Problems with Protease Inhibitor Development Plans

Written for the National Task Force on AIDS Drug Development, February 23, 1995, Washington, D.C. Discusses development and research of protease inhibitors with recommendations for future clinical trial design.

Problems with Protease Inhibitor Development Plans

by

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edited by Mark Harrington

for the

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Virus load may well prove to explain, in part, the mechanism for drug action. However, current studies of very limited size and moderate treatment effect make it difficult to interpret the impact of adjustment for virus load on the estimated crude treatment effect... Larger studies should be planned to produce stable estimates of treatment effects.

-- Seth L. Welles, Ph.D.

Markers must be evaluated in comparative studies... [You] need large studies to obtain sufficient clinical events though markers may be studied in carefully selected subsets of patients without much loss in efficiency.

-- Michael Hughes, Ph.D.

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Contents

1. Introductionby David Barr

The development of protease inhibitors offers the National Task Force on AIDS Drug Development the opportunity to best fulfill its promise of shepherding a coordinated effort to develop new drugs for HIV disease. If it rises to this opportunity, the Task Force could help coordinate the development of a new and possibly exciting class of drugs that may lengthen and improve the quality of life of millions of HIV-infected people. By articulating the significant problems we face in developing the protease inhibitors and then implementing a coordinated strategy towards addressing these problems, the Task Force could present an approach to drug development heretofore unseen, an approach that would place quality research and concern for public health above all other concerns. If the Task Force fails to take this opportunity today, then it has failed in its overall mission, has wasted precious resources and time, and most importantly, has lied to those of us so desperately looking for leadership in the fight against AIDS.

This report provides an analysis of the current development plans for protease inhibitors and raises many of the important questions that must be addressed if these drugs are going to be developed responsibly. Once again, a small and committed group of community activists has undertaken the challenging task of collecting the information, analyzing it and asking the questions that remain outstanding. The first and most puzzling question is why are we the only ones doing this? Certainly there are statisticians who can question the statistical power of the proposed studies better than we. Certainly there are researchers who can more expertly articulate concern about the appropriateness of the control arms. There must be virologists who can debate what the impact of lowering levels of virus may have on disease progression. There are several government agencies which are charged with the responsibility to protect the public health by devising, implementing and reviewing drug development plans to ensure that these potentially important new therapies are studied not just quickly, but well. Yet here is the first report that takes a comprehensive approach to protease development. We had to fight just to ensure that the agenda of this meeting would allow for a full discussion of the issues raised herein. How sad, how discouraging.

After attending a meeting at which the largest drug company in the world presented its meager plans for protease development, I wondered how those doctors felt about their work. Do they believe that their trials are sufficient to answer critical questions about their drug? Does the FDA believe that sufficient data exist to approve drugs on the basis of changes in viral load? If not, what are they doing about it? Is the NIH comfortable about having no role at all in this effort, one of the most important aspects of AIDS drug development? The Task Force presents us with our only opportunity to look at these drugs, not as individual products in a race toward the marketplace, but as a class of therapies about which several issues must be resolved if we are going to be able to use any one of these drugs effectively. The Task Force can articulate the issues and determine which parties can best answer each specific question. These questions include not only the validation of the markers, the issue of cross-resistance, and the appropriate statistical power of the clinical studies, but also questions about drug supply, expanded access, standards for accelerated approval and a framework for post-marketing study design, execution and analysis.

Some individuals within the community of which I am a part, in their desperation, seem willing to forego any standards whatsoever, just for the opportunity of putting a new pill into their mouths. I, for one, am not willing to accept a standard of care based on desperation. I still want to know if the pill works. Not just for myself, but because there are tens of millions of people who will

be faced with making these difficult treatment decisions long after I am gone. They will want to live long, productive lives. They will want to believe that when their doctor gives them medicine, it will work. We have a responsibility to them. A responsibility to learn from our mistakes in the past. A responsibility to look past our own desperation, ambition or greed. A responsibility to the public health.

Early access and accelerated approval of protease inhibitors must be part of any development plan. Let me say that again, lest someone did not hear it the first time -- early access and accelerated approval of protease inhibitors must be part of any development plan. The Task Force can play an important role in determining how best to provide access quickly, given the high demand and the real problems of drug supply. However, just as I am desperate for the earliest access possible to these drugs, I am equally desperate to know what a moderate and time-limited treatment-induced reduction in viral load means, how best to approach the problems of drug resistance, and how to obtain meaningful information about using these drugs in combination with the existing standard of care. Very few other parties in this debate seem committed to obtaining this information. If that is not true, then prove it. Begin here, at the place where all the relevant players are represented. If not here, then where? If not now, then when?

