1 Can we do more substantively? We have
2 identified the issue. I don't think that any of us
3 have got any more of an answer yet, though. I
4 think Dr. Cornetta put it as well as anyone could.
5 DR. WILSON: I think you are right that
6 this is a difficult issue which we probably won't
7 be able to come to a definitive answer on today,
8 and a number of important points have been raised
9 for our own internal consideration and discussion.
10 Probably, for the sake of time, we should go ahead
11 and move on for now.
12 DR. SALOMON: Dr. Cornetta, I don't get
13 any physical input because I can't see you. Are
14 you okay with that? Again, I want to respect the
15 fact that you brought it up.
16 DR. CORNETTA: No; I don't think it is a
17 thing that you are going to be able to answer today
18 and I think the overall point, and I think that was
19 probably Carolyn, was that I think it is something
20 the FDA is going to have to think hard about and,
21 just as they went through with the retroviruses and
22 coming up with guidelines for testing, this is
23 going to be something that they are going to have
24 to struggle with.
25 I think all the appropriate comments have

at

1 been made.

2 DR. SALOMON: Then we will move on. I
3 think it would be fair to say, since I have been
4 sort of giving you guys a hard time about this
5 particular one, that I do think that you have--as
6 all the other sponsors appropriately acknowledged,
7 that this is an area of difficulty and you have
8 used what are available guidances to try and help
9 you to figure it out.

10 So I do commend you for what I think was a
11 good-faith effort, very much so, in this and it is
12 not your fault that we haven't solved it yet.

13 Are there additional in vivo studies that
14 need to be performed is c), regarding now the
15 safety testing of VRX. I think we have gone over
16 that, too.

17 DR. WILSON: I think we have really
18 covered c) and d) already.

19 DR. SALOMON: Good. I was going to try
20 and agree with that.

21 Question 3. "Please discuss whether
22 vector mobilization is considered an advantage or a
23 safety concern for the proposed clinical trial and
24 consider. Please consider the following,
25 specifically." Now we clearly had a discussion of

at

1 mobilization yesterday. I know Dr. Mulligan had to
2 leave to the airport, so we will try and remember
3 and be faithful to some of the comments that he
4 made yesterday.
5 "Are the data available from the assays to
6 assess vector mobilization by wild-type HIV
7 sufficient? Are there additional preclinical
8 studies to assess vector mobilization that should
9 be performed and, if some, discuss the optimal
10 study design."
11 Dr. Allan, we have discussed the monkey
12 study; right? So that is on the record. I make a
13 joke of it just not to take myself too seriously
14 but not to trivialize it. That was a good
15 discussion.
16 So, are there additional studies? Do we
17 think that the data here was sufficient? So I will
18 jump in there and say, yes; it was sufficient to
19 demonstrate to me that there was a lot of
20 mobilization. Again, now, we are doing adjectives;
21 low mobilization, high mobilization.
22 To me, what I calculated out in the in
23 vitro culture system, which is reasonably what has
24 been studied, was about 1000 copies per ml. I
25 wrote that down. Yes; 1000 copies of

at

1 packaged/mobilized, depending on which terminology
2 you want to use, per ml is occurring.
3 To me, that is a lot when one copy of HIV
4 theoretically can infect a cell and set off an
5 infection of a patient.
6 The studies in the mouse show that there
7 is mobilization to CD4 cells. The studies of
8 failure to mobilize to the B-cells, I would
9 suggest, are uninterpretable because there were not
10 enough CD19-positive cells, when you are looking at
11 1 or 2 percent, to find it. So I think those, you
12 would have to go back, if you want to sell those
13 studies, and do much higher injury levels of CD19
14 cells.
15 DR. ALLAN: Do other target cells need to
16 be considered there? Is there tropism,
17 necessarily, uniformly to all non-CD4-positive
18 cells so should macrophages or some other cell type
19 be considered?
20 DR. TORBETT: And that issue is relevant
21 because, as was mentioned before, you are changing
22 or stressing the envelope nature of this. If you
23 would think about it in antibody terms where an
24 antibody has to be qualified against as panel of
25 cell types, it would seem reasonable, since we are

at

1 trying to detect the nonprobable but bad thing to
2 happen, that that issue be explored a bit further.
3 DR. SALOMON: Yes; it suggests
4 experiments. Again, I don't want to get down into
5 the detail, but there are a lot of other things
6 that could be relatively simply done; for example,
7 putting EGFP into H9 and putting H9 into the--or
8 Jerkit or Mold4, different cell lines into the SCID
9 mice to see whether it was mobilization to
10 noninfected T-cells, for example.
11 Again, the details of that; all I am
12 saying is that, from my point of view, just to
13 start this, I think that you have demonstrated that
14 there is mobilization. I think the question now
15 is, unless someone says no, I disagree with you and
16 that is what I am waiting for, but if you agree
17 that there is mobilization, whether it is a little
18 mobilization or a lot of mobilization, I don't know
19 what that means in terms of the biological
20 significance of it, and therefore is that an issue
21 now?
22 Is that a problem? Are we going to accept
23 mobilization in this system.
24 DR. ALLAN: What struck me as the fact
25 that it wasn't clear to me what was being mobilized

at

1 and whether they are actually recombinants or not,
2 because the data was presented, which was good,
3 which was it directly looked at either the
4 antisense vector or--let me see; what else was
5 looked at. My consideration is whether you have
6 got some sort of recombinant in there, not that it
7 is replication-competent, but which could be, at
8 some point later, which is like a gag/pol
9 intermediate or something else, that has been
10 mobilized.
11 So not just that the vector has been
12 mobilized but anything else.
13 DR. TORBETT: I think the question is is
14 the vector getting mobilized and you are asking is
15 the vector now becoming infectious; is that right?
16 DR. ALLAN: Not necessarily infectious but
17 that, beyond the vector being mobilized, which they
18 have demonstrated, are there other things being
19 mobilized. It is just a question of terms. I
20 think it is terminology.
21 DR. TORBETT: I guess it is two different
22 questions, really. I mean, the question of vector
23 mobilization was very hard to assess in any of
24 their animal models. All I can say is it occurred.
25 To what degree, how much, is unclear to me and what

1 is coming out is unclear.

