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by Lynne Peterson

SUMMARY

Protease inhibitors for HCV: Both Schering-Plough's SCH-503034 and Vertex's VX-950 appear effective, but q8h dosing could be problematic. Abbott's Norvir may prove useful as a booster for both of these. ♦ **Polymerase inhibitors for HCV:** Idenix/Novartis's valopicitabine (NM-283) has problems both in terms of efficacy and GI and pancreatic side effects. The safer, lower doses (200-400 mg) were effective in naïve but not experienced patients. Roche's R1626 is in earlier development but does not appear to have the same problems. ♦ **Interferons for HCV:** Doctors were optimistic about Human Genome Science's albuferon with Q2W dosing, but Roche's R7025 also bears watching. ♦ **Ribavirin for HCV:** Valeant's viramidine likely will require another trial, which may put its approvable date so far in the future as to make it either unlikely to be pursued or unlikely to be a major product. ♦ **HBV:** Idenix/Novartis's telbivudine looks very promising, and so does Anadys's ANA-380, though it is much earlier in development.

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EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

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The most exciting thing at EASL, according to Dr. Jean-Michel Pawlotsky of France, the Scientific Secretary of EASL, as well as other sources, was Abbott's presentation on the use of its Norvir (ritonavir) to boost protease inhibitors in hepatitis C (HCV). He said, "The ritonavir boost is very exciting and encouraging. This is something that has to be explored. This is the most important thing I've seen at this meeting. It is very new, original, and provocative, and it opens a door, which is increasing exposure tremendously with the combination. It may allow some patients to be treated orally – the easy responders." An industry source said, "The ritonavir boost is impressive but not unexpected."

Dr. Pawlotsky pointed to four areas he thinks are very promising, and other sources concurred that these are the key products to watch:

1. *New interferons, particularly* HUMAN GENOME SCIENCE'S albuferon and **ROCHE/MAXYGEN'S R7025.** He said, "Albuferon has shown good efficacy and safety, and the every two-weeks administration is progress. The monthly dosing not working is a little disappointing, but it still might be okay for QM dosing for genotype-2 or -3. It could be a third (interferon) player if it makes it in terms of long-term safety, but I think it has a green light…Roche is pegylating R7025, and it is potentially very interesting. It could be more potent, and it is very, very interesting because it is pegylated."

2. *An alternative to ribavirin* – VALEANT'S viramidine. Dr. Pawlotsky commented, "It failed at the dose used…The questions are: Would it be good at a higher dose with the same side effect profile? Can they increase the dose to a higher level? Even if it had the same anemia but better efficacy than ribavirin, would it be useful? I would not kill this. The approach is dead, but the drug is not…I think the company will continue it." However, sources were dubious that the EMEA will approve it without additional tests.

Dr. Pawlotsky believes ribavirin will be around for a long time, probably longer than interferon (IFN), "Ribavirin is very useful for HCV. It cures HCV, and it may be very useful with other drugs. So, it might survive the loss of IFN or failure of specific inhibitors in terms of efficacy and safety."

3. *Specific inhibitors,* particularly the polymerase inhibitors **[IDENIX/ NOVARTIS'S valopicitabine (NM-283)** and **ROCHE'S R1626],** and the protease inhibitors **[SCHERING-PLOUGH'S SCH-503034, VERTEX'S VX-950**, and **INTERMUNE'S ITMN-B]**. Dr. Pawlotsky said NM-283 looks additive to IFN, even though the data on the 400 mg dose was not statistically significant in

previous IFN non-responders, "They (Idenix) have a problem. They have to decrease the dose. This one is not in very good shape." R1626 has completed Phase I and is about to start Phase II trials. He described SCH-503034 as "not quite as good" as VX-950, saying, "It really needs ritonavir boosting."

Dr. Pawlotsky called ITMN-B, which is in preclinical development, interesting. Another expert said *in vitro* ITMN-B reportedly has shown different resistance from SCH-503034. There will be a talk and three posters (structural biology, liver assay for compound design, etc.) on this at DDW 2006. InterMune hopes to file in Europe in 3Q06 for permission to start a human clinical trial. An official said, "The intent is to do the Phase I trials in Europe, and then Phase II in the U.S."

4. ***Immune therapies.*** Dr. Pawlotsky said, "There is no proof of concept yet, but the idea of a vaccine is good."

HEPATITIS C (HCV)

More than 3 million Americans are affected by HCV, which is spread through direct contact with the blood of infected people. HCV significantly increases the risk of developing long-term infection, chronic liver disease, cirrhosis, or death. The current standard of care is IFN + ribavirin, but this only provides sustained benefit in ~50% of patients with genotype-1, the most common strain of the virus. Several new approaches are being investigated, including polymerase inhibitors, protease inhibitors, and toll-like receptors. "In HCV, it is relatively simple to see what is ongoing, but it is not simple to see what will work," Dr. Pawlotsky said.

PROTEASE INHIBITORS (PIS)

Initially at least, protease inhibitors are likely to be used in combination with peg-IFN+ribavirin (RBV), but doctors are looking forward to using them in combination with each other, with polymerase inhibitors, etc. An expert said, "We need to do all we can to avoid resistance, and there is still the emergence of resistance with protease inhibitors, so there will be at least some population where triple therapy will be useful, especially in genotype-2 and -3."

Protease inhibitors for HIV must be taken indefinitely, but it is likely that HCV patients will only need to take a PI for as long as it takes to ensure adequate viral suppression or clearance, which could be as little as 24 weeks.

Dr. Stefan Zeuzem of Homburg, Germany, a key investigator on protease inhibitors, made several points including:

- Schering-Plough's Peg-Intron recently got a new label in Europe. It now has additional approval for 24-week treatment in genotype-1 patients with a low viral load who become HCV RNA negative at Week 4 and are RNA negative at Week 24.
- Hepatitis C (HCV) patients with genotype-1 (HCV-1) with a low baseline viral load (≤800,000/mL) – and that is about 35% of all genotype-1 patients:
  - If they are PCR negative at Week 4, they do not need 48 weeks of therapy; 24 weeks is sufficient to achieve an SVR of 85%-92%.
  - If they are PCR negative at Week 12, they do better with 48 weeks of therapy to achieve an SVR of 85%-90%.

The results of an ongoing, prospective study in Germany should be interesting. It is comparing:

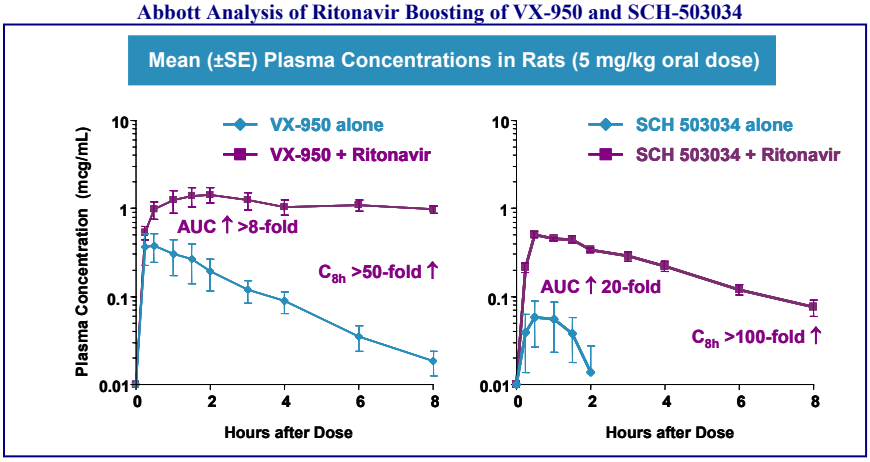
- Peg-Intron (peg-IFN-α-2b 1.5 mg/kg) + ribavirin 800-1200 mg for 24 weeks.
- Peg-Intron (peg-IFN-α-2b 1.0 mg/kg) + ribavirin 800-1200 mg for 24 weeks.
- Peg-Intron (peg-IFN-α-2b 1.5 mg/kg) + ribavirin 800-1200 mg for 16 weeks.

The problem with the protease inhibitors in development – at least the ones furthest along – is the dosing schedule, which is TID for Schering-Plough's SCH-503034 and q8h for Vertex's VX-950. Abbott researchers may have found a solution for this, turning them into BID or QD agents.

ABBOTT'S Norvir (ritonavir) – a booster for protease inhibitors?

An Abbott researcher, Dr. Dale Kempf, told a packed symposium that rat research indicates ritonavir (which is used to boost trough levels of protease inhibitors used for HIV) also can effectively boost the effect – and extend dosing – of both Vertex's VX-950 and Schering-Plough's SCH-503034. The presentation left many in the audience thinking that the addition of ritonavir might convert those protease inhibitors into BID or QD drugs, and it created quite a buzz at the meeting.