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2. Update & Commentary on Protease Inhibitor Development Plans

a. Roche INVIRASETM Saquinavirby Mark Harrington

Background. ACTG 229, a randomized comparison of AZT/Saquinavir and AZT/ddC to AZT/ddC/Saquinavir showed that the three-drug regimen conferred modestly better virologic and immunologic effects than the 2 two-drug regimens (which were virtually indistinguishable) in 302 patients enrolling with 50-300 CD4 cells/mm3 and over 4 months' previous AZT use. The sponsor, Hoffman-LaRoche, conferred with FDA in summer 1994 over whether these results justified an application for accelerated approval. Since only 99 patients received the three-drug regimen, and there was no large-scale safety data and just one small phase III trial underway, the FDA demurred, and Roche mounted an extensive phase III program.

Phase III Development Plans. Roche is the only HIV protease inhibitor developer whose phase III program is well underway. Its trials are the largest designed to date, and it is the only company to have committed to a meaningful (N=4,000) expanded access program, which is slated to begin in the third quarter of 1995. There are two pivotal studies. Both were redesigned last summer, partially in response to concerns raised by us and others. The first-line trial was complicated and enlarged, and the second-line trial simplified and shrunk. These changes are ample evidence that Roche, FDA and others with a stake in the process, including the community, are struggling for a resolution to many complex issues: How should protease inhibitor trials be designed? How should they be controlled? How large should the trials be? What level of treatment effect should the trials seek to distinguish? Unfortunately, there has never been a systematic discussion of the comprehensive development of the protease inhibitors as an entire class. Instead, questions with significant public health consequences for all people living with HIV are being addressed individually and privately by Roche, Merck, Abbott and other protease developers. The time has come to evaluate protease inhibitor development as a whole, as a single class of new drugs, the evaluation of which poses common dilemmas and problems.

* First-line therapy. Roche's SV14604C is a four-arm, 80-week study enrolling 3,300 antiretroviral-naive participants with CD4s between 50-300; they are being randomized to AZT vs. AZT/ddC vs. AZT/Saquinavir vs. AZT/ddC/Saquinavir. Primary endpoints include time-to-first AIDS-defining-event or death, and secondary endpoints include viral burden, CD4 levels, emergence of viral resistance and syncytium-inducing phenotypes, weight gain, Karnofsky performance status and quality of life. 800 participants will receive more intensive virological monitoring. A planned interim surrogate marker analysis will be submitted to FDA whenever Roche is ready to apply for accelerated approval (probably in the third quarter of 1995).

* Second-line therapy. NV14256B is a three-arm, 48-week study randomizing HIV-infected patients with between 50-300 CD4 cells who received previous AZT therapy or are AZT-intolerant to ddC monotherapy, ddC/Saquinavir or Saquinavir alone. This is both a pre-marketing validation study for Saquinavir and a postmarketing validation study for ddC (HIVIDTM brand zalcitabine). Participants will be stratified by baseline CD4 levels (>/<100; only 25% of subjects will be in the lower stratum. Primary and secondary endpoints are the same as in SV14604C. A planned interim analysis will occur when 150 patients per treatment group (half of the study's target enrollment) have received at least 16 weeks of treatment. Presumably, the surrogate marker results of this analysis, if they resemble those seen in ACTG 229, will be bundled off by airmail to Rockville for consideration by FDA for accelerated approval. The impact of accelerated approval on the ability to complete the two pivotal Roche trials remains unclear.

* Advanced patients: expanded access. Roche has committed to opening, in the third quarter of 1995, an expanded-access program for HIV-infected persons intolerant to or refractory to approved and available therapies (the nucleoside analogues). Initially drug will be available for 4,000 participants. We salute Roche for responding positively to our request for a salvage protocol in July 1994, and the community consensus statement on a Saquinavir Parallel Track from November 1994. Roche is considering enrollment through a lottery process. Hopefully Roche will take steps to ensure that people with the greatest need (or at greatest risk of death) will receive priority treatment.

Comments. Clearly, of the two studies, the larger, first-line therapy study appears likelier to lead to a clear answer about clinical benefit. SV14604C was designed to have a 90% power to detect an increase in event-free rates over 80 weeks from 75% to 82.5% (a relative reduction of 30%) between two treatment groups, or from 82.5% to 89% (37% relative reduction). Differences of this magnitude have yet to be seen in first-line active-controlled studies (with the exception of ACTG 114). With 750 participants per arm, this study is certainly larger than previous active-controlled antiretroviral efficacy studies, however, and we can certainly salute Hoffman-LaRoche for at least moving (if not far enough) in the right direction towards larger studies which are more likely to detect moderate but clinically meaningful treatment differences.

