

UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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ANTIVIRAL DRUGS ADVISORY COMMITTEE

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PUBLIC HEARING

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Tuesday, May 5, 1998

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The Advisory Committee met in Salons C, D,
and E, the Gaithersburg Hilton, 620 Perry Parkway,
Gaithersburg, Maryland, at 8:00 a.m., Dr. Scott
Hammer, Chairman, presiding.

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PRESENT:

- SCOTT M. HAMMER, M.D., Chairman
- JUDITH FEINBERG, M.D., Member
- JAMES J. LIPSKY, M.D., Member
- ROGER J. POMERANTZ, M.D., Member
- JOHN D. HAMILTON, M.D., Member
- JOHN B. BASS, M.D., Consultant
- JOSEPH S. BERTINO, JR., Ph.D., Consultant
- RALPH D'AGOSTINO, Ph.D., Consultant
- PHILIP C. HOPEWELL, M.D., Consultant

ORIGINAL

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PRESENT (Continued):

STEVE SELF, Ph.D., Consultant

DIXIE EDWARD SNIDER, M.D., Consultant

RHONDA W. STOVER, R.Ph., Executive
Secretary

ALSO PRESENT:

DIANNE MURPHY, M.D., FDA

MARK GOLDBERGER, M.D., M.P.M., FDA

PAUL FLYER, Ph.D., FDA

THOMAS HAMMERSTROM, Ph.D., FDA

JOYCE A. KORVICK, M.D., FDA

CHARLES GORODETZKY, M.D., Ph.D., HMR

MICHAEL ISEMAN, M.D., HMR

ELAINE WALLER, Pharm.D., HMR

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C O N T E N T S

	<u>PAGE</u>
Conflict of Interest Statement	5
Introductory FDA Comments, Dr. Goldberger	7
Hoechst Marion Roussel Presentation:	
Elaine Waller, Pharm.D.	13
Charles Gorodetzky, M.D., Ph.D.	19
Michael Iseman, M.D.	51
Elaine Waller, Pharm.D.	62
FDA Presentation:	
Clinical Efficacy, Joyce Korvick, M.D.	117
Statistical Summary, Thomas Hammerstrom, Ph.D.	124
Safety Review, Joyce Korvick, M.D.	137
Tuberculosis/HIV Infected Patients, Neil Schluger, M.D.	144
Public Comment, Dr. Richard O'Brien	165
Charge to the Committee, Dianne Murphy, M.D.	180
Committee Discussion	183

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P R O C E E D I N G S

(8:04 a.m.)

1
2
3 CHAIRMAN HAMMER: I'd like to call this
4 session to order.

5 I'd like to welcome the panel of committee
6 members and guest and members, representatives of the
7 FDA and also particularly the sponsor, Hoechst Marion
8 Roussel.

9 We're here today to consider the
10 application of rifapentine for the treatment of
11 pulmonary tuberculosis under the accelerated approval
12 guidelines, and I'd like to start by having members of
13 the Committee introduce themselves for the transcript
14 and the record.

15 I'll start on my left with Dr. Bass.

16 DR. BASS: I'm John Bass. I'm from
17 Mobile, Alabama.

18 DR. HOPEWELL: Phil Hopewell from the
19 University of California, San Francisco.

20 DR. SNIDER: Dixie Snider, Associate
21 Director for Science, CDC.

22 DR. BERTINO: Joseph Bertino from Clinical
23 Pharmacology Research Center, Bassett Health Care in
24 Cooperstown, New York.

25 DR. D'AGOSTINO: Ralph D'Agostino, Boston

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1 University.