2 DR. SALOMON: So I think the suggestion

3 would be to better characterize--I think, as an

4 overall safety concern, is the idea that what is

5 happening is mixing, matching and evolution of the

6 species in the system as a model for what might

7 happen in humans.

8 I think that, to understand better the

9 mixing and matching, we go back to a discussion we

10 have already had, that we are going to need to see

11 more data in longer-term in vitro cultures with

12 both characterization--I don't want to restate what

13 we have already agreed on and restated.

14 I don't know whether I want to go into

15 saying--get into the details now because I think we

16 are then going into the study-section mode again,

17 whether you should do it in the NOD, or the NOD-

18 SCID, or how you should do it. Again, I would love

19 to have those conversations, but I don't think that

20 is appropriate for today.

21 DR. NOGUCHI: Some of this is sounding, to

22 get back into that, "We would like to see something

23 else like a nonreplicative recombinant, and an

24 assay for that." Yet there has been a discussion

25 as well, maybe that is too much to ask at this

at

1 time.

2 DR. SALOMON: I don't think that is too

3 much to ask. I don't think anybody told you that

4 was too much to ask. I think everybody here is

5 saying that we want evidence that there is not a

6 real evolution, if it is non-replicative, of viral

7 sequences in this kind of a system and, if there

8 is, I think we need to know about it and try and

9 regulate on that and consider its safety

10 intelligently.

11 DR. TORBETT: I think this is an important

12 point because we are using not a self-enacting

13 vector but something that has an active LTR which

14 can make a full-length transcript which increases

15 the chance for recombination.

16 So I think these are serious

17 considerations. I don't know which vector is

18 better, whether it is a SIN or an active, but I

19 think if you are using it as a full-length

20 transcript, then some of this information needs to

21 come out for safety concerns.

22 DR. EMERMAN: This is Mike Emerman, again.

23 It was alluded to that SIN vector wouldn't work.

24 It would be interesting to note that was actually

25 tested. I guess my sense of this is that the

at

1 antiviral effect depends on copackaging. If it
2 does depend on copackaging, it is hard for us to
3 ban vector mobilization except to have it
4 characterized.

5 DR. SALOMON: I think, in terms of an
6 assay design for assessing mobilization, I think
7 what we all agree on is that it should be done in
8 long-term, more complex, multicellular in vitro
9 cultures.

10 Now, whether or not you should also
11 include animal studies, sort of building on--you do
12 have some expertise and have been pretty successful
13 with your SCID studies. I am, again, trying to
14 articulate a decision here, or a recommendation. I
15 think that would be a positive.

16 I am not certain, though, as I said, that
17 I would insist that you do that because I think
18 that--I am not sure how that--that is science.
19 That is not necessarily simple testing.

20 DR. DROPULIC: It is an extreme amount of
21 work to do that.

22 DR. SALOMON: As I said, as my laboratory
23 does it, I absolutely agree. It is a lot of work.
24 Are we done with Question 3?

25 DR. WILSON: Part b) of Question 3 is more

at

1 specific to the study subjects.

2 DR. SALOMON: Yes; I missed that right

3 now. But you are right. So what should we do--we

4 have gotten so focussed on this first part that we

5 haven't talked enough about what is happening in

6 the study subjects which is what we are being

7 reminded of now.

8 So what should be done on the study

9 subjects in terms of looking for vector

10 mobilization?

11 DR. TORBETT: Many of the things that we

12 discussed, the technology is very similar, whether

13 it is before you put the cells in, do it in culture

14 or coming out of the patients. That is very

15 similar.

16 So I think that the same kinds of studies

17 we have discussed in the past need to be applied to

18 the patients as well. I am opening that up for

19 discussion, I guess.

20 DR. SAUSVILLE: I would echo that. I

21 think that is the logical follow-through, the issue

22 about the evolution of this virus or viruses into

23 something that--we don't know exactly what we are

24 going to see in the clinical situation.

25 I would just note that, in the long list

at

1 of things that are going to be looked for in the
2 clinical trial, I didn't go back and look, but this
3 issue of variants that emerge, I think, is very
4 important and should be captured. That would
5 include whether you mobilize some aspect of the
6 vector or whether you change the population of the
7 HIV that is running around.
8 DR. SALOMON: Dr. Zaia?
9 DR. ZAIA: I just want to say that within
10 the clinical-trial groups, AIDS clinical-trial
11 groups, that are looking at fitness of virus
12 relative to new drug additions, that technology is
13 well worked out so you are going to very rapidly
14 detect changes in fitness in this population of
15 patients who clearly will have virus in their
16 blood.
17 DR. REITZ: I think, also, you want to
18 follow the virus populations with some sort of
19 genotype analysis over a period of time. You will
20 learn stuff from it.
21 DR. SALOMON: I think that there is
22 nothing but logical follow-through here in terms of
23 saying that the same concerns we have of mixing and
24 matching viral parts leading to evolution of the
25 species is as big a concern after the treatment as