The second-line study, NV14256B enrolls a population similar to that which enrolled in ACTG 155, substituting Saquinavir for AZT in its design, and a similar (N=900) sample size. As we all remember, ACTG 155 showed that, overall, there was no difference between AZT alone, AZT/ddC or ddC monotherapy in delaying progression, but that AZT/ddC was 50% more toxic overall. The trial lacked the power to make finer distinctions, though unplanned subset analyses suggested that there might be additional benefit in people with CD4>150, and additional harm in people with CD4<50, to combination vs. monotherapy. Surrogate marker changes on Saquinavir-containing regimens in ACTG 229 do not suggest that Saquinavir will outperform AZT in ACTG 155, and so the ability of NV14256B to

provide clear evidence of clinical benefit appears slender. The study designers assumed, based on event rates from ACTG 116B/117, 155 and CPCRA 002, that 12-month progression-free rates on ddC monotherapy would be 75% (25% would progress in 12 months). They powered this study to detect an increase in progression-free rate from 75% to 88%! This would amount to a relative reduction in event rate of 52%, which could be detected with 90% power, and assuming a 20% dropout rate. It strikes us as exceedingly naive and over-optimistic to plan for such a dramatic clinical difference when the only second-line study to show clinical benefit to date, ACTG 116B/117, showed only a relative difference of 15% in time-to-AIDS event or death. The tragedy here is that if a much smaller benefit (or harm) occurs, this trial will be unable to measure it, and we will be plunged back into the disputatious world of post hoc subset trend analysis.

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b. Merck L,735-524 (MK639) by Michael Ravitch

Background. Merck's HIV protease inhibitor, L-735,524, or MK639, has been in clinical trials since February 1993. Since then, the company has discovered several important facts: L-524 produces a profound initial drop in viral load (as measured by viral RNA), but this antiretroviral effect is as limited in duration (12-24 weeks before return to baseline values) as that seen with the ostensibly weaker (less profound initial drop) nucleoside analogue RTIs. The company has shown uncontrolled data suggesting that CD4+ T cells may return to baseline at a slower rate than viral RNA levels, but this has yet to be proved, and its clinical significance, if real, remains unclear. The drug seems to be well-tolerated, although at the dose chosen for phase III studies (800 mg q8h), some patients have experienced kidney stones as well as so far aclinical hyperbilirubinemia. Low-level resistance develops to L-524 after 12-24 weeks of therapy, and high-level resistance after 48-52 weeks (although high-level resistance was seen in one patient receiving 600 mg q6h after only three weeks). High-level resistance appears to be associated with cross-resistance to many other HIV protease inhibitors as well. Whether resistant strains are as virulent or pathogenic as wild-type strains remains to be determined.

Phase III Development Plans. We have been discussing the prospective phase III plan with Merck for nearly a year, over which their study proposals have become progressively less rigorous; over this time, the original director of clinical research in infectious disease, Dr. John Ryan, has left the company. On February 10, 1995, Merck outlined their latest, and thus far worst, plans -- trials which seem to have been designed to answer the concerns of the marketing division, not of scientists. According to Merck representatives, they plan to file for registration of L-524 in the summer or fall of 1996, which by a marvelous coincidence overlaps with the exact time at which their new dedicated facility will come on-line and be ramping up for mass production of L-524. In the meantime, they lack sufficient drug either to rigorously study the agent, to prove efficacy clinically, or to provide expanded access. Merck's first four phase III studies are expected to begin within the next two months, while studies 5-6 will take longer to launch, and may not even begin until 1996:

* AZT-naive patients. Two studies are planned. Each will enroll 700 patients, and each will compare AZT vs. L-524 vs. AZT/L-524.

1. The first study will use clinical endpoints in Brazil; patients will be given PCP and TB prophylaxis. Participants will enroll with 50-250 CD4 cells/mm3

2. The second study will use surrogate endpoints in the USA and Europe, enrolling patients with 50-500 CD4 cells/mm3.

* AZT-experienced patients. Three studies are planned:

3. 450 AZT-experienced patients with 50-350 CD4 cells/mm3 will be randomized to d4T vs. L-524 vs. d4T/L-524, using surrogate endpoints.

4. 90 patients with 50-400 CD4 cells will be randomized to receive AZT/3TC, L-524, or AZT/3TC/L-524, using surrogate endpoints.

5. 900 AZT-experienced patients with undetermined CD4 levels will be randomized to an undetermined regimen and followed for the development of clinical endpoints. This study has no design; Merck doesn't know what an appropriate control arm would be; it will begin at an unspecified time, possibly not until 1996.

* Advanced patients. One study is planned:

6. 150 people with fewer than 50 CD4 cells/mm3 would be randomized to AZT/3TC vs. L-524 vs. AZT/3TC/L-524 (after study 4 has defined the safety of these regimens and followed for surrogate or clinical endpoints.

* Pre-approval expanded access/parallel track. Merck has no current plans to provide L-524 to people with advanced disease who are refractory or intolerant to available therapies before the time of marketing approval

Comments. Merck & Co., the world's largest and wealthiest pharmaceutical company, has invested significant resources in AIDS research. Merck has a solid reputation for scientific integrity and community good will. For all of these reasons, we are especially disappointed to see that Merck's phase III program for L-735,524 (MK639) turns out to be so weak and small, even when compared to those of its competitors in an admittedly disappointing drug development contest: 1) Merck is the first manufacturer of a major antiretroviral agent to refuse to undertake an expanded access or parallel track program for seriously ill patients who have failed standard therapies. 2) Although they have assured us for years that they would pursue studies with clinical endpoints, this has become their last priority. Their current crop of studies is poorly controlled, badly designed, inadequately powered and unlikely to provide useful information on the drug's clinical utility. 3) Merck's envisioned NDA package will be smaller than that for any previous antiretroviral. At the same time, Merck is pursuing a broader indication (CD4 from 0-500, AZT-naive and experienced) than ever seen before. This would allow them to sell their product to patients along the entire spectrum of HIV disease without proving that the drug works for any of them.