Abbott Analysis of Ritonavir Boosting of VX-950 and SCH-503034



* Slide courtesy of Dr. Dale Kempf, Abbott

Right now, VX-950 appears to be best dosed at 750 mg q8h (a very specific TID dose), but the addition of ritonavir might allow QD dosing. In rats, the data appeared to indicate that SCH-503034 would go from TID (not specifically q8h) to BID with the addition of ritonavir, but Dr. Kempf warned against assuming VX-950 would get preferential dosing; he said that in humans ritonavir may also boost SCH-503034 enough for QD dosing. He said, "I would caution against extrapolating the patterns of rats to what we might expect in humans because we need to look at the PK in humans to really understand whether there is a potential for BID or QD…I wouldn't assume from what we showed that one is QD and one is BID."

Dr. Kempf said Abbott now plans to do dog studies. In the rat liver microsomes and *in vivo* rat studies, Dr. Kempf found that:

- ~70% of VX-950 is metabolized within 30 minutes, but if you add 0.4-4 μM of ritonavir, metabolism is largely or completely inhibited. There is an 8-fold increase in exposure over 8 hours and clearance is substantially lowered, so the half-life becomes very long, and plasma concentration is increased >50 times at 8 hours.
- ~80% of SCH-503034 is metabolized within 30 minutes, but if you add 0.4-4 μM of ritonavir, metabolism is "almost completely inhibited." Alone, SCH-503034 is poorly absorbed and cleared within two hours, he said, adding, "When combined with ritonavir, exposure increases 20-fold, and now we see measurable and significant levels even 8 hours after a single dose."
- The effect of ritonavir is likely due primarily to the CYP450-3A system.
- Enhancement of plasma levels of both drugs is likely with co-dosing with ritonavir.
- There is no evidence of incremental hepatotoxicity from combining ritonavir with a protease inhibitor in HIV patients.
- A low dose of ritonavir (100-200 mg/day) is required for boosting either drug, and ritonavir exposure is only 5%-8% of that of the original full dose (600 mg BID) of ritonavir.

The difference in the response curves of the two drugs accounts for the possible difference in boosted dosing. VX-950 lasts about 8 hours, but, in both rats (the Abbott study) and humans (a Schering study), SCH-503034 has a very sharp bell-shaped response curve. Dr. Kempf explained that there is a high correlation between plasma trough levels and virologic response. He said, "With VX-950 in monotherapy…only ~50% difference in mean plasma trough levels in the group with continued decline on therapy vs. those with viral breakthrough. Similarly, with SCH-503034 there is a pretty high correlation between plasma trough levels and virologic response, but it is not clear if it is linear regression or a more typical sigmoidal response. But it is a high correlation that is also seen in another drug class – HIV protease inhibitors."

Other points Dr. Kempf made about the use of ritonavir to boost HCV protease inhibitors included:

- The effect of peptide HIV protease inhibitors is also correlated to plasma trough levels.
- The plasma trough levels of HIV protease inhibitors are greatly enhanced by co-dosing with ritonavir.
- At least 75% of HIV protease inhibitor use is in ritonavir-boosted regimens today. Because you get increased efficacy (with the combination), that allows for more convenient BID or QD dosing and delays the development of drug resistance.
- Abbott's Kaletra (lopinavir) when given alone in humans gives very modest plasma levels that rapidly cleared through the liver, but when co-dosed with ritonavir, the half-life becomes much longer, and the combination of Kaletra + ritonavir is now QD in the U.S.
- Resistance over two years is >20% in HIV unboosted HIV patients but zero in boosted patients.
- The chemical structures of VX-950 and SCH-503034 resemble many HIV protease inhibitors – both are very large for small molecule drugs, equivalent to a pentapeptide or hexapeptide. Both are also highly hydrophobic and are metabolized exclusively by CYP450-3A.

Sources believe that Abbott's patent is very strong on combination use of ritonavir, suggesting that Vertex and/or Schering want and probably need to license ritonavir. One source suggested that even off-label use of ritonavir by doctors in combination with either SCH-503034 or VX-950 may become problematic from a patent standpoint.

SCHERING-PLOUGH'S SCH-503034

The data on SCH-503034, an NS3 protease inhibitor, appeared to indicate that SCH-503034 is not quite as efficacious as Vertex's VX-950, sources suggested. A competitor said, "There is a minimum 2 log HCV RNA reduction with VX-950, and some patients have up to a 5 log reduction, but the reduction with SCH-503034 is less.

Yet, all doctors questioned still believe it is good enough to go forward, and it could have a dosing advantage. Some sources also speculated that if Schering does a deal with Abbott and boosts SCH-503034 with ritonavir and Vertex doesn't, SCH-503034 could come out on top of, or comparable to, VX-950.

A Schering official discussed early data on SCH-503034 saying it has shown strong antiviral activity in HCV-1 IFN non-responders. Phase I safety studies, toxicology studies to support 48 weeks of therapy, and additional dose escalations beyond 400 mg have been done. A combination trial with

peg-IFN-2b in genotype-1 non-responders also has been completed.

Among the points he made were:

- It has indirect activity as well as direct activity.
- It is at least additive to IFN-2b and perhaps synergistic.
- Doses from 10 mg BID to 400 mg TID were tested in a study in HCV-1 patients. The BID regimens had a "modest reduction" in HCV RNA, which rebounded when the drug was stopped, but there was little difference in efficacy among the BID doses. The 400 mg TID dose had the most profound viral reduction, and it also had rebound when discontinued. He said, "This suggests that, like HIV, drug concentration through the interval is very relevant, and perhaps disproportionately relevant, to controlling the virus." This probably means that adherence to a TID dosing schedule would be critical to efficacy, making the TID dosing problematic. He also indicated that the company can and will test even higher doses (above 400 mg).
- It was well tolerated, with no unusual adverse events. The most common adverse event was headache (12% vs. 29% with placebo).
- Clinical lab values were not different from placebo – no increase in bilirubin, creatinine, or prothrombin time.
- He said they did ECGs in the dose-finding study because Boehringer Ingelheim's BILN-2061 had cardiotoxicity issues, but he also said SCH-503034 showed "no clinically significant ECG changes from baseline."
- BILN-2061 was not active in non-genotype-1 populations, but SCH-503034 showed similar PD in non-responders in genotype-1 in a 14-day, 61-patient, double-blind study (200 mg BID, 200 mg TID, 400 mg BID, and 400 mg TID). Again, the 400 mg TID dose had the best response. Mean viral load was reduced 2.06 $\log_{10}$ from baseline.
- PK studies found:
  - T_{max} is ~1-2 hours.
  - There are dose related increases in C_{max} and AUC.
  - It is absorbed quickly.
  - It has biphasic clearance – $T_{1/2}$ = 5-7 hours.
- When SCH-503034 is given with ritonavir, the dose of SCH-503034 will probably need to be adjusted.

A Phase II study of SCH-503034 has been initiated to select the dose for Phase III in combination with Peg-Intron ± ribavirin, with duration of treatment 24 weeks and 48 weeks. For the first week, all patients will get Peg-Intron alone, then Peg-Intron + Rebetol and one of these seven arms:

- Placebo.
- 100 mg SCH-503034 TID for 48 weeks.
- 200 mg SCH-503034 TID for 48 weeks.
- 400 mg SCH-503034 TID for 48 weeks.
- 800 mg SCH-503034 TID for 48 weeks.
- 400 TID for 24 weeks with follow-up for another 24 weeks.
- 800 mg TID for 24 weeks with follow-up for another 24 weeks.

Schering is also planning trials in:

- HCV-1 treatment-naïve patients.
- Genotypes-2, -3, and -4.
- Special populations – e.g., African-Americans, HCV/HIV co-infected, liver transplants, renally impaired, and pediatrics.
- Different durations of therapy, based on the findings in Phase II. This could be shorter, more intense, and other combinations.

A moderator commented, "The early SCH-503034 results are encouraging…but IFN-based regimens will remain the backbone of therapy for the next five years."

Dr. Zeuzem presented data on an open-label, three period, crossover study of SCH-503034 in non-responders to peg-IFN+RBV in HCV-1. All patients received all three regimens, just in different order:

- Peg-IFN as monotherapy.
- 200 or 400 mg SCH-503034 TID.
- Combination of peg-IFN + either 200 or 400 mg SCH-503034 TID.