2 DR. SELF: Steve Self, Hutchinson Cancer
3 Center in University of Washington.

4 DR. FEINBERG: Judith Feinberg, University
5 of Cincinnati.

6 DR. HAMILTON: John Hamilton, Infectious
7 Disease, Duke University.

8 CHAIRMAN HAMMER: Scott Hammer from the
9 Beth Israel Deaconess Medical Center in Harvard
10 Medical School in Boston.

11 MS. STOVER: Rhonda Stover, FDA.

12 DR. POMERANTZ: Roger Pomerantz,
13 virologist, Infectious Disease, Thomas Jefferson
14 University, Philadelphia.

15 DR. LIPSKY: Jim Lipsky, Clinical
16 Pharmacology, Mayo Clinic, Rochester, Minnesota.

17 DR. FLYER: Paul Flyer, FDA.

18 DR. HAMMERSTROM: Tom Hammerstrom, FDA.

19 DR. KORVICK: Joyce Korvick, FDA.

20 DR. GOLDBERGER: Mark Goldberger, FDA.

21 DR. MURPHY: Dianne Murphy, FDA.

22 CHAIRMAN HAMMER: Thank you.

23 I'd like to turn now to Rhonda Stover, who
24 will read the conflict of interest statement.

25 MS. STOVER: The following announcement

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1 addresses the issue of conflict of interest with
2 regard to this meeting and is made a part of the
3 record to preclude even the appearance of such at this
4 meeting.

5 Based on the submitted agenda for the
6 meeting and all financial interests reported by the
7 participants, it has been determined that all
8 interests in firms regulated by the Center for Drug
9 Evaluation and Research that have been reported by the
10 participants present -- have been reported -- excuse
11 me -- by the participants present no potential for a
12 conflict of interest at this meeting with the
13 following exceptions.

14 Dr. John Hamilton has been granted a
15 waiver which permits him to participate in all matters
16 concerning Priftin. A copy of the waiver statement
17 may be obtained by submitting a written request to the
18 agency's Freedom of Information Office, Room 12A30 of
19 the Parklawn Building.

20 In addition, we would like to disclosed
21 that Dr. El-Sadr is excluded from participating in the
22 discussions and vote concerning Priftin.

23 Lastly, we would like to disclose that Dr.
24 Dixie Snider is the Associate Director for Science for
25 the Centers for Disease Control and Prevention. The

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1 CDC has contracted with the Veterans' Administrative
2 to study Priftin.

3 In the event that the discussions involve
4 any other products or firms not already on the agenda
5 for which an FDA participant has a financial interest,
6 the participants are aware of the need to exclude
7 themselves from such involvement, and their exclusion
8 will be noted for the record.

9 With respect to all other participants, we
10 ask in the interest of fairness that they address any
11 current or previous involvement with any firm whose
12 products they may wish to comment upon.

13 CHAIRMAN HAMMER: Thank you.

14 And I'd like to turn to Dr. Mark
15 Goldberger who will give the FDA introductory
16 comments.

17 DR. GOLDBERGER: Thank you.

18 I'd like to start by welcoming Dr. Hammer
19 and other members of the Committee, our invited
20 consultants, the company, and also all of the other
21 participants in the audience.

22 I'd like to start by thanking the company
23 for putting the effort together to bring this
24 application forward. TB drug development has been an
25 area where, as I'll talk about in a few moments, we

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1 have been making some efforts to try to increase the
2 amount of products that might be available, and it is
3 gratifying in this case to see a firm that has been so
4 cooperative in attempting to do this.

5 When we were preparing for this meeting,
6 I went back and actually looked at the new drug
7 application review for rifapentine, and actually a
8 couple of things came out of just looking at that
9 material. The first is just seeing how the regimens
10 as originally studied, when rifapentine was first
11 approved by the FDA, how much they change over time,
12 and it is unlikely and really would be rather
13 surprising to see a perfect regimen created the first
14 time one attempts to study the drug.

15 There has been a remarkable evolution in
16 how we use rifapentine today in terms of what was
17 originally in the studies in the new drug application.

18 The second thing that came out of looking
19 at the NDA for rifapentine was the date of that
20 review: 1971. It has been over a quarter century
21 since a new drug for tuberculosis actually was
22 approved by the FDA, and I think that that also says
23 something.

24 In an effort to try to improve TB drug
25 development -- and I should also mention that even

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1 leaving aside the perception that tuberculosis at
2 least in this country was, you know, an improving
3 problem, we should remember that it's been over ten
4 years since the CDC first began to track an increased
5 number of cases of tuberculosis even in this country,
6 to actually get an application before the Committee,
7 and we need to keep in mind obviously the impact of
8 tuberculosis on a more global perspective, and I
9 believe the applicant will talk perhaps a little more
10 about that.