Merck's phase III program will enroll approximately 3,000 patients, of whom 2,000 will receive L-524. This is only half the number who will receive Saquinavir on Roche's expanded access program! It is smaller than the number of patients enrolled in a single Roche study, SV14604C. The Merck NDA database will be smaller than that of any antiretroviral yet approved, with less safety data, no parallel track, little or no clinical efficacy data, and only a modicum of partially-controlled randomized surrogate marker data. The most urgent question for Merck to answer, from a public health perspective, is whether its drug produces a clinical benefit in AZT-experienced, symptomatic patients, who will be the first, and the most, to use it. Apparently, however, that question is Merck's last priority, as they have not yet even bothered to design that trial,

and have shuffled it off to an indefinite future. Instead, Merck has substituted an ill-assorted array of arbitrary control arms and unrealistic statistical assumptions. Even though the duration of antiviral treatment effect seems to be not much longer than that of AZT (albeit deeper), Merck's trials seem to be based on the assumption that L-524 will be dramatically more effective. If these estimations are overly optimistic, these trials will not tell us if the drug is worth taking. Undoubtedly the drug will be licensed midway through 1996 all the same, and taken by tens of thousands of people with HIV, many of whom might develop high-level cross-resistant viral mutants within a year, possibly rendering the entire class of protease inhibitors worthless to them.

Consider first the trials designed to show whether L-524, used alone or with AZT, should be first-line therapy in HIV disease. Merck's two first-line studies ask different questions with different endpoints in different populations, but each enrolls 700 patients -- another striking coincidence which makes us wonder whether these trials are scientifically driven or determined by available drug supply and marketing imperatives. Trial 1 is the only one being launched in the near future designed to produce data on clinical efficacy. Yet it is smaller (N=700, with only 233/arm) than the only two active-controlled antiretroviral studies which have yet shown a clinical difference between arms (ACTG 114 and 116B/117), and smaller than others which failed to define such differences (e.g., ACTG 116A, 155, 193). Moreover, study 1 will take place in Brazil, where the standard of medical practice is quite different from that in the USA. No pivotal efficacy trial for an AIDS drug has ever taken place outside the USA. The differences in clinical care between the two countries might distort the applicability of the Brazilian data to the US population. Merck says it moved the trial to Brazil because it has more advanced patients (CD4<250) who are AZT-naive. The study may produce coherent data, but will not answer many real-world questions faced by patients and physicians in the USA.

Trial 2 does not address clinical endpoints, but is calculated to enlarge a marketing opportunity without elucidating difficult answers about L-524's efficacy. We wonder why Merck doesn't consider combining these two studies into one, which would give more statistical power to answer the scientific question, combining sites in North America, Brazil and Europe, and nesting the surrogate marker studies (virology and immunology) within a 1,400-patient study including clinical endpoints.

Inevitably the great majority of the thousands of patients who will take first advantage of an accelerated approval for L-524 will be patients with lower CD4 counts who have already tried available antiretroviral therapies. The difficulties of designing appropriately controlled trials for this population are well-known. But the importance of studying this group cannot be overstated. Results from first-line patients will not necessarily apply. Merck's trial 3 uses d4T (vs. L-524 vs. both) in a completely arbitrary manner. There is no clinical data yet to suggest that d4T is optimal or even acceptable as second-line therapy (it is approved as salvage). Patients are unlikely to comply with such an arbitrary regimen, and may tend to create their own nucleoside regimen, thus distorting the study. Comparing three unknown values (d4T, L-524, and both) does not constitute a controlled trial. In December, Merck said this trial would enroll 900 patients. Now it is slated to enroll 450. Either the drug became twice as effective in the last four months, or Merck found a new, more pliable statistician.

Trial 4, the "probe" study of AZT/3TC vs. L-524 vs. all three, is an exploratory effort (like its successor, 6) to ratify the latest nucleoside craze as a potential "best" second-line therapeutic regimen. Controlled data on this

combination remain scanty, and clinical data non-existent. If AZT plus 3TC can be considered "standard therapy" on the basis of surrogate marker data on a handful of patients, we have truly passed into the land of the mad. This triple combination remains as speculative and arbitrary as any other.

Trial 5, the second-line trial with clinical endpoints (N=900) remains the most critical trial in Merck's development plan, because it reflects the population most likely to use the drug after approval. In the rush to study randomly chosen combinations, this trial has been postponed indefinitely. It is a pity that Merck does not understand that this will be the truly "pivotal" trial when it comes to determining how its drug will be used (and be most useful) in the real world.