Dr. Zeuzem reported no dose-related increase in the frequency of adverse events. There was one serious adverse event leading to discontinuation – a woman with a seizure whose history later revealed a past history of this that was not mentioned during enrollment. Clinical lab values and ECGs were reported to be similar to peg-IFN alone. He concluded that SCH-503034 is "at least additive" to peg-IFN, and 4 of 10 non-responders became negative within two weeks with SCH-503034 400 mg TID.

In a sequence analysis for HCV protease, 18 of 19 patients had no detectable variants. One patient had a single mutation at

SCH-503034 Trial Design

Cohort	Period 1	Period 2	Period 3
Group A	SCH-503034 200 or 400 mg for 7 days	Peg-IFN for 14 days	Combination for 14 days
Group B	Peg-IFN for 14 days	Combination for 14 days	SCH-503034 200 or 400 mg for 7 days
Group C	Combination for 14 days	SCH-503034 200 or 400 mg for 7 days	Peg-IFN for 14 days

SCH-503034 Results

Cohort	Number of patients	HCV RNA reduction				
		0-1 $\log_{10}$	>1-2 $\log_{10}$	>2-3 $\log_{10}$	>3 $\log_{10}$	Negative
Peg-IFN	22	13	7	2	---	---
SCH-503034 200 mg	12	6	6	---	---	---
SCH-503034 400 mg	10	1	7	2	---	---
Peg-IFN + 200 mg SCH-503034	12	---	6	2	4	1
Peg-IFN + 400 mg SCH-503034	10	---	1	5	4	4

Adverse Events with SCH-503034

Side effect	Peg-IFN	SCH-503034 200 mg BID	SCH-503034 400 mg BID	Peg-IFN + SCH-503034
Headache	9	3	N/A	9
Myalgia	7	0	N/A	7
Fever	0	0	N/A	2
Rigor	5	0	N/A	6
Leukopenia	3	0	N/A	2
Neutropenia	4	0	N/A	6

Patients were dosed with VX-950 for 14 days, followed by a 14-day follow-up period, and then more follow-up for 3-7 months, and mutation patterns were analyzed. All VX-950 patients returned to baseline at the end of the study; at 3-7 months, only low level resistance remained in patients. In placebo patients, no significant change from baseline in HCV RNA was observed. All patients given VX-950 experienced a sharp initial decline in HCV RNA in the first three days, and then one of three patterns occurred:

- Viral breakthrough (n=13). At 3-7 months, only low level resistance remained.
- Plateau (n=8). At 3-7 months, most patients returned to wild type.
- Continued decline in HCV RNA (n=7). At 3-7 months, low level resistance was replaced by wild type.

position T54 with both monotherapy and combination therapy with SCH-503034. However, the assay used was not as sensitive as the assay Vertex used for VX-950, and Dr. Zeuzem said this needs to be repeated with SCH-503034 with the more sensitive assay. A speaker said the variant becomes non-detectable after the washout period. Quasi-species analyses are underway.

VERTEX'S VX-950

Sources all believe this drug will succeed, but at the same time, some experts injected a note of caution. One said, "I'm optimistic but not enthusiastic." Resistance occurs early in 3 or 4 days, so the key question is dosing, but reformulation or boosting with Abbott's Norvir (ritonavir) may solve that problem. Side effects, interaction with ribavirin, animal toxicology all appear to be non-issues. A competitor said, "There are a number of questions. What is the DLT? What is the cardiovascular profile? What is the size of the pill or how many pills will patients have to take? Protease inhibitors are notoriously insoluble compounds, so excipients are used to slow down the release, but those excipients could raise issues. Vertex is contracting out the manufacturing and getting ready, so they are pretty confident."

A Vertex official presented a **substudy from a Phase Ib trial** presented at EASL last year. These data looked at whether mutations conferring various levels of resistance are selected in some patients during dosing with VX-950. The study looked at whether wild-type HCV NS3 protease (the virus phenotype present before treatment) re-emerges during follow-up after 14 days of dosing with VX-950 in HCV-1 patients. The answer was: Yes, but combining VX-950 with peg-IFN + RBV may prevent this.

The study found that long-term (3-7 month) viral sequencing follow-up data showed that (1) in patients previously dosed with VX-950 as a single agent for 14 days (a sub-optimal treatment period), wild-type virus supplanted treatment-emergent variants, and (2) sensitivity to future treatment regimens that include VX-950 or other HCV protease inhibitors may be regained. Vertex said the findings suggest that viral variants associated with decreased susceptibility to VX-950 may have reduced replicative fitness in patients, and some patients may regain sensitivity to VX-950, so that treatment failure may not compromise future therapeutic options.

A Vertex official concluded, "Mutations conferring various levels of resistance are selected in some patients during dosing…The clinical indications are that resistance to VX-950 can occur rapidly under some circumstances. Can we prevent that? Two preliminary studies indicate that combining VX-950 with IFN may prevent selection of resistant variants." Data will be presented at DDW showing the 28-day results of a 12-patient study combining VX-950 with peg-IFN+RBV.

Several people asked whether resistant variants are archived forever and eventually come back in HCV as they do in HIV. The Vertex official doubted there is a reservoir for HCV that would result in rebound of resistant virus, but the audience members, as well as the moderator, suggested this still needs to be studied and proven.

This resistance/mutation study appears to have set a new bar for other companies. A researcher presenting data on Schering-Plough's SCH-503034 had less detailed data because a less sensitive assay was used, and he indicated Schering probably will have to go back and do a more complete analysis, given the findings with VX-950.

In a poster, Vertex researchers described results of a **whole genome analysis** that suggested that the expression level of IFN-sensitive genes may be restored with VX-950 treatment. Vertex said the data suggest a normalization of gene expression in peripheral blood cells in HCV patients responding to VX-950 at levels similar to those of healthy, uninfected patients. Researchers identified 258 genes that are differentially expressed in chronic HCV infection, including a large number of genes associated with viral response, cellular defense, and immune response. In patients who achieved the greatest reduction in plasma HCV RNA following 14 days of dosing, sustained levels of IFN-sensitive gene expression were observed in peripheral blood cells.

14-Day Study of VX-950 with Pegasys

Measurement	VX-950 750 mg TID +Pegasys on Days 1 and 8 n=8	VX-950 750 mg TID N=8	Pegasys alone on Days 1 and 8 n=4
Completers	8 patients	8 patients	4 patients
HCV RNA at end of dosing	-5.5 $\log_{10}$	-4.0 $\log_{10}$*	-1.0 $\log_{10}$**
HCV RNA below limit of quantitation	6 patients	0	0
HCV RNA below limit of detection	4 patients	1 patient	0
Increase in HCV RNA levels during dosing	0	0	N/A
Safety			
Headache	63%	25%	50%
Rash	38%	13%	0
Muscle aches	63%	25%	50%
Dry skin	38%	25%	25%
Nausea	38%	13%	25%

*** There was a 3 log decline by Day 3, and then the curve flattened.**
**** There was a 3 log decline by Day 3, and then RNA continued to decline but more slowly.**

Initial results from a 20-patient, 14-day **Phase Ib study** (Study VX04-950-103) of the viral kinetics and safety of VX-950 in combination with peg-IFN-α-2a (Roche's Pegasys) in HCV-1 patients were presented by researchers from the Netherlands. In the study, VX-950 was well tolerated, with no serious adverse events.

The most common adverse events were headache, muscle aches, dry skin, diarrhea, and nausea, with each event more frequent in the combination and peg-IFN alone groups than in the VX-950 group. The only adverse event exclusive to VX-950 was mild rash, but a Vertex official said that the rash:

- Is not similar to the fulminate acne associated with ImClone's Erbitux (cetuximab) or Genentech's Tarceva (erlotinib). He described it as a mild, localized, surface rash on various parts of the body. The longest patients had it was five days, and it resolved while they were on treatment.
- Is not correlated with response to VX-950.

After patients finished this 14-day study, they were offered combination therapy, and after an additional 12 weeks all of these patients had undetectable levels of virus and continue to stay on therapy. A Vertex official said they will be followed for an undetermined amount of time, so there will be additional anecdotal data on them even though they are not technically in a study any longer.

What is the development outlook and path for VX-950? Sources do not believe there is any interaction problem between VX-950 and ribavirin, and a Vertex official said the 14- and 28-day studies didn't indicate any negative interaction, but more analysis of the 28-day study is ongoing.

