone in treatment-naïve genotype 1 HCV patients. The study is fully enrolled with 1,099 patients. This is one of 2 registration trials. RVR after 4 weeks of boceprevir (treatment week 8) is being used to determine which boceprevir patients can stop all treatment at 28 weeks.
- **RESPOND-2** is evaluating 36- and 48-week regimens of boceprevir (600 mg TID) + pIFN-R (with a 4-week pIFN-R lead-in) vs. pIFN-R alone in HCV patients who failed prior treatment (relapsers and non-responders). The trial has enrolled 404 patients. This is the second of 2 registration trials. RVR after 4 weeks of boceprevir (treatment week 8) is being used to determine which boceprevir patients can stop all treatment at 36 weeks.

SCHERING-PLOUGH's SCH-900518, a next-generation protease inhibitor

Researchers presented early phase, proof-of-concept data for SCH-900518, the company's next-generation protease inhibitor. Two dosing regiments were tested – 7 days of monotherapy with either 800 mg TID monotherapy and 400 mg BID boosted by ritonavir, with both followed by 14 days of combination therapy with pIFN in treatment-naïve and treatment-experienced patients. "518" was well tolerated, with no drug-related serious adverse events.

Pharmacokinetic (PK) and pharmacodynamic (PD) modeling from this study was used to design NEXT-1, the ongoing Phase IIa dose-finding study of SCH-900518 (200 mg, 400 mg, and 600 mg QD) + low-dose ritonavir (100 mg) + pIFN-R in treatment-naïve genotype 1 HCV patients. NEXT-1 has arms with and without a 4-week pIFN-R lead-in.

Using boosted SCH-900518 will require a change in thinking by hepatologists. Dr. Zeuzem said, "There is a debate starting at this Congress with hepatologists not used to sophisticated medications the infectious disease people have. We are now entering a period where precise dosing and timing are needed. The majority of hepatologists – 90%-95% – can't imagine using a protease inhibitor in conjunction with a PK-optimizing second agent such as a ritonavir-boosting strategy. If you ask what benefit optimization of PK brought to the HIV field, I would not dismiss the opportunity that indeed a similar situation could occur in the HCV field, that by optimizing PK profiles with ritonavir, you could have further breakthroughs than one that has been seen with maximum suppression in the HIV field."

Asked who will manage these patients in the future – infectious disease specialists or a specialized group of hepatologists, Dr. Zeuzem said, "I definitely believe that hepatologists are able to train hepatologists to do that…I require from the infectious disease people that they get a little more knowledge about liver disease because they need to get trained in dealing with (liver) complications...Both groups have learning curves, but both groups should be responsible."

Asked if lypoatrophy is likely with this boosted approach, Dr. Zeuzem said, "I don't think this will be a big problem…but we don't have long observation periods. It probably occurs with treatment much longer than 12-48 weeks with a protease inhibitor. I don't expect this to be a big issue."

Several posters were presented on SCH-900518, including:

- **Preclinical study.** In an enzymatic assay, SCH-900518 was active against genotypes 1-4. In a replicon assay, the IC_{50} was 20 nM and the IC_{90} was 40 nM. Resistance was reduced 10-fold when SCH-900518 was combined with PegIntron. SCH-900518 was cross-resistant to mutations raised against boceprevir.
- **PK study.** This study in 64 healthy volunteers studied doses from 50 mg to 2000 mg found that administration with a high fat meal increased bioavailability. The most common adverse events were headache, rhinitis, and abdominal pain.
- **GI absorption study.** This single dose (100 mg) study looked at using a direct-to-the-GI delivery system, and it found the rate and extent of absorption were decreased with this delivery method (vs. IR formulations).

VERTEX's telaprevir (VX-950)

Telaprevir is far and away the current leading new therapy on the horizon, and doctors are anxious for it to get approved. However, they are not yet warehousing patients for this drug. Most hepatologists interviewed said that they might start doing that once the Phase III data are available, but until then they are encouraging patients to take the available pIFN-R therapy. "Just too much can still go wrong," one doctor commented, adding, "We need to see the Phase III data."

Rash. The rash and anal pruritis (itching) are well recognized as side effects now, but hepatologists have learned to deal with it, primarily using topical steroids. Doctors not involved in the clinical trials are divided as to how much of an issue this will be in clinical practice. Some believe that patient discontinuation will be greater outside of trials, but others believe patients will put up with it if the therapy is only 24 weeks. Comments included:

- *France:* "The rash has settled down as an issue…People learned to manage it. It used to be a surprise, and now they have learned how to manage it. It is a problem for the patient, but we know what to do."
- *U.K.:* "We all got alarmed and had anxieties and concerns…I had a patient with 60% of the body covered in drug-related rash…(But) we are starting to understand it and are developing strategies to treat it. Although it looks ugly, it can be treated successfully, and we can keep patients on therapy. In our own practice, we are getting a little more relaxed as we are getting better at treating it (rash)."
- *U.S.:* "Rashes with telaprevir often occur after Month 2. That's why the FDA asked for a (Phase III) arm with just eight weeks of therapy – to see if they can get the same results but stopping before a major serious adverse event."
- *Germany:* "The (telaprevir) rash is not a drug-limiting toxicity because we are more aware of it now, and we can treat the rash earlier. Few patients get rash so severe we have to stop the drug. The rash is manageable…Trial patients are different from real-world patients. The rash may be less important in the maintenance phase."

Phase III. Three Phase III trials are ongoing. The naïve trial was fully enrolled in mid-February 2009, but no one could say if patients have been fully dosed yet. The other two Phase III trials are still enrolling patients, and investigators could not estimate when those will be fully enrolled, though several sources suggested that it may be as early as mid-2009. If there are no serious adverse events in the first month after full dosing, that would be reassuring, but experts insisted that it still doesn't mean there won't be a surprise. As one put it, "As we learned from the interim analyses of PROVE-1 and -2, you have to wait for the final results…You never know what will happen in Phase III, but telaprevir should be okay."

Dosing. There was no news at EASL on the telaprevir trial comparing BID dosing to Q8H dosing. However, numerous experts emphasized that the Q8H dosing is likely to be problematic in clinical practice. Many experts are concerned that patients will not be compliant with the dosing and will, at best, take it TID, which could increase resistance and breakthroughs. One said, "Q8H dosing does matter, but it is for a short duration." A source said that the telaprevir BID study is a proof-of-concept study only, that it is not powered for regulatory approval, though doctors may use it off-label BID if the data are good.