1 before. I think everyone has said that.
2 Therefore, if you agree, the advice would be that
3 it should be characterized biologically, on
4 multiple cell lines with different tropisms but,
5 also, some of it has to be done molecularly either
6 through genotyping or through specific--I think
7 what Dr. Zaia is saying is interesting because it
8 also implies that some of the things could be just
9 looking at changes in drug resistance which could
10 be done more rapidly than full sequencing and
11 trying to imply changes on that basis.
12 Is that right, Dr. Zaia?
13 DR. ZAIA: Yes, but I was just thinking
14 about fitness of the virus, per se. If we are most
15 concerned about that, we could easily do that.
16 DR. SALOMON: So fitness would be like a
17 quantitative assay that demonstrated just an
18 increase in the rate of spread through a given
19 indicator cell line. Okay; I stand corrected.
20 Dr. Long?
21 DR. LONG: I would just like the ask the
22 panel to consider what kind of assay would be
23 appropriate given the fact that they only detect
24 one variant when the screen 240-some clones
25 sequencing.

at

1 DR. SALOMON: No; you didn't get that
2 right. There were hundreds of variants. About 80
3 percent of them were changed. That is a rough
4 calculation. It was 264 clones. 240 had various
5 mutations.
6 DR. DROPULIC: No. They had all
7 deletions. Most of them were deletions. There
8 were relatively few that had the base substitutions
9 that we are seeing. 91 percent were deletions.
10 DR. COHEN: I am Ruben Cohen. I manage
11 the clean room for VIRxSYS. I would like to just
12 offer kind of a global perspective in terms of
13 patient safety. I have graduated from GTI so I
14 know a little about the patient trials there having
15 been involved in training the medical centers that
16 were involved in collaboration.
17 I also would like to say that one of the
18 reasons I am happy with the way VIRxSYS is handling
19 this is because I have also come through the
20 agricultural world. The fact that I consider this
21 vector is under a sentinel control, its expression
22 is limited to the cells that basically have some
23 activity going on with relationship to what the
24 problem is.
25 One of the lessons I would like the FDA to

at

1 be thinking about is that, having come out of the
2 agricultural world and working in molecular biology
3 there, the antisense tomato is not something we buy
4 in the market. The reason, I think, for its
5 failure is because it was under a constitutive
6 promotor, it was always expressed. It was
7 everywhere and everybody was afraid of that.
8 The fact that this has a kind of a
9 sentinel function, it only works where it is
10 needed, I think is both expressing something
11 towards both the safety and the appeal of the way
12 this product is being handled.
13 DR. NOGUCHI: I think the point is well
14 taken. However, I think that the reason that we
15 are actually having this extensive discussion is
16 that the absence of evidence is not evidence of
17 absence. The fact that this is to be a sentinel-
18 only function is, in fact, the question.
19 We agree that the scientific basis for
20 this is to have it work only in that which is
21 affected, but what biology teaches us, and, from
22 GTI, you know this as well, what we believe today
23 is not what we know to be true tomorrow and it is
24 very likely not to be what will be approved.
25 So we need to be able to go through this

at

1 in an open a fashion as we possibly can. I think
2 the fact that we have spent such a grueling set of
3 time here really going over all the pluses and
4 minuses and the pros and cons really does
5 illustrate the intense interest in being able to
6 develop something that does have this type of
7 specificity.
8 As is often said, now we are getting down
9 to the details and both god and the devil are
10 always in that. So your point it absolutely well
11 taken, but we need to be assured that, in fact, the
12 sentinel remains specific for only one particular
13 cell.
14 DR. DELPH: I have a question. If
15 mobilization occurs into other tissues, is it
16 necessary to look at viral reservoirs and
17 characterize HIV species there. I am asking that
18 because the species that you find in viral
19 reservoirs may be very different from what you find
20 in blood.
21 DR. SALOMON: I think that is fair. One
22 of the difficulties, of course, is sampling and
23 characterizing viral reservoirs. So, again, I
24 would defer to my colleagues who do HIV as their
25 primary business.

at

1 Dr. Zaia?

2 DR. ZAIA: I would suggest that that is a

3 question for the phase II study.

4 DR. ALLAN: You could actually look at

5 macrophages and see if you get mobilization of the

6 macrophages and, if you do, what effect that might

7 have on function. So I think there are some things

8 you can do even within the blood compartment.

9 DR. DELPH: You can look at semen.

10 DR. SALOMON: Yes. You can. That is a

11 point. I think we should let it stand and I think

12 Dr. Zaia's comment about whether that should come

13 in in a phase I or a phase II is also well taken.

14 I think we are done in the sense that,

15 what I was going to say is Question 4, we have

16 really covered. I think we all agree on the basic

17 principles here. I think we have also articulated

18 for you up to the edge how far we can go without it

19 getting gray.

20 Yes? Dr. Zaia?

21 DR. ZAIA: There is one aspect, though, of

22 Question 4 that I think needs to be discussed and

23 that is the safety assessment is linked to the

24 rules of escalation. The rules say that we will

25 look at 28 days and look for toxicity. If the

at

1 toxicity is not there, we will escalate.

2 I just have a problem with that. I don't
3 think 28 days convinces me that you can see some of
4 the things that we have been talking about. But,
5 more importantly, I don't even think this study
6 needs to be a dose escalation, unless you want to
7 dose escalate the transducing agent. But that is
8 not the research agent, or the investigational
9 agent.