Trial 6 is a pathetic micro-mini effort (N=150, with expansion planned just around the time of approval) which purports to compensate for the lack of an expanded access program. It offers 150 lucky ones among the desperately ill, many of whom have become intolerant to AZT and most of whom have failed it already, a two-thirds chance of being randomized to AZT again! The study demonstrates ignorance and incomprehension about the needs, experience and condition of people with fewer than 50 CD4 cells. The trial represents poorly-conceived research and is the farthest thing from compassionate access. Merck should reconsider this proposal and either randomize people to two doses of L-524, with complete freedom as to their other antiretroviral therapy ("standard-of-care"), or collaborate with other protease inhibitor sponsors to randomize participants to one of several protease agents (again over nucleoside choice). Best of all, Merck could simply include patients with CD4<50/mm3 in one of its larger studies of AZT-experienced people.

In studying the AZT-experienced, all the options are imperfect. However, Merck has chosen the worst of all possible options, rather than simply using the tiny amount of drug they have to mount one or two well-designed studies (for example, one study of 1,500 in AZT-naive patients, and one study of 1,500 in AZT experienced), which would use the same amount of drug they now anticipate having for six studies. The first-line study could use the AZT control as currently, and the second-line study could use the standard-of-care control arm, as planned by Abbott and Glaxo. The FDA approved Abbott's and Glaxo's use of this control arm strategy, and presumably would approve Merck's as well, if Merck only asked. In public, Merck's Dr. Emilio Emini criticized the standard-of-care control as unworkable, but in private he said Merck would use it if they had enough drug (T. Smart, personal communication). They do! It would make the trial more attractive to patients, increase compliance, come closer to real-world conditions for the use of this drug, and increase the chance that Merck's phase III trials would provide useful clinical information. The virology, resistance and immunology studies which they now plan in trials 2, 3 and 4 could be nested within the larger clinical endpoint studies.

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c. Abbott Laboratories ABT-538by Derek Link

Background. Abbott Laboratories has examined ABT-538, its protease inhibitor compound, in two early-phase clinical studies. The company now believes 600 mg bid is the preferred dose based on these two studies. A twelve-week phase I/II dose-ranging trial of 23 patients found ABT-538 decreased viral load levels, measured by Chiron's branch-chain DNA (bDNA) assay, by an average of two logs and increased CD4 levels on average by three-fold. Side effects observed thus

far include diarrhea (at least one episode of which occurred in 75% of trial participants), nausea and transient serum SGOT increases. Three patients at 600 mg bid had elevated SGOT levels; two of them reported prior episodes of viral hepatitis. This small study offers preliminary evidence that ABT-538 is well-tolerated and active against HIV in vivo for at least 12 weeks. Viral resistance to ABT-538 is still not fully characterized, but ABT-538-induced resistant viruses may be cross-resistant with at least the Merck compound; this has been observed in patients after six months of therapy. Although Abbott believes the 600 mg bid dose is preferred, it is conducting a 700 mg bid pharmacokinetic/safety study at Duke.

Phase III Development Plans. Abbott plans three efficacy studies of ABT-538. These studies are still in planning stages, so revision is likely. No draft protocols could be obtained.

* Advanced patients. Abbott plans a study in advanced patients with fewer than 100 CD4 cells/mm3, who have had a previous opportunistic infection, and who have had greater than nine months' experience on available antiretroviral agents. Abbott anticipates enrolling 700 patients into this study. Abbott proposes using a novel "standard-of-care" control arm for this study. Patients will be allowed to take any nucleoside analogue they wish, with the possible exception of 3TC. The patients will then be randomized to receive either ABT-538 or a matching placebo on top of their chosen nucleoside regimen. If patients progress while on study, they will be offered open-label ABT-538. The study will collect clinical and virologic endpoints. Virologic endpoints will be collected on 75 patients per arm. Abbott is in negotiations with the FDA on the CD4 cut-off for this study.

* Middle patients. Abbott plans a "middle study" of people with between 200-500 CD4s who have a moderate experience with nucleoside treatment. This study will investigate the value of switching to ABT-538 in patients who are beginning to progress but are not yet at an advanced stage of disease and who have some experienced on antiretroviral agents. Abbott anticipates 900 patients will be enrolled in this study, which is still in very early planning stages; little specific information is available on proposed designs.

* Early patients. Abbott plans a study of ABT-538 as first-line treatment in early infection [how early?], enrolling 250-300 patients. Patients will be randomized into one of three arms: ABT-538 alone, AZT alone, or the two drugs combined. No clinical endpoints will be collected in this study. The study will rely on virological endpoints. Since this study will examine people with early disease, Abbott proposes a viral load threshold for participants in the study. Participants must have at least 15,000 copies of the virus, which is the lower limit of detection with available assays.