Phase II changes. There was a rumor that Vertex altered the Phase II endpoint or drew the cutoff after the data were in. An expert explained, "What happened is that the company initially planned to pull together the two groups (arms) with the same duration of therapy – one with triple therapy (telaprevir + pIFN-R) and one with double therapy (telaprevir + pIFN and no ribavirin). When they realized the non-ribavirin patients were not responding, they split it and did what they had planned as a secondary analysis. PROVE-2 was published in the ***New England Journal of Medicine*** on April 30, and all the details were in that article.

PROVE-3 results. PROVE-3 showed telaprevir is effective in patients who failed pIFN-R therapy. PROVE-3 was a randomized, multicenter, Phase IIb clinical trial in 453 genotype 1 HCV patients who did not achieve SVR with prior pIFN-R therapy. Non-responders were defined as patients who never achieved undetectable HCV RNA during or at the end of prior treatment; relapsers were defined as patients with undetectable HCV RNA at completion of prior treatment but relapsed during follow-up (did not achieve SVR). The study was not designed to provide results by type of pIFN-R failure (non-response, relapse, breakthrough). In this trial, despite the anemia, EPO use was rare (<1%).

Dr. Nelson commented, "PROVE-3 generated a lot of excitement. There was no advantage for longer duration. When you don't have ribavirin, you don't have very good activity…It is clear telaprevir won't be used longer than 12 months because of adverse events…and I think you will see 12 months (+36 months pIFN-R) for non-responders…There was no impact of cirrhosis (on efficacy). That was a very important finding. (PROVE-3) is very, very interesting data. It will give non-responders the hope that there is a new advance coming in a few years."

Genotype 4 patients. Telaprevir showed little activity in this genotype – which comprised ~40% of HCV patients in Europe – and doctors concluded it just doesn't work for these patients.

Dr. Yves Benhamou presented an interim analysis of the C210 trial of telaprevir ± pIFN-R in genotype 4 patients. He said that with monotherapy most patients responded and then rebounded on therapy. He concluded, "It is clear that telaprevir has less viral activity against genotype 4 compared to what we have seen with genotype 1…(but) it has more antiviral activity against genotype 4 than pIFN-R."

A doctor asked, "We were disappointed by the ~1 log drop in genotype 4. Do you think a 1 log decline warrants further development in genotype 4?" Dr. Benhamou responded, "Very frankly, I don't know. I really don't know. I think we need to do more virological work to try to really understand… before making a definite statement."

Results of Telaprevir in Genotype 4 Patients

Measurement	Telaprevir monotherapy n=8	Telaprevir + pIFN-R n=8	Placebo + pIFN-R n=8
Discontinued due to adverse events	1 patient	0	0
Primary endpoint: Mean viral drop at 2 weeks	-0.9	-3.4	-2.0
Breakthrough at Day 15	5 patients	1 patients	0
Mean viral load at Day 3	-1.2	-2.1	-1.0
Any adverse event	100%	100%	88%
Serious adverse events	13%	0	0

24-Week, Phase IIb PROVE-3 Trial of Telaprevir (TVR) in HCV Non-Responders

Measurement	TVR 12 weeks pIFN-R 24 weeks n=115	TVR 12 weeks pIFN-R 48 weeks n=113	TVR 24 weeks pIFN 24 weeks (no ribavirin) n=115	CONTROL: pIFN-R 48 weeks n=114
Completed therapy	75%	49%	52%	32%
Discontinued for Week 4 non-response	4%	11%	25%	33%
End of treatment response	76%	67%	54%	30%
SVR at Week 24				
Overall	51%	52%	23%	14%
Prior non-responders	39%	38%	10%	9%
Prior relapsers	69%	76%	42%	20%
Patients with cirrhosis	53%	45%	18%	8%
Patients without cirrhosis	51%	54%	25%	15%
RVR at Week 4				
Prior non-responders	50%	34%	32%	0
Prior relapsers	76%	68%	71%	0
Viral breakthrough at Week 24				
Overall	11%	10%	21%	3%
Prior non-responders	17%	17%	24%	3%
Prior relapsers	2%	0	13%	2%
Breakthroughs	14%	0	27%	0
Adverse events				
Fatigue	67%	61%	46%	56%
Rash	37%	45%	29%	18%
Pruritis	34%	44%	36%	15%
Anemia	26%	27%	8%	8%
Diarrhea	32%	43%	26%	19%

Genotype 2-3 patients. Interim results from the multinational C-209 Study were presented at EASL, and researchers reported that telaprevir works in Genotype 2, but not Genotype 3. Dr. Graham Foster said, "Adding telaprevir to pIFN has no effect. This worked for genotype 2 but sadly not for genotype 3…The glass is half empty because of the poor responses in genotype 3."

REALIZE. The Phase III REALIZE trial in null- and partial-responders as well as relapsers is ongoing.

POLYMERASE INHIBITORS

ABBOTT's ABT-333, a non-nucleoside polymerase inhibitor

Abbott researchers presented three posters on ABT-333.

- A **preclinical study** found that it works in genotype 1a and 1b HCV, with a low potential for CYP induction, suggesting a low potential for clinically significant drug-drug interactions.
- A **PK study** of escalating single, oral doses in healthy adults found that doses from 10 to 1200 mg were safe and well tolerated. Food had minimal impact on the bioavailability, and the man half-life was 5-8 hours. The most common adverse events were mild nausea, abdominal pain/discomfort, and headache.
- An **ascending dose study** in healthy volunteers looked at doses from 200 to 1000 mg BID for 10 days, with no accumulation and steady state achieved on Day 2. PK parameters were similar with morning and evening doses, indicating minimal diurnal variation in PK. When administered in combination with ketaconozole, there was no drug-drug integration.