10 So I would really encourage the sponsors
11 to rethink the design of this study because they
12 are not asking how to get T-cells expanded and
13 infused safely. I mean, there are several other
14 studies I am sure the FDA knows more about than I
15 do where they are infusing cells around the same
16 level, 3 times 10^{10}, and we all know how safe that
17 is.

18 I don't think there is anything about
19 these cells that make them more dangerous in
20 regards to infusion-related toxicity. What is
21 different about these cells is these other
22 toxicities that we are talking about which are
23 more, I guess, virological or less easy to
24 elucidate within the normal observation periods
25 that we look at in the standard trial.

at

1 So I think that is a critical question
2 that the sponsor has to contend with, I think, is
3 how can they use this dose-escalation rule for the
4 kinds of toxicities that we are most concerned
5 with.
6 DR. SALOMON: Actually, that is perfect.
7 What I was going to say is I think we are kind of
8 done with the questions. What I would like to do
9 now, in coming to a close, is for people to weigh
10 in with other things here because I have got a
11 list, too, and I wonder if some of you don't.
12 We have addressed the questions. I would
13 say that there were a couple of things that
14 bothered me. That was one. I don't think it is
15 very clear to me whether the dose escalation--and
16 the way I get it is the dose escalation is in
17 different patients. Part of me is going, well, why
18 not--you could do a dose escalation in the same
19 patient.
20 Certainly, I would echo Dr. Zaia's
21 comments that a 28-day--the things that are really
22 safety concerns to me; 28 days? No; I don't think
23 so. I would say more like three to six months.
24 DR. CHAMPLIN: Although these are not
25 dose-related issues so much.

at

1 DR. SALOMON: No.

2 DR. CHAMPLIN: So the issue of infusion
3 toxicity is sort of all you are looking for
4 realistically in the short term toxicity analysis
5 and the emergence of resistant virus, of course,
6 over a longer period of time and is probably going
7 to be dose independent. So you could sort of
8 minimize the importance of the dose escalation
9 because that is just to establish the tolerance to
10 the infusions. But, really, you are looking at the
11 sort of long-term phase-I aspects of the biology
12 of the whole approach.

13 DR. SALOMON: That is good point. But,
14 then, I might say, that you don't need 28 days to
15 find out. I guess I am a little confused on the
16 premises here. There is toxicity from infusion.
17 You know that in two or three days.

18 DR. HIGH: But if what we are talking
19 about is doing better characterization of what is
20 happening to HIV variants, you would like to at
21 least wait 28 days, probably, before you even drew
22 that blood. Then, once you have got it, it is
23 going to take a little while to characterize it.

24 So you might not want to enroll the second
25 patient before you have analyzed at least, at 28

at

1 days, what is going on with the first one.

2 DR. SALOMON: Yes. I guess what I am

3 saying is I agree with you, Dr. High, and that is

4 the conundrum. I think the way Dr. Zaia and I were

5 coming at it was 28 days is not long enough to see

6 the safety issues that we are concerned. But Dr.

7 Champlin said, but the safety issues concerned

8 with the dose escalation is simply a dose effect of

9 the infusion.

10 My response to that is, okay, good point,

11 but that is three to five days. We have got to be

12 consistent here, logically. If the concern is an

13 evolution of the viral species present, then I

14 think a couple of months is probably appropriate.

15 But that should be discussed.

16 DR. SAUSVILLE: Recognizing that that gets

17 into the issue of why the dose escalation. It does

18 lead to the protocol-design issue as to what are

19 you going to consider your endpoint here.

20 Certainly, matters related to the infusion, while

21 we don't think they are going to be a big issue,

22 they are formally something that does have to be

23 captured and scoped out.

24 Certainly, if we are looking at the

25 incidence of variants mobilization et cetera, a

1 dose response relationship to input would be
2 certainly of interest to also capture. So I guess
3 I sort of come down in the middle, but I agree 28
4 days is probably a little soon. I do believe there
5 is a role for dose escalation here and I do believe
6 that there is a role for longer periods of
7 observation before doing the dose escalation.
8 Let's put it that way.
9 DR. SALOMON: Dr. High, did that capture
10 kind of where you were going?
11 DR. HIGH: Yes.
12 DR. SALOMON: Dr. Allan and then Dr.
13 Torbett.
14 DR. ALLAN: Safety is also--you are hoping
15 to get some efficacy with this or you wouldn't be
16 doing it. But you know there is always the
17 possibility that it is not going to have a good
18 outcome. That outcome might not happen for six
19 months or longer.
20 So my question, then, is do you need to
21 rush doing dose escalation anyway. What is the
22 need to have to do it after 28 days. If this is
23 the first patient or the first three patients who
24 get this, do we want to sit back and go, okay, what
25 is going to happen, let's see what happens before

at

1 we do anymore and let's see if we get a--not to
2 look at efficacy but to look at is there an outside
3 possibility that it may not be a good outcome.
4 So I would say you want to wait.
5 DR. CHAMPLIN: You need well defined early
6 stopping criteria, what events would make you not
7 enter another patient. You need to define exactly
8 what those things are and then work out your
9 accrual of patients accordingly. So, obviously,
10 the faster you do the initial process that allows
11 additional accrual, the faster they can complete
12 the trial.
13 If you ask for a year follow up for every
14 patient before you enter another one, it is going
15 to take forever. So there has to be some sort of
16 middle ground where you have an accrual of a
17 reasonable number of patients that you can observe
18 and then make it a go/no-go kind of determination
19 should you continue the trial.
20 DR. SALOMON: Dr. Torbett and then Dr.
21 Sausville.
22 DR. TORBETT: I guess I have a little bit
23 more fundamental question. In some of the earlier
24 data, it was shown that, depending on the number of
25 integrins per cell--that is, the number of hits per