The q8h dosing (vs. TID not equally spaced) could be a problem since resistance develops quickly – within 3 or 4 days, experts estimated. However, a Vertex researcher said they didn't see it until a week after stopping the drug, adding, "It doesn't last long; it's mostly gone by 3-7 months." Dr. Pawlotsky, the head of EASL, said, "Q8h does matter…and they (Vertex) themselves have shown that exposure is a major determinant of response." Another expert said, "With IFN, it doesn't matter if you miss a dose, but it will matter with VX-950."

However:

- Q8h dosing does not appear to have been a problem in the 14-day and 28-day studies since the response rate was so high. While trial patients are expected to be more compliant than patients in general clinical practice, the company finds this data fairly reassuring.
- Even if strict compliance to q8h is required, patients may only have to do it for a short time, which may make it an acceptable regimen. A Vertex official said, "In HIV adherence has been studied closely, and in HIV through 3-4 months adherence is pretty good. It is only later that adherence falls off, which is a reason for potential short-duration therapy with VX-950. Adherence may be less of an issue because we are not dosing long."
- Dosing with ritonavir could turn VX-950 into a QD drug. However, Vertex does not appear in any hurry to strike a licensing agreement for ritonavir with Abbott, which, at this point appears willing to license ritonavir for a "small" fee to any company with a protease inhibitor. Vertex has done its own single-dose study of VX-950 with ritonavir, but isn't discussing the results. However, a Vertex official said, "We are aware of the potential to boost with ritonavir. We'll see. We feel fairly confident in our clinical trial plans now. Ritonavir doesn't change those plans." He said that a multidose interaction study should be anticipated.

- The q8h dosing was based on a monotherapy regimen and is being continued in Phase II, but it may not need to be that strict in combination with peg-IFN+RBV.
- A speaker suggested that, despite a protocol for q8h, standard TID dosing may be acceptable. However, there are no data on this.
- Vertex is working on new formulas of VX-950. The official said, "We have a tablet formulation that we are very happy with for clinical development. We could look at other, different dosing intervals. It is not necessarily a q8h drug…Dosing is q8h in development – all Phase II trials will be q8h – but don't assume that is what it will be in the market." An expert said, "Vertex could optimize a slow release formulation. They need to play around with it (formulation)."

Three-month animal toxicology studies have been completed in two species. The company also has initiated a six-month animal toxicology study to support six-month dosing of VX-950. This has to be completed before a six-month dosing study can begin in humans, but a Vertex official said the company expects to be able to start a six-month study in humans by the end of 2006.

Vertex is expanding its Phase II program for VX-950 with more than one combination study in a total of >500 additional patients. These new trials will include the following arms (not necessarily all in the same trial). The first data from any of these are expected in 1Q07, and that will be 24-week data from Arm C and/or E.

A. **Triple therapy** (VX-950+peg-IFN+RBV) for 12 weeks, followed by double therapy with peg-IFN+RBV for 12 weeks, and then another 24 weeks of post-treatment follow-up (total 48 weeks). A 12-week post-treatment (at Week 36) viral load assessment is planned, with SVR assessed at 24-weeks post-treatment (Week 48).

B. **Triple therapy** (VX-950+peg-IFN+RBV) for 12 weeks, followed by 9 months (36 weeks) of double therapy with peg-IFN+RBV, which is then stopped and patients are followed for another 6 months (24 weeks), (total 72 weeks). SVR will be assessed at 24 weeks post-treatment (Week 72).

C. **Triple therapy** (VX-950+peg-IFN+RBV) for 12 weeks and no additional therapy, with follow-up unspecified. There will be a 12-week post-treatment assessment (Week 24).

D. **Control – standard-of-care therapy** (peg-IFN+RBV) – for 48 weeks, and then follow-up for 24 weeks (total = 72 weeks). SVR will be assessed at 24 weeks post-treatment (Week 60).

E. **Double therapy** (VX-950+peg-IFN) for 12 weeks and no additional therapy, but followed for an additional period of time. There will be a 12-week post-treatment assessment (Week 24), and SVR will be measured at 24 weeks post-treatment (Week 36).

F. **VX-950 in combination** either with peg-IFN or as triple therapy for 6 months in patients who have failed standard-of-care therapy. Additional details on this arm are not available.

A Phase III trial will be designed based on the 24-week data from one or more of these trials, but the Phase III will not actually be started until there is 36-week data (12 weeks of VX-950 and 24 weeks of follow-up). Thus, adjustments to the Phase III design can be made if the Phase II results suggest that is advisable.

So far, the peg-IFN used in the VX-950 trials has been Roche's Pegasys, but a Vertex official said the company plans to do studies "with all the interferons out there as well as other HCV drugs if they get approved or that are in late stage development." Combining two drugs that are not-FDA approved poses regulatory hurdles, but he pointed out that this is "an area of a lot of unmet need."

POLYMERASE INHIBITORS

The outlook for polymerase inhibitors is a little less certain than for protease inhibitors, but Roche may be the come-from-behind kid.

IDENIX/NOVARTIS'S valopicitabine (NM-283)

Both efficacy and safety issues were raised about NM-283. The data in treatment-resistant patients showed no improvement over peg-IFN+RBV at the doses going forward, though another trial in treatment-naïve patients showed comparable efficacy at 200 mg as at 800 mg (an effective dose that was discontinued for safety reasons). The safety issues are GI toxicity and possibly pancreatitis.

Final end-of-treatment data and SVR data from the 48-week, 178-patient, randomized, multicenter, active-control, Phase IIb trial of NM-283 in peg-IFN-α-2a + ribavirin non-responders (at ≥12 weeks) with HCV-1 will be available in 2H07, but the 24-week results were presented at EASL. In this trial, patients were discontinued on NM-283 unless they had an HCV RNA reduction of ≥0.5 log at Week 4, ≥1.0 log at Week 12, and >2 log at Week 24.

Sixty patients discontinued by Week 24: 19% who failed to have a viral response at either Week 4 or Week 12, 8% for adverse events (only one of which was on 400 mg), and 7% who withdrew consent for other reasons. The trial is ongoing, with 118 patients who continued past Week 24. One patient in the 800 mg monotherapy arm discontinued due to GI side effects.

Side effects in this and in a trial in treatment-naïve patients led to a protocol adjustment, eliminating the 800 mg dose by moving those patients to lower doses (a maximum of 400 mg), but this occurred after Week 24 in the non-responder trial. All 13 patients with HCV RNA >1000 IU/mL were discontinued. A second protocol amendment allowed patients to remain on treatment up to a maximum of 72 weeks or until PCR was undetectable.

In the 24-week data, there was no statistically significant efficacy at the 400 mg dose, raising questions about the viability of this drug at the doses now going forward. Four patients (3%) discontinued due to GI side effects, which included vomiting and dehydration, and there were 24 serious adverse events, including anemia, dehydra-tion, one case of pancreatitis, and one case of gram-negative bacteremia secondary to a urinary tract infection. A researcher also reported "sporadic elevations of amylase, lipase, AST, and ALT." He said there were more severe GI side effects in another study in naïve patients than in this study.

There were three serious adverse events that led to the dose reduction in the ongoing Phase IIb trials (one trial in treatment naïve patients and another trial in treatment-resistant patients) from 800 mg to 200 mg or 400 mg. Two were serious nausea and vomiting within the first 12 weeks, and the third was a case of pancreatitis.

- In the treatment-naïve trial, some of the 800 mg patients had their dose reduced to 400 mg, and some had it reduced to 200 mg. Patients already on 200 mg did not have a dose change.
- In the treatment-refractory trial, the 800 mg patients were reduced to 400 mg, making two separate 400 mg arms, since there already was a 400 mg arm.

Besides the one case of pancreatitis, **the concern is pancreatic enzyme** (amylase and lipase) elevations in patients. Apparently, there were "transient" elevations of these enzymes in a number of patients. The questions will be (1) whether the FDA views pancreatic enzymes as equally worrisome as liver enzyme elevations, and (2) whether the elevations will lead to additional cases of pancreatitis in a larger patient population.

Idenix sources insisted that the side effects are not cumulative and do not occur late, so there is not a concern that side effects will occur later at lower doses compared to the 800 mg dose.

- The expectation is that this drug will be used as part of triple therapy (with peg-IFN + ribavirin, protease inhib-itor + ribavirin, or polymerase inhibitor + ribavirin).
- A drug-interaction study of NM-283 + ribavirin will start before July 1, 2006.
- The next data on NM-283 are expected at AASLD in October 2006 in Boston.