Polymerase Inhibitors for HCV

Company	Drug	Status
Non-nucleosides		
Abbott	ABT-333	Phase I
Abbott	ABT-072	Possibly still Phase I
Anadys	ANA-598	Phase II to start mid-2009
Boehringer Ingelheim	BI-207127	Phase IIa
Gilead	GS-9190	Phase II
Japan Tobacco	JTK-003	Discontinued
Merck	MK-3281	N/A
Pfizer	Filibuvir (PF-00868554)	Phase IIb to start mid-2009
Vertex/ViroChem Pharma	VCH-222	Phase II
Vertex/ViroChem Pharma	VCH-759	Phase Ib completed
Vertex/ViroChem Pharma	VCH-916	Phase I
ViroPharma/Wyeth	HCV-796	Discontinued for adverse events
Nucleosides		
Idenix	Valopicitabine (NM-283)	On hold for adverse events
Idenix	IDX-102	N/A
Idenix	IDX-184	Phase I/II nearing completion
Merck	MK-0608	Phase I
Pharmasset	PSI-7851	Phase I
Roche	R-1626	Moving to Phase II
Roche/Pharmasset	R-7128	Phase IIb starting
NS5A inhibitor		
Boehringer Ingelheim	BMS-790052	Phase II

ANADYS' ANA-598, a non-nucleoside polymerase inhibitor

In a 3-day, Phase Ib study in HCV patients, ANA-598 demonstrated rapid and sustained reductions in HCV RNA, but the efficacy data were unimpressive, with little difference between the 400 mg and 800 mg doses. The 400 mg data were skewed and thus less interpretable due to missing data on one responder. Dr. Eric Lawitz of Alamo Medical Research in Texas, said there is no added viral suppression in genotype 1b patients by increasing the dose >800 mg or giving it longer. He added, "400 mg BID may be an interesting dose to go forward…400 mg BID also may be the dose for genotype 1b, though some may say to push it higher…There is no viral rebound, but this is just a 3-day study."

Phase Ib Results with ANA-598

Median viral load reduction on Day 4	ANA-598		
	200 mg BID	400 mg BID	800 mg BID
All patients	2.4 $\log_{10}$	2.3 $\log_{10}$	2.9 $\log_{10}$
Genotype 1a patients	1.4 $\log_{10}$	2.8 $\log_{10}$	2.5 $\log_{10}$
Genotype 1b patients	2.6 $\log_{10}$	2.5 $\log_{10}$	3.2 $\log_{10}$
Viral rebound on drug	0	0	0

A speaker presented data suggesting that ANA-598 retains activity against mutations which confer resistance to other HCV therapies. *In vitro* studies of ANA-598 with other antivirals suggested that ANA-598 is synergistic with IFN, telaprevir, PSI-6130 (a nucleoside inhibitor), and ANA-773.

There were no data at EASL from the 14-day healthy volunteer study of ANA-598, but the company announced the results in a press release, and Anadys officials at EASL commented on it. That PK study tested three doses: 400 mg QD, 600 mg BID, and 800 mg QD. Three subjects developed rash: 2 at 800 mg QD and 1 at 600 mg BID. The rash did not develop immediately; it occurred after 7-8 total doses. Dr. Lawitz said no rash has been seen in the HCV patients, but the late rash and the fact that it occurred in both QD and BID dosing cast a shadow on development of this drug. However, the company still plans to start a Phase II trial in mid-2009 in combination with pIFN-R.

BOEHRINGER INGELHEIM's BI-207127, a non-nucleoside polymerase inhibitor

A poster reported on safety, PK, and the antiviral effect with 5 days of therapy in a double-blind, sequential, dose-escalating, 14-day Phase Ib trial. As of EASL, the 1200 mg Q8H cohort was still ongoing. The study found that BI-207127 may be able to be dosed TID rather than Q8H. There was good tolerance and no signal of viral breakthrough. A Phase IIa trial will use 400 and 800 mg TID. (*See chart on page 10.*)

BI-207127 in Genotype 1 Patients

Measurement	BI-207127				Placebo
	100 mg Q8H n=9	200 mg Q8H n=9	400 mg Q8H n=9	800 mg Q8H n=9	n=12
Mean viral log drop	0.6	1.1	1.9	3.1	0
Viral load drop >4 log_{10}	0	0	0	5 patients	0
Adverse events					
Nausea	1 patient	1 patient	2 patients	1 patient	2 patients
Vomiting	1 patient	0	0	0	1 patient
Diarrhea	0	0	1 patient	1 patient	0
Headache	1 patient	2 patients	2 patients	2 patients	2 patients
Rash	0	0	0	2 patients *	0
ALT change (U/L)	-25	-20	-38	-43	+14
Platelets (10^9/L)	+6	+8	-1	-2	+5

* mild, not requiring discontinuation

IDENIX's IDX-184, a nucleoside polymerase inhibitor

Dr. D. N. Standring of the U.S. reported on a study in 6 chimps over 7 days, which found resistance develops slowly, with the only known resistance S-282T. He also said a Phase I study in 8 healthy volunteers found the drug (25 mg, 50 mg, 75 mg, and 100 mg QD) was safe and well tolerated. A Phase I/II proof-of-concept study is enrolling, and Dr. Standring said enrollment has been "challenging" because there initially were only sites in the U.S., but sites in Europe and South America have been added, so enrollment has picked up, and the study is expected to be finished in mid-2009.

PFIZER's filibuvir (PF-00868554), a non-nucleoside polymerase inhibitor

As monotherapy, filibuvir (100-450 mg BID or 300 mg TID for 8 days) has demonstrated dose-dependent inhibition of viral replication, with mean maximum HCV RNA reductions of -0.97 to -2.13 log_{10}. A Pfizer researcher said a Phase IIb trial will start mid-2009, but this will be a small trial.

The primary resistance is 423, but 422K has been seen. A researcher explained that this was in a non-responder, "We looked and found one patient at the end of treatment with no viral rebound. We don't know yet what the role of the 422K mutation is. We don't know the fitness of the virus with 422, but we think it is not very fit – though that wouldn't stop a small number of patients from having that." There may be more data on this at the American Association for the Study of Liver Diseases (AASLD) meeting in Boston October 30-November 3, 2009.

Why is a polymerase inhibitor less potent than a protease inhibitor? A Pfizer researcher offered several reasons:

1. The hypothesis is that a protease inhibitor cleaves to innate protein in the cell.
2. Resistance is easier with a non-nucleoside polymerase inhibitor than with a nucleoside polymerase inhibitor.
3. A protease inhibitor binds to the active site so mutations occur slower.

The researcher said Pfizer plans to continue development of filibuvir but the ultimate goal is to combine it with a protease inhibitor.

Two posters on filibuvir were presented:

- **In combination with pIFN-R.** A randomized, 28-day study in 35 treatment-naïve genotype 1 patients found the combination was well tolerated and increased the number of patients achieving RVR. With this combination therapy, early viral suppression persisted following cessation of filibuvir administration on Day 28. All patients who achieved RVR continued to have undetectable HCV RNA at Week 12. Virologic breakthrough was observed in patients with poor intrinsic response to pIFN-R. A Phase IIb study of filibuvir + pIFN-R in treatment-naïve patients is planned.
- **8-Day monotherapy.** This double-blind, randomized, placebo-controlled, sequential dose escalation study tested 4 different doses of filibuvir, finding the predominant mechanism of resistance to the drug was mutation 423 (in 11 of 24 patients), though 2 patients developed an uncommon mutation, 422K.