Comments. Abbott's proposed "standard-of-care" control arm is a novel and well-considered approach to clinical trials design. Allowing patients their choice of available, approved antiretroviral agents may reduce patient non-compliance and withdrawal, and increase the attractiveness of the study. It also recognizes that some advanced patients use multiple antiretroviral therapies simultaneously. This study design may allow for a real-world assessment of the role of ABT-538 in advanced disease. It is critical, however, for Abbott to complete drug interaction studies before this trial can begin. While the standard-of-care control arm offers maximum patient/physician autonomy in choice of concomitant medical treatment, it must be noted that previous proposals for the use of such a control were predicated on the enrollment of a much larger sample size. In the study proposed by Abbott, there is a risk that wide heterogeneity in use of

concomitant medications will be unevenly distributed, which sometimes leads trial analysts into the temptation of post-hoc subset trend analysis. Abbott's development plans, with the exception of the study in advanced patients, do not envision collecting data on clinical events. This is a major impediment to the search for information on how to use this therapy. Thus far, Abbott has not articulated a strategy for determining the clinical role of ABT-538 in early or less-advanced disease.

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d. Agouron AG1343 by Theo Smart

Background. Agouron, in conjunction with the Japan Tobacco Company, is developing AG1343, an HIV protease inhibitor, and has completed two double-blind pharmacokinetic and safety studies. The drug seems to be well-tolerated over the short term. Moderate doses sustain drug levels far in excess of what was required to inhibit HIV in vitro, but they have no data on in vivo antiretroviral activity as yet. The two studies were in HIV-negatives in Leeds, UK. The first looked at single oral doses of 100, 200, 400 and 800 mg administered in capsules. One 100 mg dose achieved levels that stayed over the ID95 for 8 hours, and the 800 mg dose achieved levels that stayed over the ID95 for up to 24 hours. The second study looked at 400 mg q12h for 7 days vs. 300 mg q8h for 7 days. Steady-state concentrations were achieved by the fourth day, with minimum plasma concentrations 15 times the ID95. Peak levels were 50-70 times over the ID95. Feeding helps with absorption. One adverse event was noted: five minutes of nausea and flushing five hours after taking a 400 mg dose; this wasn't seen at higher doses. This is a very favorable pharmacokinetic profile compared to others seen with HIV protease inhibitors thus far; if resistance is mainly a function of sub-optimal dosing [which it probably isn't], this drug will have a competitive advantage -- if it works. The drug also has extensive tissue distribution. In animals, levels in the lymph nodes were 8 times higher than in plasma. It also gets into the brain. Will it suffer the same defeat as the Searle compound SC-52151? Possibly, if it binds to alpha acid glycoprotein, which apparently inactivated SC-52151. They haven't checked for this yet. The phase II studies will be underway before they get to it. [Curious, n'est pas?] In vitro, HIV mutants can be generated which are 125-fold less susceptible to AG1343 compared with wild-type isolates. This resistant virus would be cross-resistant to all other proteases studied other than Upjohn's pyrans, and the new Searle compound S338. The standard pattern of resistance is similar to that seen with Saquinavir; the resistant virus is 15-20-fold less susceptible to AG1343.

Phase III Development Plans. Japan Tobacco has given Agouron $6 million to complete phase I studies of AG1343, and will pay them an additional $24 million with the receipt of satisfactory results from their phase II pilot study. They appear to be in a hurry to catch up with Roche, Merck and Abbott, but have yet to start their open-label phase II study, which will be enroll 25 patients in the UK with 200-500 CD4/mm3 and plasma RNA levels above 20,000, who have taken no antiretrovirals for the past year. They will take 100 or 300 mg q8h for four weeks, with an extension if warranted. Agouron claims its compound is easier to manufacture, so it may be able to conduct larger clinical efficacy studies than its competitors.

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e. Other Protease Inhibitors

Other protease inhibitor sponsors (e.g., DuPont-Merck, KNI, Searle, Upjohn, etc.) are not yet committed to phase III development, and many of them have yet to undertake phase I studies of any kind. We await with interest the results of their planned or ongoing preliminary studies.

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3. Questions + Comments About Protease Inhibitor Development Plans

A. Virology, immunology & resistance

* What magnitude and what duration of antiviral activity in peripheral blood are necessary to produce a clinical benefit? Is a two-log reduction (in viral RNA or DNA) better than a one-log reduction if virus returns to baseline in both cases just as quickly? How long does the virus need to stay below baseline for the drug to confer clinical benefit?

* Which viral assays are most useful for guiding clinical practice? Which viral levels are markers for drug failure or a time-to-switch? Many studies have noted the temporal dissociation between a post-therapy rise in various viral markers, e.g., p24 antigen or viral RNA in plasma vs. cellular DNA in cells vs. the emergence of a resistant phenotype or genotype. Which changes tell us the most? How can these measurements be compared and validated in studies which demonstrate clinical differences between therapies?

* What magnitude and what duration of a CD4+ T lymphocyte rise in peripheral blood are necessary to produce a clinical benefit? Is an increase of 100 CD4+ T cells clinically better than one of 50 CD4s if in both cases CD4+ T cells return to baseline at the same time? How long do CD4 levels need to stay above baseline for the drug to confer clinical benefit?