On a more positive note, the data from the dose-finding Phase IIb trial in naïve patients were positive and appear to indicate that the 200 mg dose is as effective as the discontinued 800 mg dose in naïve patients. (*See chart on page 9*)

Where does NM-283 go from here? A researcher said the GI toxicity side effect needs to be investigated further, an investigators meeting will be held soon, and a dose-interaction study will start shortly, and if that shows no interaction with ribavirin, then triple therapy will be evaluated. He said drug resistance is being monitored, but no rebounds in monotherapy have been observed that would suggest clinical drug resistance. However, another source pointed out that there was interaction between ribavirin and DDI (Bristol-Myers

24-Week Post-Treatment Results of Phase IIb Trial of NM-283 in Peg-IFN Failures

Measurement	NM-283 800 mg QD monotherapy n=21	NM-283 400 mg QD + peg-IFN QW n=41	NM-283 400 mg QD titrated to 800 mg QD + peg-IFN QW n=41	NM-283 800 mg QD + peg-IFN QW n=41 *	Peg-IFN QW + RBV retreatment n=34
HCV RNA mean log change from baseline	0.46	2.45	2.99	3.29	2.27
>2 log reduction in viral load	0	56% (Nss)	73% (p<.01)	71% (p<.01)	47%
PCR negative	0	17%	12%	24%	18%
Adverse events					
Any	95.2%	100%	100%	100%	100%
Nausea	66.7%	73.2%	80.5%	80.5%	32.4%
Vomiting	47.6%	48.8%	51.2%	78.0%	8.8%
Diarrhea	33.3%	31.7%	61.0%	34.1%	14.7%
Fatigue	14.3%	51.2%	48.8%	61.0%	64.7%
Headache	9.5%	38.0%	36.6%	28.3%	26.5%
Decreased appetite	23.8%	12.2%	19.5%	26.8%	14.7%
Anemia	0	7.3%	4.9%	14.6%	23.5%
Neutropenia	0	22.0%	22.0%	24.4%	11.8%

*None of these patients continued beyond Week 12

12-Week End-of-Treatment Results of Phase IIb Trial of NM-283 in Naïve Patients

Measurement	Group A 3 weeks peg-IFN monotherapy, then by 800 mg NM-283 n=34	Group B * 200 mg NM-283 continuously n=34	Group C 400 mg NM-283 followed by 800 mg NM-283 n=34	Group D 800 mg NM-283 continuously n=36	Group E Peg-IFN followed by 800 mg NM-283 n=35
HCV RNA reductions at Week 4	1.87	2.92	3.12	3.67	3.18
HCV RNA reductions at Week 12 (log_{10})	4.27	3.93	4.32	4.46	3.99
PCR negative at Week 12 (100% of patients)	70%	71%	77%	77%	65%
PCR negative at Week 16 (~75% of patients)	83%	73%	76%	80%	67%
Adverse events					
Nausea	53.1%	61.3%	78.1%	83.3%	81.8%
Vomiting	28.1%	29%	46.9%	N/A	N/A
Discontinuations by Week 12	18 (14 for adverse events, mostly GI)				
Serious adverse events by Week 12	8 (all at 800 mg): 2 attributed to NM-283 or the combination of NM-283 and peg-IFN, including renal insufficiency and pancreatitis				
Grade 3-4 lab abnormalities	9 patients with elevations of AST (at 800 mg) 2 patients with lipase elevations (at 800 mg)				

*** This is the only dosing group that did not have a dose modification due to the protocol changes.**

Squibb's Videx, didanosine), a nucleoside reverse transcriptase inhibitor – symptomatic mitochondrial toxicity (symptomatic hyperlactatemia and pancreatitis) – and he suggested this may explain the need for drug-drug interaction studies with ribavirin before proceeding to triple therapy.

ROCHE'S R1626. This nucleoside analog is only one of several polymerase inhibitors that Roche has in development, but it is the furthest along. Dr. Nick Cammack from Roche Research in Palo Alto CA said Roche has identified more than 70 polymerase structures. Dr. Cammack said, "For us polymerase is a very attractive target…and the nucleoside analogs are particularly interesting. They are less likely to have drug-drug interactions, and they have less potential for rapid drug resistance compared with other antivirals (such as protease inhibitors)."

Doses from 500-1500 BID have been tested, and it reportedly has shown high efficacy and high selectivity *in vitro*. Roche also plans to test even higher doses. Phase II combination therapy clinical trials are planned to start in 3Q06.

The interim (14-day) results for two of four doses were presented from a randomized, placebo-controlled, multicenter, multiple ascending dose study in chronic HCV-1 naïve patients in Australia. Dr. Cammack said sequencing of isolates has not yet but will be done with respect to viral load.

One expert described the response at 1500 BID as "variable," but most questions about this data centered on the drop in hemoglobin (0.8 mg/dL more than peg-IFN). Dr. Cammack said, "It was mild. We will continue to watch it carefully. What we do know is that it does not seem to be due to hemolysis."

Roche has a helicase in preclinical development for HCV as well as other polymerase inhibitors, including:

- R1656 in preclinical development.
- R7128.
- Unnamed agent in preclinical development.

Interim Results of Ascending Dose Study of R1626

Measurement	Placebo n=5	500 mg BID n=9	1500 mg BID n=9
C_{max}	---	3.7	9.8
T_{max}	---	2.9	3.6
AUC	---	23.8	66.6
Elimination half-life	---	25.6	22.9
Mean viral load change at Day 14	---	---	-1.2 log (range 0.5-2.5)
Mean ALT change	---	---	-33 U/mL (Down ~50% from baseline)
Adverse events			
Any event	9 events	4 events	23 events
Headache	1	5	7
Dizziness	0	2	2
Fatigue	1	0	2
Herpes simplex	0	2	0
Back pain	0	0	2
Change in hemoglobin	Down ~0.5	Down ~1.3	Down ~1.3

TOLL-LIKE RECEPTORS (TLRS)

There are at least 10 TLRs in humans, an expert estimated. Following is information on two in development for HCV.

ANADYS/NOVARTIS'S ANA-975, a TLR-7

A data progress update on a 28-day international (including U.S.) study in HCV is expected in summer 2006. Anadys declined to release the names of any researchers. ANA-975 reportedly induces IFN and a wide variety of other cytokines but decreases circulating IFN. An Anadys official said the HCV RNA log drop is comparable to peg-IFN.

Asked how ANA-975 compares to Coley Pharmaceutical's Actilon (CPG-10101), an Anadys official said, "Ours is a small molecule and theirs is a large molecule. We believe their drug works by activating TLR-9 with the result of circulating cytokines. We act on TLR-7, and it is the drug that circulates, not cytokines, so I think we will have fewer side effects – if you believe it is the circulating cytokines that cause side effects."

COLEY PHARMACEUTICAL GROUP'S Actilon (CPG-10101), a TLR-9

Positive interim (4- and 12-week) data were presented from a 74-patient, five-arm Phase Ib trial of Actilon (by subcutaneous injection of 0.2 mg/kg QW) alone and in combination with peg-IFN + ribavirin in treatment-refractory HCV patients. Patients who achieved >2 log reduction in HCV RNA were eligible to continue on Actilon therapy for a total of 48 weeks and will be followed for an additional 24 weeks to monitor for SVR. The study found Actilon appears to improve early antiviral activity and may have some synergism with peg-IFN+RBV. The moderator at the session called it an "interesting agent."

Pyrexia, fatigue, headache, and nausea were the most common side effects, and they were mostly mild or moderate. The key additional adverse event with Actilon was injection site reactions, and these were mostly mild. Six patients withdrew from the trial, and two of these were drug-related, one of which was a serious adverse event – injection site cellulitis and necrosis in a patient on Actilon+peg-IFN. The other was a case of rash. Two patients withdrew consent, one was non-compliant, and one was lost to follow-up. There was one additional Actilon-related serious adverse event at Week 12, an immediate hypersensitivity with Actilon+peg-IFN.

A randomized, 48-week, 90-patient Phase II study is currently enrolling patients looking at Actilon (0.2 mg/kg and 0.5 mg/kg) + peg-IFN+RBV in HCV-1 patients who failed to respond to treatment with peg-IFN+RBV. Interim results are expected by the end of 2006.

4-Week and 12-Week Phase Ib Results of Actilon

Measurement	Peg-IFN + RBV n=15	Actilon + peg-IFN+ RBV n=14	Actilon + peg-IFN n=16	Actilon + RBV n=15	Actilon n=14
Week 4					
Rapid virologic response	13%	50%	31% (p=0.050)	0	0
Week 12					
HCV RNA undetectable	13%	50%	13% (p=0.050)	0	0
Early virologic response	60%	86%	50%	20%	0
HCV RNA mean log reduction	2.33 $\log_{10}$	3.26 $\log_{10}$	2.4 $\log_{10}$ (p<.050)	N/A	N/A

INTERFERONS

PEG-INTERFERON (peg-IFN)

An Italian retrospective database study compared Schering's Peg-Intron (peg-IFN-α-2b) and Roche's Pegasys (peg-IFN-α-2a) in 187 HCV naïve patients. The researchers concluded that the SVR rate is similar in naïve patients, but a lower relapse rate was observed with Peg-Intron, and they thought that deserved further study.