Filibuvir + pIFN-R in Genotype 1 HCV

Measurement	Placebo n=8	Filibuvir 200 mg BID n=10	Filibuvir 300 mg BID n=9	Filibuvir 500 mg BID n=8
Undetectable HCV RNA at Week 2	20%	25%	50%	0
Undetectable HCV RNA at Week 4	60%	75%	63%	0
Undetectable HCV RNA at Week 12	80%	88%	63%	50%
Mean change from baseline in HCV RNA	-0.48 log_{10}	-2.34 log_{10}	-2.73 log_{10}	-2.83 log_{10}
Virologic breakthrough (>0.5 log_{10} increase)	---	1 patient	1 patient	3 patients
Safety				
Headache	2 patients	4 patients	6 patients	3 patients
Fatigue	3 patients	2 patients	2 patients	4 patients
Insomnia	2 patients	4 patients	1 patient	4 patients
Nausea	1 patient	3 patients	3 patients	2 patients
Serious adverse event: creatinine elevation	0	0	1 patient	0

Filibuvir Monotherapy

Measurement	Placebo	Filibuvir			
		100 mg BID	200 mg BID	300 mg BID	500 mg BID
Mean maximum HCV RNA reduction (log_{10})	N/A	-0.97	-1.84	-1.74	-2.13

ROCHE/PHARMASSET's R-7128, a nucleoside polymerase inhibitor

This agent generated a lot of interest at EASL. It has shown very high viral reduction in treatment-naïve genotype 1 patients, and data presented at EASL suggest that it has a high barrier to resistance. A speaker said it works across all genotypes. Dr. Nelson said this is because "it doesn't look like you can develop resistance to it…they have only found 1 resistance *in vitro* with extensive trying…and it is a variant that doesn't seem very important…This may be combined with all protease inhibitors in the future…And it offers the possibility of a non-interferon therapy in the future…It also looks like it works across all genotypes."

The kidney toxicity seen in monkey studies has not been seen in humans.

VERTEX/VIROCHEM

- **VCH-222, a non-nucleoside polymerase inhibitor.** In a poster, ViroChem researchers reported the potency is affected by the presence of human albumin, the *in vitro* therapeutic index is ~4,000, which they said indicated a high anti-HCV specific activity. The researchers reported in another report on the results of a test in 39 healthy volunteers, which found all the patients had a >3 $\log_{10}$ reduction in HCV RNA after 24 hours, with a mean maximal reduction of 3.7 $\log_{10}$ after 3 days at 750 mg BID. No virologic rebound was observed. A Phase II study has begun to determine the optimal dose.
- **VCH-916, a non-nucleoside polymerase inhibitor.** At EASL, the results of a randomized, double-blind, placebo-controlled, dose-ranging study in HCV genotype 1 patients were presented. Throat irritation and nausea appear to be significant side effects at all doses.

VIROPHARMA/WYETH's HCV-796, a non-nucleoside polymerase inhibitor

This agent was discontinued due to adverse events. A speaker at EASL was asked if the problem could be a class effect, and he responded, "I hope it is not, but it is troublesome. There was no signal in monotherapy, and no signal until Week 8 in combination therapy. So, it says to me these drugs need to get through at least three months of combination therapy, even if there is no signal at all in monotherapy. Is it species-specific? We just don't know."

OTHER HCV AGENTS

DEBIOPHARM's Debio-025, a cyclophilin inhibitor

Dr. Nelson presented one-month data on Debio-025 in 50 null-responders (mostly genotype 1a), testing two additional doses not used before (400 and 800 mg daily). He reported that there was no significant effect by adding pIFN, and adding ribavirin also made very little difference, but when a loading dose was used, there was a big viral load drop, and the 800 mg daily dose had a big drop even without a loading dose.

The major safety issue for this compound has been bilirubin elevations, and it is highest with a loading dose, but Dr. Nelson said that there is no clinically significant hyperbilirubin, that "a lot of work is going on to explain" the bilirubin elevations, and the elevations are wholly reversible with a dose reduction and drug discontinuation. Three patients in this study had bilirubin >3 mg/dL.

At the same time, there was a marked reduction in ALT, and Dr. Nelson said it was "reassuring" that there is "no evidence of hepatoxicity."

A Phase IIb trial is fully enrolled using a lead-in dose. An expert noted that the potential for drug-drug interactions with this agent needs to be studied because it is metabolized by CYP450C3A.

Other Agents in Development for HCV

Company	Drug	Type	Status
Debiopharm	Debio-025	Cyclophilin inhibitor	Phase IIb
Gilead	GS-9450	Caspase inhibitor	Phase I
Human Genome Sciences	Albuferon (albinterferon alfa-2b)	Interferon	Phase III
Japan Tobacco	JTK-652	Entry inhibitor	Discontinued
Novartis	NIM-811	Cyclophilin inhibitor	May be discontinued
Progenics	PRO-206	Entry inhibitor	Preclinical
Scynexis	SCY-635	Cyclophilin inhibitor	Phase II

VCH-916 Results

Measurement	Placebo n=8	VCH-916			
		100 mg TID x 14 n=8	200 mg TID x 14 n=8	300 mg BID x 4 n=3	400 mg BID x 4 n=3
Mean maximal viral load reduction	--	0.8 $\log_{10}$	1.5 $\log_{10}$	1.5 $\log_{10}$	1.5 $\log_{10}$
Mean viral load reduction at Day 4	---	0.5 $\log_{10}$	1.2 $\log_{10}$	1.4 $\log_{10}$	1.3 $\log_{10}$
T_{max}	---	1.4 hours	2.2 hours	2.2 hours	3.0 hours
GI side effects (flatulence, loose stools/ diarrhea, cramps, abdominal bloating)	---	38%		34%	
CNS side effects (headache, dizziness)	---	19%		N/A	
Throat irritation	---	25%		76%	
Flushing	---	13%		N/A	

HUMAN GENOME SCIENCES' Albuferon (albinterferon alfa-2b)

The hope was that this could replace interferon, with once-monthly dosing, but doctors have been disappointed. Interstitial lung problems led to dose modification in January 2008 from 1200 µg to 900 µg. At EASL, efficacy with the Q2W doses looked comparable to pIFN, but once-monthly dosing did not look as if it would be possible. Safety remains a concern.