11 In any case, to encourage TB drug
12 development, we have been talking with companies about
13 a couple of issues. The first is we have been
14 encouraging them to consider the use of clinical
15 trials conducted primarily overseas as a basis to seek
16 approval.

17 You will be seeing today a substantial
18 amount of data from such a study. We would welcome
19 comments about your perceptions about patient
20 population, its applicability to U.S. patient
21 population, any differences that you might note that
22 might influence outcome.

23 The second thing we have been talking with
24 companies about is the use of our accelerated approval
25 regulations for the approval of new products for

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1 tuberculosis. You've all been provided with a copy of
2 those as part of the FDA background information.

3 Fundamentally, these are regulations that
4 are to be used for serious and life threatening
5 disease when one has a new therapy that appears to be
6 an improvement over current therapy, and they allow a
7 use of a surrogate marker which is reasonably likely
8 to predict ultimate outcome.

9 The reason that we have been promoting
10 this approach, given that we can get data to confirm
11 the surrogate, is that basically one of the
12 impediments to developing new drugs for tuberculosis
13 is the duration of the clinical trials required to
14 evaluate a new drug: six months of therapy, two years
15 of follow-up, with an enrollment time that may stretch
16 the overall development to five years or more, which
17 apparently has not been considered very attractive by
18 many companies.

19 As far as the applicability in this case
20 in terms of why one might think a drug like
21 rifapentine would be an improvement over current
22 therapy, this revolves around the issue of improving
23 the ability to administer directly observed therapy;
24 in this case, therefore, the ability to reduce the
25 number of supervised doses of drug that would have to

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1 be administered.

2 It is well known that failure to adhere to
3 TB regimens is probably the most important component
4 of the development of multiple drug resistant
5 tuberculosis, which is far more difficult to treat, at
6 least a substantial morbidity and not infrequent
7 mortality.

8 Therefore, at least conceptually, a
9 therapy that made this easier should qualify as an
10 improved therapy under the accelerated approval
11 regulations.

12 The surrogate that was agreed upon in
13 discussions with Hoechst Marion Roussel was, in fact,
14 looking at the relapse rate at six months after
15 completion of therapy. This data was based upon
16 discussions at an NIH led workshop about four years
17 ago on alternative endpoints in tuberculosis trials
18 and is supported by a fair amount of data from the
19 literature, although our understanding has almost
20 always been that the trial must go to completion at
21 two years to confirm what differences in relapse at
22 six months actually pan out at two years.

23 When we talked of using this approach, the
24 major concern was, in fact, that the relapse rates
25 might be relatively close six months out after

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1 completion of therapy, but in fact, two years out
2 might be somewhat wider, and that was a legitimate
3 concern that we had, some data notwithstanding from
4 the literature.

5 As you will see, the results in this
6 clinical trial are somewhat different than that,
7 although, in fact, we believe that the early relapse
8 rates were quite useful in predicting what happened as
9 more follow-up data became available and, in fact,
10 helpful in our asking the company to provide a little
11 more follow-up data than was originally intended.

12 Ultimately we will, of course, be asking
13 you in our questions to discuss the issues of safety
14 and efficacy for rifapentine for use in pulmonary
15 tuberculosis, and from our perspective that really
16 comes down to the ability to be able to label the drug
17 as perhaps who should use it or how it should be used
18 in what patient populations.

19 As we discussed the wide variety of
20 clinical data, you will see at this Advisory Committee
21 that is the question you should really keep in your
22 minds. How could we describe end product labeling how
23 this product can reasonably be used.

24 Thanks a lot.

25 CHAIRMAN HAMMER: Thank you.

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1 I'd like to turn now to the sponsor
2 presentation. It will be led off by Dr. Elaine
3 Waller.