at

1 cell--you can or can't select quickly the variants
2 coming out. Am I correct?
3 DR. DROPULIC: Can you repeat that?
4 DR. TORBETT: The question is, I think you
5 showed us originally that, if you had one integrin
6 per cell, or an MOI of 10 or 5, 10 and 20, the
7 breakthrough came slower or faster.
8 DR. DROPULIC: Right. So, as you dose
9 down the vector--I am not so sure faster.
10 DR. TORBETT: I am sorry about that word.
11 DR. DROPULIC: We saw breakthrough at a
12 transduction MOI of 5 and a challenge MOI of 0.1 in
13 that Sup-T1-cell experiment.
14 DR. TORBETT: The reason I am bringing
15 this up, it comes to the whole question--and it
16 wasn't clear from the document that I had what the
17 MOI is per number of cells. But depending on the
18 number MOI per cells, even if you can get 100
19 percent and you increase the number of integrins,
20 then the time period to look for variants coming
21 out would vary. Is that logical?
22 DR. DROPULIC: At the optimally transduced
23 cells, we haven't see any.
24 DR. TORBETT: Maybe it is the way I am--it
25 is late in the day and I haven't had any more

at

1 sugar, so maybe that is part of the problem here.
2 But if you had one integrin per cell and, at a
3 certain time, you had a turnover virus, say you had
4 more integrins, less, and you had 10 integrins per
5 cell--I am just making these numbers up--and you
6 had pretty good control but it took a longer time,
7 the length of time that you would want to look
8 could very well be longer and the time that you
9 would want to sample each time would vary.
10 DR. SLEPUSHKIN: I just would like to
11 answer it. In any case, we have specification for
12 copy number per cell. That won't change during
13 escalation. So there will be about the same amount
14 of integrins on all steps of escalation. So you
15 are just changing the amount of cell injury.
16 DR. TORBETT: So the MOI is going to be
17 constant.
18 DR. SLEPUSHKIN: Yes.
19 DR. TORBETT: Just, out of curiosity, what
20 is it?
21 DR. SLEPUSHKIN: I probably will be about
22 200 as it was in the animal or the clinical
23 experiment.
24 DR. TORBETT: So it is going to be an MOI
25 of 200.

at

1 DR. DROPULIC: That is not copy number.
2 DR. SLEPUSHKIN: Not copy number. It is
3 MOI; yes.
4 DR. TORBETT: I understand, per X number
5 of cells. Okay.
6 DR. SLEPUSHKIN: Copy number
7 specifications; copy number per cell should be
8 between 1 and 10. And, in the clinical animal
9 experiments, it was 6.
10 DR. TORBETT: So is there any data
11 suggesting--well, I guess you can't control with
12 the variability. Maybe that is something that
13 shouldn't be brought up here.
14 DR. SALOMON: Unless you guys want me to,
15 I am not going to try and come to consensus on each
16 of these points. I think we have done our job.
17 But I would like to, in this kind of concluding
18 process, have everyone share with you, and with the
19 FDA staff, additional things that were not in your
20 question list.
21 So I believe my job as chair has suddenly
22 now to just making sure that everybody gets a
23 comment and everyone gets heard. So unless someone
24 is insisting that I come to consensus, I am not
25 going to.

at

1 Dr. Torbett?

2 DR. TORBETT: This is a first trial and I

3 would like to commend the company for going

4 forward. It was a pretty brave step and I think,

5 without too many boundaries, they done a fairly

6 admirable job of starting up the stairway.

7 DR. DELPH: I would like to echo that. I

8 would also like to express some concern about the

9 patient population that has been selected for this

10 trial. I really think a CD4 count of 600 as an

11 upper limit is way to high. right now, even the

12 DHHS guidelines for treatment are really not coming

13 out in favor of recommending treatment until CD4

14 counts drop below 350.

15 In the European guidelines, they are even

16 dropping them as low as 200. Generally speaking

17 and, of course, there are exceptions, patients with

18 CD4 counts of over 200 are not that ill. So I

19 would certainly--I understand the difficulties that

20 the company says that they may have in getting T-

21 cells from patients who have CD4 counts of under

22 200, but I think we need to also need to balance

23 that with the need for the patient population and

24 what is safe for them.

25 The other thing, and I don't know what

at

1 your actual inclusion criteria are for "failing or
2 discontinued HAART therapy." But I think that
3 needs to be far more clearly defined and I would
4 recommend that you define it in terms of the number
5 of drug classes that someone is resistant to. I
6 would recommend that someone be resistant to at
7 least two of the drug classes currently on the
8 market and possibly even three, but at least two
9 protease inhibitors.

10 You are going to look at people who really
11 have few, if any, drug options left. So those are
12 my major comments.

13 DR. DROPULIC: I appreciate those comments
14 and I just want to assure you that we want to work
15 with the FDA to finalize these patient criteria.
16 It is not set in stone now and your comments are
17 well taken.