Results with Albuferon in ACHIEVE-1 and ACHIEVE-2 Trials

Measurement	pIFN n=310	Albuferon 900 µg Q2W n=312	Albuferon 1200 µg Q2W n=310
ACHIEVE-1			
Alopecia	24.5%	41.2%	40.2%
Cough	25.6%	37.6%	39.8%
Weight loss	14.7%	23.8%	23.6%
ACHIEVE-2			
Alopecia	24.9%	43.8%	42.9%
Cough	28.5%	41.2%	38.1%
Weight loss	15.2%	24.9%	27.7%
Interstitial findings	5.0%	6.3%	5.2%
Hemoglobin <10	17.5%	23.0%	23.9%

In the ACHIEVE-1 trial, Albuferon (900 µg Q2W and 1200 µg Q2W) met the primary endpoint of non-inferiority to pIFN in patients with HCV genotype 1. The treatment effect was consistent across the subgroups studied. There was more alopecia, weight loss, and cough with Albuferon.

In the 932-patient ACHIEVE-2 trial, Albuferon met the primary efficacy endpoint of non-inferiority vs. pIFN in HCV patients with genotype 2/3. Higher RVR was noted in Asian patients, but investigators couldn't explain this, suggesting it could be a chance finding but should be studied further. Concern about respiratory events, particularly interstitial lung disease, at the high dose prompted careful follow-up, including spirometry and a central blinded review of chest x-rays, but it found similar rates of interstitial pulmonary findings with Albuferon vs. pIFN.

JAPAN TOBACCO's JTK-652, an entry inhibitor

A poster presented the results of an 8-patient Phase I study in HCV patients of a 100 mg TID dose (7 patients) vs. placebo (1 patient). The drug had to be discontinued prematurely in 2 patients due to "mild" rash. At 29 days, there was no effect on HCV RNA vs. baseline. Development has been discontinued.

NOVARTIS's NIM-811, a cyclophilin inhibitor

A 14-day, multiple ascending dose study (25 mg QD, 75 mg QD, 100 mg BID, 200 mg BID, 400 mg BID, and 600 mg BID) of monotherapy vs. placebo was followed by a 14-day placebo-controlled study in 20 HCV genotype 1 relapsers using only the 600 mg BID dose. As monotherapy NIM-811 did not decrease HCV RNA, but with pIFN there was a significant decrease.

As with Debio-025, bilirubin was increased, but no patient went >2 g/dL. In this case, researchers reported "the increases in bilirubin were statistically but not clinically significant." In addition, platelets declined with NIM-811 therapy. NIM-811 is hepatically metabolized, and it has a risk for drug-drug interactions because of the bilirubin changes.

EASL's Dr. Pawlotsky said, "I think we have a problem… This drug is not doing anything in monotherapy…I understand it has been chosen by ability to bind to cyclophilin *in vitro*… We know other cyclophilins are effective monotherapy, and this isn't…We probably should forget this."

NIM-811 Results

Measurement	NIM-811 + pIFN	Placebo + pIFN
HCV RNA change	- 2.7 $\log_{10}$	- 0.58 $\log_{10}$
Change in platelets	- 104,000	- 37,500

PROGENICS' PRO-206, a small molecule entry inhibitor

The PK profile in rats indicates this agent has 34% bio-availability, good oral exposure, no interaction with CYP450, broad phenotype activity, and likely QD dosing in humans. It is currently undergoing IND-enabling studies to support initiation of human clinical trials in HCV. The company is hopeful that it will have an advantage over other agents in preventing viral rebound. A speaker said, "We believe it is broadly active. When combined with pIFN, it is additive…It has high permeability, suggesting the potential to be well absorbed *in vivo*."

SCYNEXIS' SCY-635, a cyclophilin inhibitor

A 15-day, randomized, double-blind, placebo-controlled proof-of-concept study found that a 900 mg daily dose of SCY-635 was associated with statistically significant and clinically relevant reductions in plasma viremia but not rapid reductions. Doctors were not very excited about this data, and none would speculate on whether this pattern of viral load reduction is consistent with the expectation of long-term viral load suppression. On the other hand, there was no evidence of viral rebound over the 15-day period.

COMBINATION THERAPIES

Hepatologists are very excited about new oral combination therapies. Some are warehousing patients in anticipation of a fully oral therapy without pIFN-R, but most are not, particularly not until it looks as if the therapy is within six months of reaching the market. Yet, doctors expect that patients themselves are likely to increasingly want to wait for this type of oral therapy and may decline treatment if that is

feasible. Dr. Berg said, "The decision has to be made individually, but it is fair to inform patients what the future will bring. The state of disease does matter…If it is a young, female patient with a positive response, and she is willing (to undergo therapy), there is no good reason to wait several years."

Among the other companies with both a protease and a polymerase inhibitor in the pipeline or in the planning stage are:

- **BOEHRINGER INGELHEIM** – with the protease inhibitor BI-201335 and the polymerase inhibitor B-207127. The company has been quietly working away on these without a lot of fanfare, so they may be underestimated.
- **JOHNSON & JOHNSON/TIBOTEC** now has both a protease and a polymerase.
- **MERCK's MK-7009 + MK-3281** – MK-7009 is a protease inhibitor, and MK-3281 is a non-nucleoside polymerase inhibitor. There were data on both of these at EASL. A chimp proof-of-concept study found that combining the two agents quickly and dramatically reduced viral load – and kept it undetectable. The combination appears to work in genotype 3, though nausea remains a concern. A Merck researcher said *in vitro* data show the combination is not antagonistic, which the FDA wants to see, "We cured a chimp with two direct antivirals. The FDA said if the combination did okay in Phase II, then it would be open to a combination with pIFN-R…Fourteen days is probably not long enough. We probably have to dose 48 weeks, stop dosing, and wait 6 months to see if viral load comes back…We would like to forget injections, simply dosing, and ideally have a fixed dose combination."
- **PFIZER** – While Pfizer doesn't have a protease inhibitor yet, sources said Pfizer folks were "shopping" for one at EASL to go with the non-nucleoside polymerase inhibitor filibuvir (PF-00868554).
- **VERTEX** – with its protease inhibitor telaprevir and the polymerase VCH-222, which it acquired with ViroChem Pharma.

ROCHE's R-7128/ITMN-191 plus R-7227

Researchers presented the results in the first 4 cohorts of the INFORM-1 trial of the R-7227/R-7128 protease/polymerase combination in naïve patients, and the data looked very good. Even competitors couldn't find anything much to criticize. However, a Roche investigator insisted that this is a proof-of-concept study only, showing that two antivirals are additive and delay or prevent the emergence of resistance, "Before the FDA would allow the reduction or elimination of pIFN-R, more studies with different durations of the combination would be required. The goal is to increase the tolerability and efficacy beyond the current ~50% in genotype 1 and provide access to patients intolerant to interferon. From HIV, we know adherence to treatment is essential to reduced the emergence of resistance, so we hope this will be BID or QD…The antiviral effect of the polymerase/protease combination is more than additive; it is synergistic."