Peg-Intron vs. Pegasys

Measurement	Peg-Intron n=122	Pegasys n=65
SVR		
All	60%	54%
Genotype-1	33%	33%
Genotype-2	83%	78%
Genotype-3	75%	50%
HCV RNA <800,000	71%	61%
HCV RNA ≥800,000	44%	46%
Relapse rate		
All	5%	17%
Genotype-1	10%	17%
Genotype-2	2%	11%
Genotype-3	0	33%

Dr. John McHutchison of Duke University, an investigator for many drugs, spoke at both a Valeant- and a Schering-sponsored session. The takeaway messages were:

- **IDEAL.** This ~4,000-patient, 48-week study comparing Schering's Peg-Intron (peg-IFN-α-2b) + Rebetol (weight-based RBV) and Roche's Pegasys (pegylated interferon-α-2a) + Copegus (semi-weight-based RBV) is now fully enrolled, and data should be available in late 2007. This FDA-mandated trial is powered to show a 7% difference between the two regimens, and the primary endpoint is SVR at 24 weeks.
  - High dose Peg-Intron (1.5 mg/kg/week) + Rebetol (800-1400 mg).
  - Low dose Peg-Intron (1.0 mg/kg/week) + Rebetol (800-1400 mg).
  - Pegasys (180 µg/week) + Copegus (1000-1200 mg/day).

➢ **Substudies of IDEAL, including**:

- >50% of patients in each arm will get the same dose of ribavirin, so an apples-to-apples comparison will be possible.
- COMPARE-II, an ethnic substudy, looking at African-Americans.
- PROFILE, a neuropsychiatric substudy being done in conjunction with psychiatrists at Emory University, looking at the development of neuropsychiatric side effects during IFN + ribavirin therapy by examining relative power of a series of candidate genes (such as serotonin-, norepinephrine-, and dopamine-related proteins).

HUMAN GENOME SCIENCE'S albuferon

Sources were generally optimistic about the outlook for albuferon (a recombinant protein consisting of IFN-α genetically fused to human albumin) – but as an every other week (Q2W) dosing schedule, not monthly as had been hoped. Still, doctors insisted that Q2W dosing is an improvement over current dosing regimens and would lead to widespread use. A knowledgeable source said Human Genome Science has already done a deal for albuferon with a major pharma, but he declined to say which one.

A competitor said, "What struck me is that they started with a low dose and need to push the dose for efficacy…I think coupling to albumin might interfere with how the interferon works with the virus. IFN needs to interact with receptors on the virus, and albumin may interfere with that. I showed the press release to our investigators, and they were not impressed with the efficacy."

In a pre-specified, 12-week, interim, intent-to-treat analysis of a Phase IIb trial in HCV-1 patients, albuferon + RBV met the secondary endpoint (EVR at Week 12), with the maximum antiviral activity observed at the 1200 µg dose administered Q2W. Control (peg-IFN-α-2a + RBV) and the 900 µg Q2W dose had comparable response rates, and the 1200 µg Q4W dose had a lower response rate. The differences in the albuferon cohorts vs. peg-IFN started at 4 weeks and continued increasing through Week 12.

The primary endpoint (SVR at Week 24) will be evaluated when that time point is reached. Higher doses also are being investigated.

12-Week Albuferon Phase IIb Results

Measurement	Peg-IFN + RBV n=114	Albuferon 900 µg Q2W + RBV n=118	Albuferon 1200 µg Q2W + RBV n=118	Albuferon 1200 µg Q4W + RBV n=118
Secondary endpoint: EVR at Week 12	88.6%	83.9% (p=0.2981)	90.0% (p=0.7340)	75.9% (p=0.0108)
HCV RNA reductions at Week 12	---	---	Most	Least
HCV RNA <LOQ	68%	69.5%	74.5% (p=0.1517)	53.4%
ANC ≤750 x10^3/uL	20.2%	22.0%	21.8%	6.0%
Hemoglobin <12 g/dL	64.9%	69.5%	73.6%	51.7%
Hemoglobin <10 g/dL	11.4%	12.7%	17.3%	6.0%
Antibodies				
Emergent anti-IFN antibodies	17.5%	1.8%	4.2%	2.6%
Neutralizing antibodies	0.9%	0	1.8%	0
Emerging anti-HAS antibodies	---	0.9%	N/A	1.7%
Safety				
Discontinuations due to adverse events	2.6%	2.5%	7.3%	6.9%
Interferon dose reductions due to adverse events	3.5%	3.4%	3.6%	3.4%
Headache	49.1%	52.5%	46.4%	54.3%
Fatigue	46.5%	43.2%	54.4%	45.7%
Pyrexia	38.6%	42.4%	48.2%	39.7%
Insomnia	29.8%	25.4%	15.5%	22.4%
Depression	15.8%	8.5%	9.1%	11.2%
Pruritis	24.6%	21.2%	10.9%	24.1%
Rash	8.8%	10.2%	12.7%	9.5%
Cough	13.2%	23.7%	31.8%	18.1%
Dyspnea	5.3%	9.3%	20.9%	6.9%

Albuferon Phase IIb Results

Measurement	Albuferon 900 µg Q2W + RBV n=23	Albuferon 1200 µg Q4W +RBV n=24	Albuferon 1200 µg Q2W + RBV n=24	Albuferon 1500 µg Q2W + RBV n=22	Albuferon 1800 µg Q2W + RBV n=22
HCV RNA mean reduction at Week 8 (log_{10})	1.7	1.2	1.9	1.6	2.8
Patients with ≥2 log reduction in HCV RNA at Week 8	48%	29%	42%	32%	64% (p<.05 vs. other cohorts combined)
RNA negative at Week 24	35%	25%	29%	32%	N/A
Neutropenia	24%				

Dr. Stefan Zeuzem of Germany, who presented the data, said there "seems to be a trend in terms of psychological side effects in favor of albuferon, and the SF-36 mental health domain suggested less impact on psychologic well-being across all albuferon groups. In terms of efficacy, he said that at Week 12, the 1200 µg Q2W dose showed the highest HCV RNA negativity and the most rapid time to achieving that. Adverse events were comparable across all albuferon cohorts. Dr. Zeuzem said peg-IFN-α-2a (Peg-Intron) was chosen because it had the most comparable PK profile. He concluded, "Efficacy and safety may be at least as good as peg-IFN-α-2a, with an improved dosing schedule."

Data also were presented from a 115-patient, Phase IIb, dose-finding trial that started with the same three albuferon doses, but, based on safety data, was expanded to include two higher doses – 1500 µg Q2W and 1800 µg Q2W. An investigator predicted that the final dose will be 1500 µg Q2W. He said the side effects with albuferon are similar to peg-IFN, but fewer, and they are similar across doses. Very few patients in the trial had to be dose discontinued. He said, "It looks great in terms of ease and comfort for patients…There is a hint that it shows so far a 20% SVR rate in peg-IFN non-responders. That is a pretty nice jump…This was not an efficacy trial, but the preliminary data show it clearly has a role in non-responders to peg-IFN…IFN will be around for the next several years, certainly, and I think albuferon will be a good substitute for peg-IFN."

OCTOPLUS/BIOLEX'S Locteron. This is a microsphere formulation of IFN. It is not pegylated or albuminated. Rather, it is injected subcutaneously and then releases gradually over a two-week period. Biolex makes the IFN, and OctoPlus makes the microspheres. The company says it is ready to start Phase II in chronic HCV in a dose-ranging study. A PK/PD study presented at EASL found that Locteron is well tolerated from 20-320 µg, with an adverse event profile similar to Peg-Intron.

ROCHE/MAXYGEN'S R7025. This is an enhanced interferon from gene shuffling technology that Roche is developing with Maxygen. Human clinical trials are expected to start later this year. R7025 was described as a potentiation molecule that can be pegylated much as Pegasys is – "and maybe even better," Dr. Cammack said. He also said production could easily be scaled for R7025.