18 DR. DELPH: I also suggest that you work
19 with the HIV community on that.

20 DR. DROPULIC: Okay. Yes. Thank you.
21 Yes.

22 DR. LEVINE: Let me address the issue of
23 the cell number, if I could. Once you get below
24 200 cells, there are increasing difficulties with
25 the transduction and the culture. I think if we

at

1 could make an analogy about immunologic treatment
2 in a different setting, with Cliff Lane's studies,
3 where he has given IL2 to the patients, there was a
4 real dichotomy with the effectiveness of raising
5 the CD4 count with patients who came in with a
6 count above 200 versus those that came in with a
7 count below 200; that is, there was not an
8 effective of the IL2 once you had patients coming
9 in below 200.
10 So I think, at that point, the immune
11 system has suffered what may be irreparable injury
12 and would make any trial safety and feasibility
13 more difficult.
14 DR. NOGUCHI: The question is not simply
15 one of difficulty. I will point out that
16 interleukin 2 has been actually approved for the
17 treatment of renal-cell carcinoma so that the
18 parameters of experience are far different than
19 what we are talking about here. But we do
20 understand the technical aspects of this particular
21 approach which is trying to take cells and expand
22 them. There very well may be areas that we will
23 need to really fine tune.
24 DR. CHAMPLIN: They are few and far
25 between, but the availability of identical twins

1 sometimes can give you sort of an opportunity to
2 treat a seriously ill patient who now has a normal
3 twin that you can get unlimited numbers of
4 leukocytes from. So, for proof of principle kinds
5 of things, that offers, sometimes, unique
6 opportunities.
7 DR. SALOMON: Dr. Golding.
8 DR. GOLDING: I just to bring a little
9 perspective from the Office of Vaccines. Our group
10 is responsible for a lot of HIV vaccine including
11 therapeutic vaccines. Most of the therapeutic
12 vaccines, as you know, are done in the context of
13 antiviral therapies. So what are sort of
14 guidelines that we are using in terms of the safety
15 monitoring of the patient.
16 Of course, just like in this case, when an
17 outcome can be either no effect or worse disease
18 progression, is the same thing we have to deal with
19 when we deal with when you deal with therapeutic
20 vaccine, that even though you gave something that
21 is supposed to help to control viremia, you
22 actually have a negative effect.
23 I think that can be seen relatively
24 quickly by measuring viral-load changes in the
25 patient. So I think it is important, once the

at

1 cells have been transduced into the individuals is
2 to really take multiple measurements of viral loads
3 over this first period, whether it is one month or
4 six weeks, and to actually have a sense of the
5 slope of viral load measurement as well, of course,
6 of CD4 counts because you are talking about all
7 kinds of toxicities.
8 There is the infusion toxicity. There is
9 potential emergence of more fit viruses that, down
10 the road, can dominate the patients. But I think
11 if you have a really adverse reaction, you have
12 something really bad in your product, what you are
13 going to see is much more rapid increase in viral
14 load.
15 For that, you have to have patients that
16 are not in the millions of viral loads to start
17 with. You have to have a window that would really
18 allow you to see some really enhanced increased.
19 DR. SALOMON: Right. The logic to what
20 you have said, Dr. Golding, though, is that you are
21 probably going to want to choose a patient
22 population that is not all that far gone and wildly
23 rising HIV viral loads on the day that treatment is
24 initiated.
25 DR. GOLDING: I wouldn't say total failure

at

1 of anti-HAART with a million copies because I
2 really don't think you will be able to see this
3 type of adverse reaction that you want to use to
4 allow you to go to the next patient.
5 DR. SALOMON: So we have to put that in
6 the context with what Dr. Delph shared with us in
7 terms of the patient selection.
8 I had some other concerns I wanted to put
9 on the table. One would be, in terms of the CD3,
10 CD28, beads, you have less than 100 beads per 3
11 million cells which means you could literally be
12 putting in thousands of beads into someone. I do
13 not buy that one at all. I think you would cause a
14 pulmonary embolus. But maybe you have experience
15 to answer that.
16 DR. LEVINE: That number was developed in
17 consultation with the FDA. There have been
18 toxicity studies done by what used to be Baxter
19 Immunotherapy infusing a large number of beads into
20 rats looking for that sort of thing. There were no
21 toxic effects at levels of beads very much higher
22 than what we are infusing.
23 We are also very much below that number of
24 100 beads per 3 million cells. What we are able to
25 achieve currently is a depletion of greater than

at

1 six logs to what we start with. So if we were to
2 stimulate 50 million cells, 100 million cells, a
3 billion cells, and have, say, a 3-bead-to-cell
4 ratio of, let's say, up to 2 to 3 billion, we would
5 anticipate easily being able to deplete six logs of
6 those beads.
7 DR. SALOMON: Another issue; I think I
8 understand why you want to activate these cells is
9 because you think you are going to have very low
10 numbers and you want to get up to these higher
11 numbers of 10^{10} and higher in your infusion.
12 Pheresis, even--I am not getting into the
13 state of the T-cells when you are really getting
14 down to 150, 200 CD4 cells. Your comments stand on
15 that. But I don't understand that. I don't
16 understand why everyone wants to ignore the biology
17 of T-cells and activate them and culture them in
18 nonphysiological concentrations of interleukin 2,
19 inject them back in the patients.
20 I mean, the whole purpose of a lentiviral
21 vector is it is incorporated into non-replicating
22 cells. So my murine Moloney leukemia virus
23 backbone, I have to activate my T-cells and I am
24 not happy about it. But you don't. For studies
25 that you are trying to maintain a normal immune