The three higher doses showed similar antiviral activity. Glucose and LDL were increased, while phosphate and neutrophils decrease, but all the lab abnormalities were Grade 2.

No safety issues were raised other than one patient with hypophosphatemia, which was transient. The efficacy was ~4-5 log reduction at Day 14 at all doses tested. The viral suppression appeared to be synergistic – a reduction of 0.6 log more than the additive effect of the two drugs. Dr. Sulkowski said, "It was great to show that it is possible and that there are no drug-drug interactions…It is proof-of-concept that it is feasible." Dr. Nelson called it a "proof-of-concept." Dr. Ed Gane of New Zealand commented, "This (combination) approach is unlikely to meet the needs of all our patients...but it may redefine the future treatment for all of our patients… This is a very attractive option." Dr. Gane said the effect of the combination therapy "was more than additive, with a difference of about 0.6 logs."

Asked why the polymerase inhibitor (R-7128) dose was increased, a Pharmasset official said it was to tighten the PK and to prevent viral breakthrough.

Asked if any patients had rebound, Dr. Gane said, "Yes, one low-dose patient met the definition of rebound, with an increase in viral load >0.5 log…and that patient was suppressed with (other therapy)…but there are no data on resistance in that patient."

Asked if the efficacy is more than additive with higher doses at end-of-treatment, Dr. Gane said they don't have that data yet. An official said, "We saw similar results with profound antiviral suppression with all doses, but we saw some intriguing observations with the higher dose…What none of us in the field know is how these early observations in viral

14-Day INFORM-1 Results of a Protease (R-7227) and a Polymerase (R-7128)

Measurement	R-7227 100 mg + R-7128 500 mg	R-7227 200 mg + R-7128 500 mg	R-7227 100 mg + R-7128 1000 mg	R-7227 200 mg + R-7128 1000 mg
HCV RNA change from baseline	-3.9	-5.2	-4.8	-4.8
HCV RNA <LLOQ	13%	63%	71%	63%
Safety				
Total adverse events	23	16	24	
Headache	6	1	5	
Rash	3	0	0	
Fatigue	2	0	1	
Nausea	2	1	0	
Dry mouth	0	2	1	
Dry eyes	0	1	2	

decline translate to SVR at end-of-treatment. What we would like to explore is higher doses and answer if these will make a difference down the line – and to study safety."

Asked about the future development path, Dr. Frank Duff of Roche said, "What we are hearing from the health authorities is they are very intrigued by the concept…We know they have concerns about long-term resistance. They are encouraged and intrigued by all this but wanting to be reasonably cautious on safety. So, it is a step-by-step approach…I think it will be quite important for us to go with all efficiency but also a top concern for patient safety. What we are discussing in the program is going beyond 14 days…We are in active discussions with the authorities to see what that (program) will be."

Asked if there was any difference in side effects by dose, Dr. Gane said no.

Asked what percent of patients at the time telaprevir and boceprevir are launched will be in a position to warehouse themselves, *assuming the Roche combination data continue to look strong*, Dr. Gane said, "That is a difficult question. That depends on what we tell the patients we think is the right approach to treatment. The patient makes the decision on treatment. That will be determined by how severe their liver disease is…It will depend on the efficacy of these new agents in combination with pIFN-R…But patients who fail current standard-of-care are more likely to wait." However, he said a delta of 10% would make the decision to warehouse easy.

Asked about one patient with apparent viral breakthrough on combination R-7128/R-7227, Dr. Gane said, "The patient was in the low-dose group – it occurred before the end of dosing. The patient rapidly suppressed after standard-of-care with pIFN-R and remains undetectable now, several weeks into standard-of-care. The patient had a half log increase – a strict definition for viral breakthrough – and rapidly suppressed thereafter. There will be a very thorough analysis which will be presented later."

Asked if patients will get 48 weeks of standard-of-care or if they can stop treatment earlier if they are undetectable earlier, Dr. Gane said, "Patients will be offered 48 weeks of standard-of-care…(But) multiple centers are involved, and it will depend on local practices."

Asked about Roche's willingness to explore combinations with either R-7128 or R-7227 with drugs outside the Roche portfolio, Dr. Duff said, "That is something we are open to longer term…Pegasys is an integral part of the things going on…We think this is an excellent combination."

Asked about adding this combination therapy on top of standard-of-care, Dr. Duff said, "There are a number of approaches that may unfold…Some degree of customization of treatment will become the norm…So, we are looking at quad therapy…I personally think that is for more difficult subsets, especially non-responders."

Asked about a non-nucleoside polymerase inhibitor/protease inhibitor combination, Dr. Duff said, "We need to do the early work on that…There is tremendous promise for the non-nucleoside class…but we have a nucleoside (that we are excited about). As non-nucleoside polymerase inhibitors progress – and those are studies that need to be done – I suspect we will start the same way."

Asked how combination HCV therapy would be similar to HIV, Michelle Berry, chief medical officer at Pharmasset, said, "It is our belief that the nucleoside will be the back-bone…because of the lack of interaction from a PK profile, the lack of drug resistance, and combination with at least additive viral suppression...The nucleosides may be a good combo with the non-nucleoside further down the line, but we do believe the nucleosides would be a background." Dr. Duff added, "In HCV we are curing, and that is a fundamental difference from HIV."

Asked if there were any Grade 3-4 lab abnormalities at the high dose (1000/200 mg), Dr. Gane said no, just a few Grade 2 side effects and none that were clinically significant – no significant hematologic or renal abnormality.

Asked what the FDA and European regulators (EMEA) will be looking for before allowing combination trials to initiate in the U.S. and Europe, Dr. Duff said, "They haven't expressed clearly what they are looking for…I suspect they are watching the data accumulate…There are no clear guidelines (yet). Dr. Steve Porter, chief medical officer at InterMune, added, "They are discussing forming joint guidelines, so we can get a little more specific guidance from them on what is required…but we haven't seen anything or been given anything on when we will get guidance."

HEPATIC ENCEPHALOPATHY (HE)

Hepatic encephalopathy is not as common as HCV, but hepatologists said there are a lot of HE patients. In the U.S. five million people are believe to have chronic liver disease. Of those, ~100,000-200,000 patients probably have cirrhosis. Of the cirrhotics, ~50% have overt HE, with a predicted mortality of 50% at 3-5 years. Liver transplant is the only cure. A U.S. hepatologist said, "HE is not common like HCV or HBV, and it is not an epidemic, but it is a major complication of end-stage liver disease. It is a problem that needs new drugs that would be used early but not before HE develops."