R7025 Compared to Pegasys

Measurement	R7025	Pegasys
Gene expression	100	1
Antiviral activity	50	1
Immunomodulatory activity	6	1
Dendritic cell maturation	10-50	1
Antiproliferative activity	2-9	1
Potential immunogenicity	No alerts	No alerts

RIBAVIRIN (RBV)

Dr. Zeuzem cited four key patient populations where ribavirin dosing is particularly relevant:

1. Patients with chronic HCV and normal ALT. This population may have a shallower response to IFN, so he said a higher ribavirin dose should be considered.
2. Obese patients with chronic HCV. Higher weight patients have lower SVR with IFN, but when ribavirin is added, the SVR is similar to normal weight people.
3. ESRD, where ribavirin is not typically used at all, but where good, SVR has been shown.
4. Older patients with chronic HCV. This is a growing population where there is a concern about using ribavirin. The older the patient gets, the less SVR there is to IFN, but the ribavirin dose has to be cut, so Dr. Zeuzem said it is important for the elderly to have a safer ribavirin to keep the virologic response rate in those patients.

So far, alternatives to ribavirin have failed, but doctors had high hopes for Valeant's viramidine.

- **Vertex's merimepodib (VX-497)** – development was discontinued.
- **Roche's CellCept (mycophenolate mofetil, MMF)** – studies to date have failed to demonstrate any benefit at all by adding this to IFN.

VALEANT'S viramidine

Doctors would like to see this agent developed – as a weight-based replacement for ribavirin – and Valeant officials continue to say they haven't given up on it, but sources are dubious that it will ever (a) make it to market, or (b) find much use. A U.S. hepatologist said, "Viramidine is dead. The FDA will require new studies. And with the dose they would have to use, they will have too many side effects." The head of the VISER-1 and VISER-2 data safety monitoring board, Dr. John McHutchison of Duke University, said, "It is clear that viramidine needs to be dosed by body weight…In retrospect, we did the study in the wrong way." Dr. Zeuzem said, "Viramidine isn't dead, but they have to start from scratch and use the appropriate dose (weight-based)… Ribavirin still has at least 8-10 years of life." A French doctor said, "The drug is active. It would get approved with another study."

In the 971-patient VISER-1 trial viramidine (at 600 mg BID) was shown to be safe, but the trial failed to meet its primary endpoint – non-inferiority to ribavirin after 24 weeks of follow-up. European and American doctors agreed that regulators will not approve viramidine either in Europe or the U.S. without additional trials. A post-hoc analysis of the data suggested that the efficacy results could have been skewed by geography or patient weight, but most sources believe those explanations are not sufficient to overcome the trial results.

Asked why viramidine failed to show equivalency to ribavirin in VISER-1, a speaker said, "It is clearly a story of interaction between body weight and efficacy. Sixty-one percent of patients at a higher dose of viramidine (19-22 mg/kg) had SVR."

Will Valeant invest the time and money in additional trials for a weight-based dose? Company officials and investigators said the company will wait for the VISER-2 results later this year before making a decision, but the consensus is that the ~900-patient VISER-2 trial will look much like VISER-1.

The big advantage to viramidine is the lower rate of anemia (5% vs. 24% with ribavirin in VISER-1). Viramidine is a liver-targeting drug, while ribavirin targets red blood cells. The C_{max} is 302 mg/L at 400 mg BID, 380 mg/L at 600 mg BID, and 412 mg/L at 800 mg BID.

MISCELLANEOUS

➢ **DEBIOPHARM'S Debio-025.** This is a non-immuno-suppressive cyclosporine for HCV in early development.

➢ **WYETH'S HCV-796.** A randomized, placebo-controlled, double-blind, single-center, 14-day Phase Ib ascending, single-dose trial tested 25-2000 mg BID in 56 healthy volunteers. A researcher said this oral agent has very low bioavailability and is very well tolerated. Headache is the most frequent adverse event, and there were no abnormal lab values and no GI side effects. It also is safe to give with or without food. AUC reached a maximum at a dose of 1000 mg, and <10% is renally eliminated.

Efficacy data will be presented at DDW 2006 from a multiple ascending dose study. (That data may show that on Day 4 about 25% of patients had ≥2 log reduction HCV RNA.) Wyeth also plans to test this in combination with peg-IFN as a double therapy and is considering triple therapy. After the Phase I double combination data, the company will plan its phase II strategy.

HEPATITIS B (HBV)

About 350 million people worldwide have chronic hepatitis B, which is the 10th leading cause of death worldwide. In Europe, nearly a million new cases of chronic HBV occur each year. HBV is transmitted the same way as HIV – from an infected mother, infected blood, or unprotected sex.

Many people don't know they are infected and feel perfectly healthy. Even routine liver function blood tests may indicate that everything is okay; asymptomatic patients need to be identified through a special blood test (HBsAg). Experts said this test only needs to be done once in a person's lifetime unless the person engages in at-risk behavior, in which case the test should be done routinely or the person should be vaccinated.

Chronic HBV is responsible for up to 80% of all liver cancer, but liver cancer can be prevented by treating HBV and suppressing the virus, even though there is no cure for hepatitis B. While there is a vaccine to prevent HBV, vaccination has no effect on the disease once a person has it. Hepatitis B is also more aggressive than hepatitis C. Early HBV DNA suppression reduces the risk of resistance.

Current therapies for HBV:

➢ **BRISTOL-MYERS SQUIBB'S Baraclude (entecavir),** which has good viral suppression and no resistance in treatment-naïve patients at two years. Even though Baraclude is FDA-approved, European HBV experts – at Bristol-Myers Squibb-sponsored sessions – stressed that it has possible safety issues (carcinogenicity at high doses in rodents).

New, 96-week data presented at EASL from the 638-patient, multicenter, Phase III BEHOLD trial showed Baraclude was more effective in viral suppression in naïve HBeAg(-) patients than lamivudine, and no evidence of Baraclude resistance was identified in patients without lamivudine resistance substitutions at baseline. (*See chart on page 14*) The 48-week data from BEHOLD have already been presented and published.

14-Day Phase Ib Study of HCV-796

Measurement	Placebo	25 mg	50 mg	100 mg	250 mg	500 mg	1000 mg	1500 mg
PK parameters								
C_{max} (ng/mL)	---	48.4	105	179	297	550	696	875
T_{max} (hr)	---	4.0	3.5	3.5	2.7	2.7	2.2	2.0
$T_{1/2}$ (hr)	---	6.1	33.8	41.2	58.4	38.1	73.4	61.8
AUC (ng hr/mL)	---	527.8	2854	4835	8540	10417	18800	18814
Adverse events								
Abdominal pain	0	0	0	16.7%	0	0	0	0
Anemia	0	0	0	0	0	16.7%	0	0
Arthalgia	14.3%	0	0	0	0	0	0	0
AST/SGOT increase	0	0	0	0	0	16.7%	0	0
Creatinine phosphokinase increase	21.4%	0	16.7%	0	0	16.7%	0	0
Headache	7.1%	0	0	16.7%	33.3%	33.3%	16.7%	0
Tachycardia	0	0	0	33.3%	0	0	16.7%	0

96-Week Results from BEHOLD Trial

Measurement	Entecavir 0.5 mg QD n=325	Lamivudine 100 mg QD n=313
Cumulative probability of response (HBV DNA <300 copies/mL)	94% (p<.0001)	77%
ALT normalization	89% (p<.05)	84%
Any adverse event	76%	80%
Serious adverse events	6%	8%
Discontinuations due to adverse events	2%	3%
ALT flare on-treatment	<1%	2%
ALT flare off-treatment	8%	11%

Researchers reported that the majority of Baraclude patients respond in the first year. Continued therapy with Baraclude maintained virologic suppression and provided additional benefits in terms of ALT normalization. Patients with recurrent viremia during the off-treatment phase experienced rapid viral load reduction when retreated. A speaker said, "What happens after discontinuation remains a question. The study was not designed to answer that, and, personally, I don't believe you can eradicate HBV with nucleoside analogs, and you really have to continue to suppress HBV DNA."

A doctor in the audience wanted to know if the results are clinically significant even though they are statistically significant, given the higher cost of Baraclude vs. lamivudine. A speaker responded, "That's a tough question…The bottom line is that today we are quite convinced that suppression of HBV DNA is probably the prescription for reduction of cirrhosis and hepatic carcinoma. The easiest way to do it is swallowing a nucleoside analog pill…At least I could say that suppression of viral load is a major goal of our treatment."

➢ **GILEAD SCIENCES' HepSera (adefovir dipivoxil),** which has low resistance and is well tolerated. However, an expert said this also has low viral suppression, only modest HBeAg seroconversion at 48 weeks, and a warning for nephrotoxicity at a higher dose.