1 repertoire yet you are doing these things that I
2 don't think there is any data here demonstrating
3 what the immune repertoire is that is left in these
4 cells after you do this. I just don't understand
5 why you want you to go there.
6 DR. LEVINE: I can tell you that the
7 maintenance of the repertoire after 60 days in
8 culture is published in 1996 in the Journal of
9 Immunology showing that we do maintain the entire
10 repertoire.
11 DR. SALOMON: Defining repertoire as the
12 CD4/CD8 ratio?
13 DR. LEVINE: As 24V beta families as
14 analyzed by the CDR3.
15 DR. SALOMON: Okay. I guess, again, this
16 is not a comment coming from the chair. We are not
17 going to try and get consensus, so just a comment
18 to you. I just don't believe that these assays
19 maintain the normal T-cell phenotype. To go into
20 these initial studies at the early low-dose effects
21 where you don't have to activate and you don't have
22 to treat with interleukin 2 just seems to me you
23 are adding another variable to prepare yourself for
24 a later thing based on an assumption that you have
25 maintained your repertoire.

at

1 DR. LEVINE: I would say that we have
2 experience with these T-cell infusions, with CD4-
3 cell infusions and with bulk T-cell infusions in
4 HIV patients and in cancer patients. We,
5 ourselves, have done 51 infusions in HIV patients.
6 CellGenesis has done with CD3-28-stimulated cells I
7 am guessing 60 or 80 infusions and, in cancer
8 patients, even more.
9 So I think we just have to agree to
10 disagree.
11 DR. SALOMON: Right. That's fine. That
12 is perfectly fine.
13 MS. KNOWLES: I would like to take Dr.
14 Delph's comments one step further and caution--in
15 terms of her comments about the other
16 pharmacological agents in the research pipeline
17 because she is right. There are more things coming
18 down the pipeline. As such, I would like to
19 caution the sponsor to not put the message forward
20 that your proposed clinical trial is going to be a
21 last-ditch treatment effort for people with HIV
22 because it is one potential of the armamentarium.
23 DR. DELPH: I have another question
24 because it wasn't clear from what you have given us
25 about the protocol. Are these subjects going to be

1 on antiretrovirals or not?

2 DR. DROPULIC: They will be failing HAART

3 and, if they are not on a therapy, then they are

4 not on. But we are not going to require them to

5 come off therapy. We think that that is unethical.

6 So, if they are on one or two drugs and they are

7 failing therapy, then they can enroll in the study.

8 That is how we have defined it so far but, again,

9 we can negotiate this with the FDA to see how we

10 approach this. That is how we have characterized

11 it presently.

12 MS. KNOWLES: If they go on study drugs,

13 are you going to pay for them? Who is going to pay

14 for the drugs?

15 DR. DROPULIC: I hadn't thought of that.

16 We will think about that one.

17 DR. TORBETT: You propose in your set of

18 criteria that you follow these individuals for

19 life. Who would pay for those, assuming that the

20 company had problems?

21 DR. DROPULIC: We plan to be around a long

22 time.

23 DR. TORBETT: In any event that you don't,

24 is there going to be--I am just curious. Would you

25 take out insurance to make sure that that is done?

1 This is a serious consideration. It has been
2 discussed before. I am just curious.
3 DR. DROPULIC: If that is a requirement,
4 we can do that.
5 DR. TORBETT: I just wanted your thoughts
6 on that.
7 DR. DROPULIC: Haven't thought about it,
8 quite frankly, because we expect to be around a
9 long time.
10 DR. SALOMON: I think one of the comments
11 I have, and this is not specific to VIRxSYS, but
12 that I think the focus of these discussions in the
13 last two days have, and perhaps very appropriately,
14 focused on the biggest risk, the low-hanging fruit,
15 if you will, of the replication-competent
16 lentivirus and shuffling of the DNA species, et
17 cetera, which is fine.
18 I guess I still feel like, as part of this
19 sort of last number of comments here--it continues
20 to bother me what is happening also to the trans
21 gene that is being delivered, the payload, if you
22 will. That, to me, is as much a part of the
23 product as the issues of safety.
24 Here, you get close to this gray area of
25 "okay." But remember this is phase I and we want

at

1 safety not efficacy. But, as Dr. Noguchi said,
2 when there is significant risk and unclear benefit,
3 it is very hard to construct risk/benefit ratios
4 and I think the rules change.
5 We have been through that with
6 xenotransplantation. So, going back to that, I
7 just think that--one of my personal comments here
8 is that, at some point, we need to also consider
9 how we are characterizing the quality and the
10 integrity of the payload through all these changes
11 because everything we have talked about, up to now,
12 has not really dealt with that.
13 DR. NOGUCHI: I would actually disagree.
14 I think there has been a lot of very good
15 discussion on that, and you note that Dr. Wilson
16 and Takefman are diligently noting these things.
17 It is actually central to some of the evaluation
18 because it does appear as though the payload may
19 actually push the virus to recombine and do
20 different mutations, deletions and so forth which
21 clearly is an activity we need to be monitoring
22 even from just the safety aspect.
23 So I think we have actually gotten very
24 good advice on that.
25 DR. CORNETTA: This is Ken Cornetta. Can

at

1 I make a comment?

2 DR. SALOMON: Yes; go ahead.

3 DR. CORNETTA: I guess just maybe to pick
4 up a little bit of what you were saying about the
5 T-cell function after transduction and the
6 stimulation process. That bothered me, too, as I
7 was reading through. While a lot of cancer
8 patients have gotten T-cells that have been
9 manipulated and given back, our experience,
10 although limited, has been that those cells don't
11 function very well, at least after allogeneic
12 transplantation.