Dr. Vincente Arroyo from Spain, an expert in hepatic encephalopathy, estimated that 20%-30% of patients in his hepatitis unit were hospitalized for HE. However, he called HE an acute condition, not a chronic condition, "If you treat the patients, they usually recover. In 3-5 days, most patients completely recover. But you may take the medicine all the time to prevent a new episode of HE. There are patients who develop frequent episodes of HE, but they are usually acute episodes. There are a few cases of chronic HE, but that is

infrequent…The first episode of HE is most often due to a precipitating event, and if you cure the precipitating event, you won't develop HE unless you develop another precipitating event – for example, an infection, GI hemorrhage, or dehydration secondary to over-diuresis. As the liver worsens, the HE episode incidence may increase."

As the liver becomes cirrhotic, it does its filtering function less, dumping toxins into the bloodstream. Those toxins can eventually travel to the brain. HE progresses from mild cognitive impairment to coma.

The most frequently used grading systems for HE are West-Haven and Conn scores as the Glasgow Coma Scale. Both West-Haven and Conn are based on changes in behavior, consciousness, and intellectual function. Both systems grade the severity of an episode. An expert said, "Some doctors hospitalize all Conn 2 patients, but sometimes these patients will recover in a few hours."

No therapy currently has FDA approval for the treatment of HE, with lactulose the most common off-label therapy for acute episodes. Lactulose is an altered sugar that is not absorbed by the body, thus causing diarrhea which flushes the bowels and drains a fairly meaningful amount of toxins. While lactulose is effective and inexpensive, patients don't like the sweet taste, and patients absolutely hate the constant diarrhea. Another altered sugar, lactilol, also is used sometimes, and Dr. Arroyo said it is better tolerated because it is not as sweet. The antibiotics neomycin and norfloxacin also are used sometimes. They improve cerebral function by preventing infections. However, neomycin toxicity, particularly ototoxicity, is a concern, and doctors worry about antibiotic resistance with long-term use of either antibiotic. Hepatologists said metronidazole (Flagyl) is not used.

Two new therapies are in development to treat HE, and there is probably room in the market for both – one for acute episodes and the other for earlier stage disease. Cost will be an issue, since lactulose is relatively inexpensive and both of these drugs are intended as long-term treatments.

HE Scoring Systems

Score	Conn	West-Haven
0	Normal	Normal, no clinical signs or symptoms
1	Mild impairment	Trivial lack of awareness, euphoria or anxiety, shortened attention span, impaired performance of addition, sleep reversal
2	Evidence of some personality change, behavioral changes, difficulty with simple computations and/or disorientation to time or place	Lethargy or apathy, minimal disorientation to time or place, inappropriate behavior, subtle personality change, impaired performance of subtraction
3	The patient is sleepy and needs to be roused and usually is completely disoriented. Patients in this condition need hospitalization	Somnolence to semi-stupor, but responsive to verbal stimuli; confusion; gross disorientation
4	---	Coma

SALIX's Xifaxan (rifaximin), a non-absorbed antibiotic

Xifaxan works on the enteric bacteria which are believed to play an important role in HE. It is approved in the U.S. and elsewhere to treat traveler's diarrhea at a dose of 200 mg x 2 TID, but ≥50% of use is off-label in irritable bowel syndrome (IBS) and hepatic encephalopathy. The FDA has granted orphan drug status for Xifaxan in HE, but it is not being developed under a Special Protocol Assessment. It was submitted to the FDA in 2008, and the FDA asked for additional data.

The Phase III results with 550 mg BID on top of lactulose vs. lactulose alone were presented at EASL, and they looked fairly good. At baseline 91% of patients were on lactulose, and the principal investigator, Dr. Nathan Bass of the University of California, San Francisco, said mean lactulose use did not vary by arm during the trial.

The trial studied primarily Conn score 2 HE patients. In those patients, Xifaxan significantly reduced breakthrough (58% reduction at 6 months) and time to first HE-related hospitalization (50% reduction over 6 months). Dr. Bass offered a positive number needed to treat (NNT) estimate: on average, for every 4 patients treated with rifaximin, 1 fewer patient experienced an overt HE breakthrough vs. placebo, and for every 9 patients treated with rifaximin, 1 fewer patient experienced an HE-related hospitalization vs. placebo.

William Forbes, PharmD, senior vice president for research and development at Salix, said both the Conn 1 and the Conn 2 patients in the trial had a statistically significant improvement, but the analysis by Conn score was not prespecified. A subgroup analysis also showed no differences by subgroup. There were no data on the severity of the episodes during the trial that would indicate whether Xifaxan reduces the severity of the episode. The duration of hospitalization data had not yet been analyzed.

There was no evidence of a survival benefit. There also are no data on whether or not Xifaxan reduces total hospitalizations over any time period. In the study, patients came out of the trial if they were hospitalized, though they could enter another open-label study (3002). Forbes said, "In the open label study we will show there is a maintenance (benefit)."

Dr. Bass said, "The study changes the landscape in one significant fashion…Right now, we are using this (Xifaxan) second-line or as an adjunctive treatment in patients not doing well on lactulose in terms of efficacy or just not tolerating it well, which is very common. These results show the addition of rifaximin to lactulose provides a significant reduction in events. The way I see it, this could set the stage for it to be considered as part of standard-of-care – that it should be added if you are trying to prevent hospitalization and recurrent episodic events."

What is the advantage of Xifaxan over neomycin? Dr. Bass said, "Neomycin is absorbed more than rifaximin…There is a potential for ototoxicity with neomycin should it be absorbed in sufficient quantity, which seems to occur. We especially see over toxicity in patients with renal impairment, to which neomycin might have contributed. I personally have seen several deaths attributed to neomycin. So, it is a good idea to avoid neomycin if we can and if there is an alternative. There are no data for neomycin vs. this. At this stage, I'd say neomycin would have to be safer, and we would need a lot more data (to prefer neomycin to rifaximin)."

These data raise some concerns:

- There is a dramatic reduction in ***first*** hospitalization during the first 90 days, but patients who did not have an event in the first 90 days were no different from lactulose-only patients during the next three months. So, is the benefit really only in the first month? Is there real justification for continuous dosing? Would insurance companies accept continuous dosing? One suggestion the company and investigators made is that the patients who stay on the drug without an event are likely to have an event if they stop the drug, so it needs to be continued indefinitely. But there are no data to prove that; there was no follow-up of patients who discontinued at the end of the study, etc.
- One-quarter of the patients were enrolled in Russia, and Russian data can be problematic upon detailed analysis.