* Is there a dissociation between CD4 changes and viral load changes after starting therapy with a protease inhibitor, e.g., so that while viral load returns to baseline at 24 weeks, CD4 levels remain higher for longer? If so, which change indicates failure of therapy -- viral load returning to baseline, or CD4 levels remaining above? Could the therapy have selected a viral mutant which is somehow equal in number but less virulent or pathogenic than the original wild-type strain(s)? What experiments are underway to explore this possibility?

* To what extent do viral load changes in peripheral blood reflect (or not reflect) viral load changes in lymphoid tissue (where most T lymphocytes and HIVs dwell)? Are studies underway to compare the antiviral activity of protease inhibitors in peripheral blood and lymphoid tissue?

* What is the median time to low-level resistance and to high-level resistance with the various protease inhibitors? What is the relationship between the emergence of a resistant phenotype and the return of viral levels to (or above) baseline? Do viral strains revert to wild-type when therapy is removed? What strategies can be developed to delay or weaken the emergence of resistant strains?

* How common is the emergence of high-level resistant virus strains which do not respond to other protease inhibitors (cross-resistance)? What are the

implications of high-level cross-resistance for early access, accelerated approval and broad distribution of protease inhibitors? Is it possible that, one year after the approval of the first protease inhibitor (presumably Saquinavir), that the thousands of people with HIV who took Saquinavir for one year would become resistant to the entire class of protease inhibitors? What are the public health implications of this? What studies need to be done to elucidate answers to these questions?

*

B. Clinical efficacy studies

* Are the proposed protease inhibitor phase III trials "adequate and well-controlled"? - What magnitude of clinical benefit are they powered to detect? Is such a magnitude of clinical benefit likely given what we know about their impact on viral and immunologic markers, compared to that of the RTIs? - Are they well-controlled? Are the control arms well-characterized and appropriate for the study populations? - Are their endpoints, whether laboratory or clinical, well-characterized and appropriate? - Are the studies likely to generate clear answers which will tell people with HIV and their providers not only whether the drugs might work, but whether they will work, and how to use the drugs?

* Is it more important to define an optimal nucleoside/protease regimen in phase III, or simply to show that protease inhibitor(s) plus nucleoside(s) is better than nucleoside therapy alone?

* Are studies planned using combinations of protease inhibitors?

* Are the size and statistical power of the studies scientifically driven or driven by the supply of drug?

* If the studies fail to demonstrate a clinical difference between regimens, what plans do the sponsors, FDA and NIH have to prove their clinical efficacy post-marketing?

* How diverse are the populations being studied? Are all stages of HIV disease under study? Are women, children and people of color enrolled in the studies at the proportion with which they comprise the HIV-infected population? What steps can sponsors take to ensure the involvement of all affected populations in the protease inhibitor studies? [The impact of the L524-induced bilirubin changes may be different in injecting drug users or people with hemophilia than in other HIV-infected groups; this needs to be studied now, not after approval.]

*

C. Expanded access programs

* Does the sponsor have a plan to study its drug in a large-scale parallel track or expanded access program in a heterogeneous real-world population with advanced HIV disease taking many concomitant therapies? If not, how will the sponsor monitor safety in the real-world post-marketing? What drug interaction studies are completed, underway or planned?

* In the absence of expanded access plans (e.g., Merck),how will the sponsor determine the safety of its compound among advanced HIV+ patients with symptomatic disease who are receiving concomitant medications, and who are likely to take the new compound after its licensure?

*

D. Post-marketing studies

* If the protease inhibitors are approved, as planned, under accelerated approval, with less information than ever before (less safety information even than on ddC and d4T), what post-marketing studies will industry or NIH design to define how best to use these drugs? What commitments will industry make to the FDA at the time of accelerated approval to design post-marketing efficacy studies (and other necessary pharmacokinetic, drug-interaction and laboratory-based studies)? How will FDA ensure that industry meets its commitments? What is the role of the ICC and of the NIH in planning, coordinating and carrying out post-marketing studies? What commitments will sponsors make, as part of their accelerated approval commitments, to provide drug to NIH or others for carrying out post-marketing studies designed to address clinical efficacy on the one hand, and non-critical path pathogenesis-directed studies (e.g., lymph node viral burden vs. blood) on the other?

*

4. Conclusions + Recommendations

* To the Food & Drug Administration

The FDA has approved each phase III development plan in isolation, without identifying problems and issues in common across the class of protease inhibitors. It is time for FDA to convene a public hearing on scientific and methodological issues around the development of the protease inhibitors as a class of drugs, to focus on 1) which viral markers will be used, and how they will be validated; 2) which trial designs, control arms and endpoints will be used to determine clinical efficacy; 3) the impact of resistance, and especially cross-resistance, on these development plans; 4) possibilities for pre-approval expanded access programs; and 5) a prospective discussion of post-marketing clinical validation studies now, before NDA hearings are held on accelerated approval, so that these studies may be designed and in some cases underway at the time of approval.

* To Protease Inhibitor Developers with Phase III Programs Underway

Roche should be commended for mounting the largest phase III program to date, and for committing to a 4,000 expanded access program. Roche should now begin designing realistically powered post-marketing clinical efficacy studies to confirm clinical benefit, so that these may be underway when Roche files for accelerated approval.