13 So, in the process, their ability to do
14 what the T-cell initially was designed to do seems
15 to be lacking. So one of the real advantages I saw
16 to lentiviruses was that you might be able to avoid
17 this in vitro stimulation. It bothered me a little
18 bit that there seemed to be a fair amount of
19 stimulation that would occur in these cells and
20 that, again, the concern that their ability to
21 function, once they got back into the patient,
22 would be not as we hoped.

23 DR. SALOMON: Do you want to comment on
24 that?

25 DR. LEVINE: Yes. We have several lines

at

1 of evidence, and I could spend an hour talking
2 about them, that, by stimulating by CD3 and 28, we
3 reverse defects of the T-cells as they are removed
4 from both cancer patients and HIV patients.
5 We have recently completed at phase I
6 study in lymphoma where we have looked at
7 intracellular cytokine response following TMA and
8 antimycin stimulation at Day 0 and at Day 12 of in
9 vitro culture and showed that we can reverse what
10 is a substantially diminished response at Day 0
11 that is increased at Day 12.
12 In the HIV setting, we have looked at
13 response to allogeneic mixed lymphocyte reaction
14 and show that we can increase in the study
15 population that we did several years ago--we
16 increased that allo-MLR response.
17 With respect to a CCR5 population that is
18 different from the population with this study, we
19 looked at CCR5 in vivo expressed on CD4 patients,
20 both before and after infusions, dose-escalating
21 infusions of 3, 10 and 30 times 10^9 and could show,
22 specifically on the CD4 cells, that we have reduced
23 the CCR5 levels.
24 Also, in vitro, we have looked at cytokine
25 production in the HIV patients both before and

at

1 after stimulation and it is very much higher. So I
2 think there is a wide spectrum of T-cell functions
3 that are improved following CD3-28 stimulation.
4 I think the point also is that it may be
5 nonphysiologic but that might be better. So, by
6 not stimulating CHLA4, by stimulating CD28
7 specifically, you are upregulating BCL2 protecting
8 against apoptosis. So there really is a wide
9 spectrum of things that are improved following CD28
10 stimulation.
11 DR. SAUSVILLE: I guess I would offer
12 that, certainly if this is successful to the extent
13 that we work through some of these issues, or the
14 sponsor works through these issues and gets into
15 the clinic, one can imagine many different flavors
16 of mix and match. That would be the subject for
17 future clinical investigations.
18 I certainly would agree that, being vested
19 in this particular way of doing it, this is one way
20 to do. And I would leave it at that.
21 DR. SALOMON: Fine. Again, as I said, we
22 had agreed to disagree a bit ago and nothing has
23 changed.
24 Any other comments or can we come to a
25 close?

1 DR. GAYLOR: I haven't said anything for
2 the last two days and feel compelled to earn my way
3 here somewhat. But, as a statistician, I need data
4 to work with. There is obviously a paucity of data
5 here for understandable reasons. It is a brand-new
6 area. So my role, I think, has changed from being
7 one that could have any scientific input to really
8 how does the man on the street feel about this,
9 somebody that not really been terribly involved in
10 this.
11 I feel very comfortable with the
12 discussions I have heard. There has been a lot of
13 thought. A lot of questions have been raised.
14 There has been a lot of good discussion and I
15 guess, again, it is a theoretical comfort because I
16 don't have a lot of data to look at.
17 But I think the committee and the people
18 involved, the research that has been done, makes me
19 feel like everything is being done that could be
20 done at this point.
21 DR. SALOMON: Again, anyone else have any
22 final comments that they would like to make?
23 DR. NOGUCHI: On behalf of the FDA, I hope
24 I could take this liberty to really thank the
25 committee, VIRxSYS especially, for being so bold as

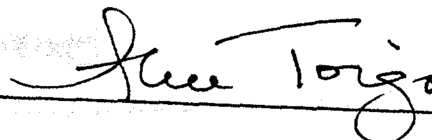
at

1 to come here and face the stings and arrows, I
2 guess, as best we can put it.
3 The committee, especially, for this round,
4 has been exceptional both in its civility as well
5 as rigor in pursuing obvious and not-so-obvious
6 questions. I would especially like to thank our
7 chair for keeping us on keel and getting us through
8 this very difficult set of questions.
9 I think that, on our side, we can say
10 that, with this advice, we are confident we will be
11 able to make the appropriate decisions to move the
12 entire field forward and we thank you for that.
13 DR. SALOMON: Thank you, Phil. Then, as
14 chair, let me speak for everyone. I think that
15 VIRxSYS, you guys did a really good job. I have
16 always said, going back a couple of years now, that
17 this committee functions the best when a sponsor
18 can step up and provide us a real protocol to look
19 at. That is when we can really deal with the kinds
20 of specifics that allow the fields to move forward.
21 You guys have done that and I respect
22 that. I also thank the sponsors who presented
23 yesterday for doing the exact same thing in a
24 situation that they even have more to lose, if you
25 will, because we were taking them on on some of

1 their things that they hadn't even brought quite as
2 far as you guys have. Again, I thank them.
3 I think everyone from the committee for
4 two to three days, depending on which group you are
5 in, hanging in there with us. To Rosanna Harvey
6 and Gail Depolito and the rest of the FDA staff who
7 worked so hard to put all this together, to get us
8 here, to take us to dinner, to move us around in
9 hotel rooms, and to the audiovisual staff and
10 everyone else involved.
11 Thank you very much. Everyone travel
12 safe.
13 [Whereupon, at 1:50 p.m., the meeting was
14 adjourned.]
15 - - -

CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



ALICE TOIGO