➢ **GLAXOSMITHKLINE'S Epivir (lamivudine),** which reduces the progression of cirrhosis and liver cancer but is less effective as resistance occurs. An expert said this has good initial viral suppression and is well tolerated but cumulative resistance occurs and there is suboptimal long-term efficacy.

➢ **Interferon.** An expert described this as effective in a subset of patients but has to be administered parenterally and has significant side effects.

New agents in development for HBV include:

ANADYS'S ANA-380 (LB80380)

ANA-380, a direct-acting antiviral agent, is designed to overcome the problems of current HBV drugs, such as resistance to lamivudine. It was described as "very different" from ANA-975, so, conceivably both ANA-975 and ANA-380 could be combined, and the company is taking both forward. Early data indicate ANA-380 looks very promising, with mean HBV DNA at 12 weeks reduced 2.8-4.1 $\log_{10}$, which compares to 2.1 for Gilead's HepSera (adefovir)10 mg, and to 5.1 for Bristol-Myers Squibb's entecavir (1 mg).

In an earlier Phase I single-center study, ANA-380 led to a >3 log reduction in HBV DNA at all doses >60 mg/day. At EASL, researchers reported on a 65-patient, open-label, ascending-dose, Phase II study of ANA-380 – a prodrug of a phosphonate nucleotide analog of guanosine monophosphate – in hepatitis B patients refractory to lamivudine. The trial was conducted entirely in Hong Kong, and all patients were Asians. All patients got lamivudine for the first 4 weeks, then ANA-380 monotherapy for 8 weeks, then lamivudine on an open-label basis for another 12 weeks. A researcher said that the effect appears across almost all the genotypes, that no clinically relevant adverse events were observed during treatment, and further development will focus on lower doses. The next Phase II trials are expected to use the 90 mg/day and 150 mg/day doses.

An Anadys official said the company is in the process of developing a complete cross-resistance profile for this against all known resistance variants, and that data will be presented in the future. He added, "We're optimistic that (ANA-380) will have a nice spectrum of activity and will be distinguishable from adefovir." So far, there are no U.S. investigators.

Results of Phase IIb Trial of ANA-380

Measurement	ANA-380 30 mg/day n=13	ANA-380 60 mg/day n=14	ANA-380 90 mg/day n=14	ANA-380 150 mg/day n=12	ANA-380 240 mg/day n=12
Completers	13	13	13	0	0
Ongoing patients (on adefovir)	13	13	13	11	12
Mean HBV DNA at Week 12	8.3	7.9	7.9	8.0	8.2
ALT normalization	3 patients	2 patients	5 patients	5 patients	2 patients
Mean HBV DNA reduction ($\log_{10}$)	2.8	3.2	3.9	3.9	4.1
PCR negative at Week 12	1-2 patients in each cohort				
Any adverse event	20	11	10	4	4
Adverse events not believed related	18	11	10	4	2

GILEAD SCIENCES/TRIANGLE PHARMACEUTICALS/ BUKWANG'S clevudine (L-FMAU)

This pyrimidine nucleoside analog was reported to have no cytotoxicity or mitochondrial toxicity, a long half-life, rapid absorption, and mostly renal excretion. In a 48-week, open-label, Phase III trial in naïve patients with chronic HBV, all patients who achieved negative HBV DNA by PCR at Week 24 showed sustained viral and biochemical responses during maintenance therapy with a lower dose. Adverse events – myalgia, diarrhea, abdominal pain, anorexia, pruritis, and rash – were mostly mild and transient. At Week 48, it showed significant viral suppression and biochemical improvement. Doctors in the audience – and the moderator – weren't convinced and want to see longer-term data.

IDENIX/NOVARTIS'S telbivudine

Final data from the pivotal Phase III GLOBE trial, a two-year, 1,367-patient, international study, will be presented at AASLD in October 2006. At EASL, researchers presented the preliminary 52-week results from GLOBE. They concluded:

- The majority of HBV suppression at 24 weeks is linked to clinical efficacy at the end of one year.
- Early viral suppression is useful and a predictive value for one year.
- Telbivudine is superior to lamivudine at 52 weeks, regardless of DNA response at Week 24.
- HBV DNA levels at Week 24 can be used for treatment decisions.

At a briefing sponsored by Idenix, a speaker was asked if he would recommend telbivudine, which can be taken with or without food, for all HBV patients, he said, "We are now defining groups of patients who need treatment…It also depends on the drugs you have. With very potent drugs you may treat patients with even lower viral loads, to suppress, absolutely suppress, the viral load. With drugs up to now, we couldn't do this because usually patients in a tolerance immune phase do not respond…With a normal ALT and a high viral load, they usually do not respond to current drugs. With the new, more potent drugs, probably we should try to treat those patients…And we have to convince patients that there are many patients who don't need any treatment…If these results are confirmed in GLOBE, telbivudine will be an excellent first-choice treatment…Resistance to lamivudine is a difficult issue, and we'll probably need different drugs (for refractory lamivudine patients). We should avoid lamivudine resistance by using other drugs with less capacity of resistance."

Asked to compare telbivudine to adefovir and entecavir, a doctor said, "Telbivudine is superior in viral diminution. There are no trials comparing these drugs, and we only have the results of entecavir after 12 weeks…Probably entecavir is potent, but there are some concerns on carcinogenicity in rodents. That is something to be cautious about, especially if you are treating for long periods of time." Another doctor said, "One thing that is apparent from the entecavir study is that it leads to profound DNA suppression, but the rate of conversion was only 20%, which is relatively low. Telbivudine's rate of conversion is higher, about 30%." A third said, "As more drugs become available (to treat HBV), the challenge will be how to use them in combination or which patients should get monotherapy because a percent will benefit from monotherapy, which is easier and cheaper."

Researchers also presented the initial results of a randomized, open-label, multicenter, 52-week trial comparing telbivudine and adefovir in HBeAg+ patients with chronic HBV. By Week 24, they reported a significant reduction in HBV DNA and significant viral suppression. There is a question whether the data are applicable to everyone since >90% of the patients in the study were Asian.

Preliminary 52-Week Phase III GLOBE Results

Measurement	HBeAg+	HBeAg-
Mean log HBV DNA reduction	6.5	5.2
Non-detectable by PCR	60%	88%
HBV DNA		
<QL	91%	94%
QL – 3 log	9%	67%
3 - 4 log	30%	40%
>4 log	5%	10%
Normalized ALT		
<QL	90%	83%
QL – 3 log	89%	74%
3 - 4 log	80%	63%
>4 log	54%	36%
Viral breakthrough		
<QL	1%	0
QL – 3 log	4%	7%
3 - 4 log	9%	17%
>4 log	14%	44%

Preliminary 24-Week Analysis of Telbivudine vs. Adefovir

Measurement	Telbivudine 800 mg/day for 52 weeks n=45	Adefovir 10 mg/day for 52 weeks n=90
Primary endpoint: HBV DNA at Week 24 (mean log_{10} change)	-6.3 (p<.01)	-4.97
ALT normalized	61.4%	62.9%
Secondary endpoint: PCR undetectable	38.6% (p<.01)	12.4%
Q - 3 log	11%	10%
3 - 4 log	18%	17%
>4 log	32%	61%
Treatment failure	5%	42%
Safety		
Any adverse event	60%	58%
URT	11%	9%
Flu-like symptoms	9%	8%
Bone pain	13%	4%
Diarrhea	13%	4%

MISCELLANEOUS

GLAXOSMITHKLINE'S eltrombopag. This drug is in development to treat ITP, and it looks very interesting. The company is exploring eltrombopag in three indications:

- **ITP**, where a Phase III trial (50 mg) has started.
- **CIT** (chemotherapy-induced thrombocytopenia), where a Phase II trial is being designed.
- **Chronic liver disease**, with the first interim data from a 33-patient Phase II trial presented in a poster at EASL. In that double-blind, placebo-controlled study HCV patients with related thrombocytopenia were administered 75 mg QD for 4 weeks (prior to antiviral therapy with peg-IFN+RBV) to determine the effect of eltrombopag on platelet counts. High response rates were observed across all three doses tested, and no patients discontinued due to adverse events. Interim data suggested a potential for eltrombopag to increase platelet counts and allow subjects to initiate interferon-based antiviral therapy.

Phase II Trial of Eltrombopag in HCV-Associated Thrombocytopenia

Measurement	Placebo n=5	30 mg QD n=8	50 mg QD n=9	75 mg QD n=11
Responders at Day 28	0	6%	78%	90%
Median platelet count	38	119	174	246
Subjects initiating antiviral therapy	0	75%	78%	100%
Serious adverse events	0	0	0	0

♦