4 DR. WALLER: Lady and gentlemen, good
5 morning.

6 I'm Dr. Elaine Waller, Vice President of
7 North American Drug Regulatory Affairs for Hoechst
8 Marion Roussel. It is my pleasure to come before this
9 panel today, along with my colleagues, to present the
10 data on Priftin, rifapentine, for the treatment of
11 pulmonary tuberculosis.

12 Priftin will be the first major addition
13 to the pharmacological treatment of pulmonary
14 tuberculosis since rifampin. Rifampin was -- in 1972,
15 over 25 years ago. It was the result of a discovery
16 and development program of anti-tuberculous drugs by
17 Dow Pharmaceuticals, one of the predecessor companies
18 to Hoechst Marion Roussel. Thus, our company has a
19 long commitment to improving the treatment of
20 pulmonary tuberculosis.

21 Tuberculosis is neither gone nor
22 forgotten. Globally it kills more people each year
23 than AIDS. It is projected that in the next decade TB
24 will infect more than 300 million people and be the
25 cause of death of 30 million.

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1 While cases dramatically dropped for many
2 years, during 1985 to 1992, TB cases in the United
3 States increased almost 20 percent, with greater
4 increases among women, children, and HIV infected
5 patients.

6 There have been dramatic changes in the
7 nature and magnitude of the disease. Globally, the
8 increasing projections of tuberculosis cases compelled
9 the World Health Organization to declare TB a global
10 emergency.

11 The rapid increase in TB cases, with
12 issues of resistance and compliance, led government,
13 industry, health planners, and researchers to look for
14 new tools and methodologies to manage tuberculosis.

15 Directly observed therapy, known as DOT,
16 is a treatment approach which has developed as a
17 global strategy in the treatment of tuberculosis. The
18 DOT philosophy encompasses patient compliance in the
19 duration and frequency of treatment.

20 DOT improves patient adherence to therapy
21 by dosing patients under the supervision of a health
22 practitioner. Adherence to therapy is critical when
23 treating a disease where long-term compliance is
24 essential to avoid relapses and resistance.

25 The most important distinguishing

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1 characteristic between rifampin and rifapentine is
2 elimination half-life. The longer elimination half-
3 life with rifapentine and that of its
4 microbiologically active metabolite allows for less
5 frequent dosing of rifapentine.

6 Proposed dosing of rifapentine is twice
7 weekly during the intensive phase of treatment and
8 once weekly during the continuation phase compared to
9 rifampin, which is recommended in traditionally used
10 regimens for daily administration in the initial phase
11 in twice or thrice weekly during the continuation
12 phase.

13 Thus, the major therapeutic advance with
14 rifapentine is related to its longer half-life, which
15 allows for longer intervals between directly observed
16 therapy, thus cutting health practitioner resources
17 needed to administer DOT with the potential of
18 increasing rifapentine compliance and increasing
19 frequency and duration of treatment.

20 The development of rifapentine has been a
21 collaborative interactive effort between Hoechst
22 Marion Roussel and the FDA Division of Special
23 Pathogens and Immunologic Drug Products since 1993,
24 when the first meeting to discuss development
25 occurred.

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1 At that time, tuberculosis incidence rates
2 were rising in the U.S. and attention was once again
3 focused on this infectious disease. Due to the
4 increase in TB incidence rates, the FDA encouraged
5 Hoechst Marion Roussel to develop rifapentine.

6 The agency was consulted and concurred
7 with the clinical development plan, including a
8 single, large pivotal trial, Protocol 8, conducted at
9 sites in North America and South Africa.

10 Since that time, both the FDA and the
11 sponsor have worked diligently to further the
12 development of the product in a timely manner.

13 In addition to working cooperatively with
14 the FDA, Hoechst Marion Roussel has also worked
15 cooperatively with the Centers for Disease Control and
16 Prevention on the development of rifapentine. CDC is
17 currently conducting a clinical trial, USPHS 22,
18 evaluating the safety and efficacy of a rifapentine
19 containing regimen compared to a rifampin containing
20 regimen during continuation phase.

21 This trial has been supported by Hoechst
22 Marion Roussel in both concept and clinical drug
23 supplies. We publicly acknowledge the support which
24 CDC continues to provide to the development of
25 rifapentine.