European as well as U.S. doctors questioned about HE said they are already using rifaximin off-label for HE, and they estimated that use is likely to double if it gets approved for HE. Most European doctors expect to use it intermittently, not as long-term therapy, while most U.S. doctors said they would keep patients on it once it is started. Xifaxan is well tolerated, but it is expensive – $500-$900 a month for the current 200 mg product. However, some U.S. payers, including Kaiser Permanente, cover it, but others like California Medicaid (MediCal) require prior authorization, and some don't cover it at all.

When do doctors start therapy for HE? Dr. Arroyo said one episode is not enough, "Very often a patient has one episode and doesn't have another for 1-2 years. Only patients who develop very frequent episodes should be treated long-term with rifaximin…Perhaps 10%-20% of HE patients require this therapy on a long-term basis." Dr. Mara said, "The rifaximin data are pretty good. I have a few patients in that condition with chronic relapses of HE that are doing full lactulose, and I am really thinking of putting them on rifaximin. The data are convincing…It is actually pretty safe to do (this treatment) long-term for weeks or months. I have one patient with relapses every 3-4 weeks. Patients don't have to be on it lifetime, but they could be. You might give rifaximin a try, and if it is ineffective in preventing a higher frequency of relapses, you can withdraw it."

If a generic 200 mg rifaximin tablet were available, some doctors said they would still write for the brand to reward Salix for doing the trials, but they expect that third party payers will require substitution. Two 200 mg tablets three times a day would be less convenient than one tablet twice a day, but the potential cost savings is likely to appeal to payers and patients who have to pay out-of-pocket.

Most doctors – U.S. and European – currently use Xifaxan for moderate patients who have suffered at least one acute episode, and they do not expect to use it, at least initially, in patients with mild HE (Conn 0-1 score) patients. Dr. Bass said when Xifaxan gets approved, he will prescribe it "for patients who have had evidence of more than 1 episode of HE, in which there was a significant event – a visit to an emergency room because of concerns about alteration of mental status – or in patients who manifest chronic low-grade or even more dramatic chronic, ongoing symptoms of HE even though we don't have the data on that. I'd be encouraged to try it out empirically in some of those patients where lactulose is not leading to any improvement…I'd give it as long as it is necessary, and that is until the patient gets a transplant."

If the FDA has any concerns with Xifaxan, doctors said it probably is one of two things:

1. **Development of antibiotic resistance with long-term use.** There are no data to this effect, but any long-term antibiotic use raises the question. Forbes said, "That (concern) is always there, and it is a fair concern…Giving an antibiotic every single day is questionable on resistance. In terms of systemic infections, we are in really good shape. (Xifaxan) patients are not getting systemic absorption like other antibiotics, and that leaves gut infections like *C. difficile*, and we are tracking that as well as we can." Dr. Bass said, "The resistance observed has not been clinically significant to date."
2. **2 cases of *C. difficile*.** These both occurred in the Xifaxan arm of the trial (vs. none with lactulose). Forbes said, "We showed 2 cases of *C. diff*…They were called super-infections…Having reviewed those cases fully on my end, they did not constitute difficult *C. diff* infections…Could it have been chance or leaving patients a little more prone to *C. diff*? That still needs to be answered…Teasing this apart is difficult because they are a patient population exposed to *C. diff* and prone to it." Dr. Bass described two cases as "almost trivial," adding that the patients had other major risk factors for *C. diff*…*C. diff* will be the focus at the FDA. It is not a sticking point. It is an issue but also a non-issue."

Asked if the decrease in hospitalizations was due to a decrease in C. diff infections, Forbes said, "The hospitalization data we showed so far was specific for HE, but we will have data on other hospitalizations as well."

Asked why doctors should prescribe Xifaxan instead of Ocera's AST-120, Salix's Forbes said, "I didn't see any efficacy data (in the Ocera study). Obviously, the reason to use our compound is the indications we are seeking are different; we are seeking prevention of an overt HE event, and 50% of those end up in the hospital. It is an unmet medical need. Obviously, the data we have show substantial and meaningful reduction in HE events. They were looking not to avert HE events but a change in minimal HE, which they didn't do. I think the whole area around the usefulness of a pharmacologic agent in proving minimal HE is something perhaps not ready for prime time and still being vetted out at academic institutions…and someone will eventually get an indication… That is a little softer endpoint and requires development of testing procedures that are still in progress…There are no data that AST-120 prevents one HE event."

OCERA's AST-120, a spherical carbon adsorbent

AST-120 are highly porous carbon spheres that provide "a sink for gut-derived bacterial products (ammonia, indoles, histamine) implicated in HE." An 8 g daily dose (2 g four times a day) provides the surface area of 10 Olympic swimming pools.

AST-120 is designed to treat mild HE only. Thus, Dr. Laurent Fischer, president/CEO, said there is a role for both Xifaxan and AST-120. Data from a four-week, randomized, multicenter, Phase II non-inferiority study were presented at EASL comparing AST-120 to lactulose in mild HE. The principal investigator, Dr. Paul Pockros of the Scripps Clinic in La Jolla CA, reported that AST-120 was as effective as lactulose, with a lower incidence of GI adverse events (diarrhea and flatulence) and a trend toward less pruritis.

The strength of this trial was the comparison to lactulose. The weakness was the small size. Is it good enough to be equivalent to lactulose? Probably, given the reduction in GI side effects. The unanswered question is how AST-120 will be priced. ♦

Week 4 Results of AST-120 in HE

Measurement	AST-120 n=24	Lactulose n=23	p-value
Evaluable patients	21	20	---
Baseline West-Haven score	1.1	1.1	---
Lactulose use at screening	76%	75%	---
Primary endpoint: ≥1 point change in West-Haven score	38.1%	35.0%	Nss (non-inferiority met)
Worsening of West-Haven score	0	0	---
Stable West-Haven score	61.9%	65.0%	---
Secondary endpoint #1: Pruritis by Visual Analog Scale (VAS)	~12	~17	Nss, 0.1
Secondary endpoint #2a: GI tolerability – diarrhea	25.0%	56.5%	0.04
Secondary endpoint #2b: GI tolerability – flatulence	33.3%	69.6%	0.02
Secondary endpoint #2c: GI tolerability – abdominal distension	25.0%	34.8%	Nss