Merck should go back to the drawing board and rethink its plans to conducting six tiny trials, none of which is likely to even hint at clinical efficacy. Merck should use the limited quantity of drug at its disposal to conduct two larger studies (one in first-line patients and one in second-line ones down to zero CD4 cells/mm3) which address both clinical and surrogate endpoints.

Abbott should be commended for adopting the standard-of-care control arm strategy, but concerns remain about the size of its program (which is rather small), its ability to manufacture sufficient drug for approval, and its lack of an express commitment to expanded access.

* To Agouron + Other Protease Inhibitor Developers In Earlier Phases

These sponsors should take the best aspects of the previous three development plans (Roche's size and expanded access commitment, Abbott's standard-of-care control arm in AZT-experienced patients) and elaborate on these to conduct studies which simultaneously validate surrogate markers and prove clinical benefit. They should also work together on strategies to overcome or delay the emergence of cross-resistant HIV.

* To the Inter-Company Collaboration for AIDS Drug Development

The ICC has been strangely silent on a front which should be its most active. Protease inhibitor development poses unique and unprecedented opportunities to coordinate research on viral burden assays, the emergence of single-agent and cross-resistance, and coordinated expanded access programs, while reducing the resource demands on a single sponsor. The ICC should conduct pilot studies utilizing combinations of protease inhibitors and should share data and experimental procedures directed to finding out more about the emergence of resistance. Industry should also provide drug to basic researchers to elucidate the impact of protease inhibitors on pathogenesis, for example in lymphoid tissue as opposed to blood, and for other innovative non-critical path studies.

* To the National Institutes of Health

The NIH has appeared to be out of the loop with regard to protease inhibitors, with the exception of ACTG 229. At the same time, problems with large scale phase IV studies such as ACTG 175 have demonstrated that the ACTG is not configured to conduct such studies well without rethinking their design and execution. NIH needs to begin planning now for a new mechanism to conduct phase IV clinical validation studies with protease inhibitors once they reach the market, and to obtain commitments from sponsors to provide drug. The new studies should include 1) small, pathogenesis-directed studies and 2) large, but low-tech, non-data intensive standard-of-care studies carried out in community settings or with a 1-800-randomize mechanism.

* To the Community

Sectors of the HIV community are now going through an understandable period of excitement at the development of an apparently active second class of antiretroviral agents. Given the current plans for development, this excitement will subside sometime after accelerated approval once it becomes clear that these drugs are not a panacea, and pose many of the problems now posed by the available nucleoside analogues, with new problems associated with the possibility of cross-resistance. Activists must continue to work to secure not only access to these agents, but answers on how best to use them, and to ensure that the populations studied fairly represent all those living with HIV. Treatment information providers should strive for objectivity in presenting news about protease inhibitors; rather than simply recycling corporate press releases, they should subject study findings to critical scrutiny.

*

5. Phase III Protease Inhibitor Trials at a Glance

Treatments Population Endpoints

Roche2 trials underway N=4,200 + 4,000 XAP NDA filed 3rd quarter '95

SV14604CAZT v AZT/SQV N=3,300, AZT-naive Time-to-AIDS or death v AZT/ddC v all 3 50-300 CD4s vRNA, CD4

NV14256BddC v SQV N=900 AZT-exp Time-to-AIDS or death v ddC/SQV 50-300 CD4s vRNA, CD4

ExpandedSQV, N=4,000 Intolerant/failed Progression access (XAP) standard therapy Survival

Merck6 trials planned N=2,990 NDA filed 3rd quarter '96

MK-01 AZT v L-524 N=700 AZT-n Clinical endpoints v AZT/L-524 CD4 50-250in Brazil

MK-02 AZT v L-524 N=700 AZT-n Surrogate endpoints v AZT/L-524 CD4 50-500in USA/Europe

MK-03 d4T v L-524 N=450 AZT-e Surrogate endpoints v d4T/L-524 CD4 50-350in USA/Europe

MK-04 AZT/3TC v L-524N=90 AZT-eSurrogate endpoints v AZT/3TC/L-524CD4 50-400in USA/Europe

MK-05 Undetermined N=900 AZT-e Clinical endpoints regimens CD4s unknown Location unknown

MK-06 AZT/3TC v L-524N=150 AZT-e Endpoints unknown v AZT/3TC/L-524CD4 <50 Location unknown

XAPNone planned NA NA

Abbott 3 trials planned N=1,700 NDA to be filed in 1995-6

AB-01 ABT-538 v placebo N=700 AZT-e Clinical endpoints + standard-of-care CD4 < 100 Crossover option

AB-02 Switch to ABT-538 N=700 AZT-e Clinical endpoints? v remain on SOCCD4 200-500 Surrogate endpoints

AB-03 AZT v ABT-538 N=250-300 AZT-nSurrogate endpoints v AZT/ABT-538 vRNA > 15,000 Final design unknown

XAPNo plans disclosed NA NA