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1 Hoechst Marion Roussel submitted the NDA
2 for rifapentine in December 1997 and requested
3 approval under the regulations for accelerated
4 approval of new drugs for serious or life threatening
5 illnesses.

6 The NDA is based on the clinical results
7 of a single, large pivotal trial agreed upon by the
8 FDA, including their concurrence to submit the NDA
9 with an interim analysis before all patients had
10 completed the two-year follow-up phase.

11 In March 1998, an amendment was submitted
12 providing additional six and 12-month follow-up data.
13 We are requesting an accelerated approval with a
14 commitment to provide additional clinical data to the
15 agency.

16 In addition to the NDA, we also submitted
17 an application for orphan drug status. Rifapentine
18 was granted orphan drug designation for the treatment
19 of pulmonary tuberculosis in June 1995.

20 From the literature, you may be familiar
21 with a form of rifapentine manufactured and developed
22 in China. This product contains rifapentine produced
23 by a different manufacturer than Hoechst Marion
24 Roussel and is a different product from Priftin, which
25 we are discussing today. The Chinese product has not

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1 been demonstrated to be bioequivalent to Priftin and
2 has been shown to have poor bioavailability.

3 For these reasons, it is not our intent
4 today to present data from clinical trials conducted
5 with rifapentine other than Priftin, nor should the
6 results reported with this other source of rifapentine
7 be extrapolated to apply to rifapentine.

8 The presentation today will follow this
9 agenda. Following this introduction, Dr. Charles
10 Gorodetzky, Vice President, North American Medical
11 Advisory with Hoechst Marion Roussel, will present the
12 results of Protocol 8, the single pivotal study
13 comparing treatment of pulmonary tuberculosis with
14 rifampin and rifapentine.

15 Following Dr. Gorodetzky, Dr. Michael
16 Iseman will provide the interpretation of pivotal
17 trial results and put them into the context of current
18 day treatment for TB. Dr. Iseman is Chief, Clinical
19 Mycobacteriology Service in the Division of Infectious
20 Diseases, National Jewish Medical and Research Center
21 for Immunology and Respiratory Medicine. He is also
22 Professor of Medicine in the Divisions of Pulmonary
23 Medicine and Infectious Diseases at the University of
24 Colorado.

25 I will return to the podium to give a

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1 brief conclusion and moderate our question and answer
2 period.

3 We ask that you hold your questions,
4 except those needed for immediate clarity until we've
5 completed all of our presentations, and at that time
6 we'll be happy to answer any and all of your
7 questions.

8 Dr. Gorodetzky.

9 DR. GORODETZKY: Good morning ladies and
10 gentlemen.

11 This presentation will summarize the pre-
12 clinical and clinical data on Priftin. It will be
13 divided into four parts: a brief background on the
14 nature and anti-tuberculous microbiology of
15 rifapentine; a summary of its pharmacokinetics; a
16 discussion of the efficacy of a rifapentine
17 containing, multi-drug anti-tuberculous regimen
18 compared to a rifampin containing, multi-drug regimen
19 in a pivotal clinical trial; and a summary of the
20 safety data from all Hoechst Marion Roussel
21 rifapentine trials.

22 First, some background information.
23 Rifapentine is a long lasting, rifamycin analog with
24 a molecular structure similar to rifampin. It will be
25 marketed as 150 milligram film-coated tablets. Its

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1 mechanism of action is similar to that of other
2 members of the rifamycin class of antibiotics,
3 including rifampin.

4 This slide presents the range of published
5 and clinical trial data for MIC values for rifapentine
6 and rifampin against M. tuberculosis obtained using
7 non-egg containing assay medium.

8 As can be seen, the range of values for
9 rifapentine is lower than that for rifampin.

10 I will now summarize the pharmacokinetics
11 data for rifapentine. The pharmacokinetics of
12 rifapentine have been well characterized using single
13 and multiple doses ranging from 150 milligrams to 600
14 milligrams in healthy men and women, in elderly men,
15 in subjects with impaired hepatic function, in
16 patients with pulmonary tuberculosis or TB, in
17 asymptomatic subjects infected with HIV, and in
18 pediatric subjects.

19 In addition, the effect of food on the
20 absorption and pharmacokinetics of rifapentine has
21 been studied, and a drug interaction trial with a
22 protease inhibitor, indinavir, has also been carried
23 out.

24 This slide presents the comparative plasma
25 concentration time profiles from the administration of

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1 single, 600 milligram oral doses of rifapentine and
2 rifampin to fasting subjects. The time to maximum
3 serum concentration for rifapentine was five hours and
4 for rifampin was two hours.

5 Rifapentine had an elimination half-life
6 of 17 hours compared to three hours for rifampin. The
7 maximum reported MICs, as shown in an earlier slide,
8 are shown on the horizontal dashed and dotted lines
9 for rifampin and rifapentine, respectively.

10 The plasma concentration of rifampin in
11 these studies fell below the MIC by 12 hours, while
12 rifapentine concentration remained above the MIC for
13 72 hours.

14 In addition, it should be noted that food
15 increases the absorption of rifapentine while it
16 decreases the absorption of rifampin.

17 Single dose pharmacokinetics of
18 rifapentine were found to predict the multiple dose
19 pharmacokinetics reasonably well. Also, rifapentine
20 exhibited similar pharmacokinetics in all of the
21 populations studied.

22 Further, rifapentine does not induce its
23 own metabolism.

24 In the HMR normal volunteer study of the
25 interaction of rifapentine with indinavir, it was

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1 found that co-administration of indinavir did not
2 affect rifapentine pharmacokinetics. The co-
3 administration of rifapentine decreased the maximum
4 serum concentration of indinavir by approximately 55
5 percent. By comparison, the co-administration of
6 rifampin has been reported to decrease the maximum
7 serum concentration of indinavir by approximately 87
8 percent and the co-administration of rifabutin
9 decreases indinavir Cmax by 22 percent.

10 The efficacy data that follow are derived
11 from the single, large pivotal study which our company
12 carried out after consultation with the FDA. In this
13 presentation, the pivotal trial will be referred to as
14 Protocol 8, which is an abbreviation of the full
15 protocol number.

16 This trial was a randomized, open label,
17 active control, multi-drug, multi-center study of the
18 treatment of pulmonary tuberculosis. It was conducted
19 at 39 sites, 29 in South Africa, and five each in the
20 United States and Canada.

21 The treatment plan of Protocol 8 called
22 for an active treatment period of six months, and all
23 patients who completed active treatment were scheduled
24 to have 24 months of follow-up.

25 As of the agreed visit cutoff date of July

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1 8th, 1997, all patients who had not dropped out of the
2 study for any reason had completed active treatment.
3 Of those who entered follow-up, 96 percent had reached
4 their six-month follow-up endpoint and 68 percent had
5 reached their 12-month follow-up endpoint.

6 Inclusion criteria allowed for the
7 enrollment of either males or females between the ages
8 of 18 and 80 years. Patients had to have previously
9 untreated, culture positive pulmonary tuberculosis as
10 documented by at least one baseline sputum culture
11 which subsequently grew M. tuberculosis.

12 In addition, serum creatinine had to be
13 less than or equal to twice the upper normal limit,
14 and both bilirubin and ALT or SGPT had to be less than
15 or equal to three times the upper normal limit.

16 Among the major criteria for exclusion
17 were any M. tuberculosis isolate which was determined
18 to be resistant to one or more of the five drugs or
19 contact with a person who had multi-drug resistant M.
20 tuberculosis.

21 Potential patients were also to be
22 excluded if they had a history of treatment for TB and
23 a clinically significant major body system disease or
24 systemic corticosteroid therapy.

25 Other exclusion criteria were ethanol

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1 abuse or its consequences, intravenous drug abuse, or
2 a positive HIV antibody test.

3 Finally, pregnant or nursing females were
4 also excluded from enrollment.

5 This slide presents the design of the
6 study. The six-month treatment period was divided
7 into an intensive phase lasting two months and a
8 continuation phase lasting four months. The 24-month
9 follow-up had visits scheduled at three, six, 12, 18,
10 and 24 months after completion of treatment.

11 The intensive phase treatment regimen
12 during which four drugs were administered to each
13 patient is shown here. Isoniazid, pyrazinamide, and
14 ethambutol were administered in each treatment arm on
15 a daily basis, with a dosing of PZA and EMB adjusted
16 for body weight. INH and PZA were used for the entire
17 intensive phase, while EMB was discontinued once it
18 was determined that the patient's isolate of M.
19 tuberculosis was sensitive to all study drugs.

20 In the event that the isolate was
21 resistant to one or more study drugs, the patient was
22 immediately discontinued from the study and treated
23 with a combination of drugs indicated by the
24 resistance pattern of the isolate.

25 The sole treatment difference in the

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1 intensive phase was the randomization to receive
2 either rifapentine, hereinafter abbreviated RPT, or
3 rifampin, hereafter abbreviated RMP.

4 Rifapentine was administered twice weekly
5 in a 600 milligram dose, while daily rifampin dosing
6 was adjusted for body weight.

7 In the continuation phase of treatment,
8 all patients received INH and either rifapentine or
9 rifampin. Rifapentine patients received INH and
10 rifapentine once weekly, while rifampin patients
11 received INH and rifampin twice weekly.

12 Rifapentine was used only in a 600
13 milligram dose, while the dosing of INH and rifampin
14 was adjusted for body weight.

15 Eight hundred and twenty-four individuals
16 were screened for enrollment into the study, of whom
17 102 failed the screening process. The remaining 722
18 individuals were enrolled in the study, with 361
19 randomized to the rifapentine arm and an equal number
20 randomized to the rifampin.

21 Each of these patients received at least
22 one dose of study drugs and was, therefore, included
23 in the safety analysis.

24 For the efficacy analyses, a modified
25 intent to treat or ITT population was defined, which

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1 included all patients who received study medication
2 and met specific protocol defined analysis criteria.

3 By far, the leading reason for exclusion
4 from the modified ITT population was negative sputum
5 cultures at baseline. This was followed by culture of
6 a resistant isolate from the baseline sputum sample.

7 The reasons for exclusion from the
8 modified ITT population were balanced between the two
9 treatment groups. The modified ITT patients were
10 composed of 286, or 79 percent, of the rifapentine
11 patients and 284, also 79 percent, of the rifampin
12 patients.

13 A second, more restrictive protocol
14 correct population fulfilling all protocol criteria
15 for treatment was also examined in efficacy analysis.
16 Since the conclusions from these analyses were the
17 same as those derived from the ITT population, further
18 details will not be presented here, although they are
19 readily available.

20 At baseline evaluation, Karnofsky scores
21 and the demographic variables of age, height, weight,
22 and race were the same for both treatment groups. The
23 predominance of black and multi-racial patients
24 reflects the racial mix encountered at South African
25 sites which enrolled over 90 percent of the patients

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1 in this trial.

2 Gender distribution shows a predominance
3 of males in both treatment groups, with a slightly
4 higher proportion in the rifapentine group.

5 Baseline signs and symptoms, such as
6 cough, expectoration, sweats, fever, weight loss,
7 anorexia, and hemoptysis, were not significantly
8 different between the treatment groups, but showed a
9 trend toward higher frequency in the rifapentine
10 group.

11 A variety of TB risk factors were also
12 recorded, such as homelessness, unemployment, drug and
13 alcohol use, and others. All were found to be
14 balanced between the treatment arms.

15 The primary efficacy analysis was
16 performed using treatment outcome at the end of six
17 months of follow-up as the primary efficacy parameter.
18 A treatment success was defined as achieving a
19 negative sputum culture during active treatment that
20 was sustained throughout follow-up.

21 It is important to note that efficacy was
22 based on the results of sputum cultures, not sputum
23 smears, and that these sputum cultures were performed
24 at single central laboratories in South Africa and
25 North America and analyzed under blinded conditions.

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1 Treatment nonsuccesses were defined as
2 treatment failures or relapses or patient withdrawals
3 before study completion for any reason.

4 A treatment failure was defined as failure
5 to achieve or sustain a negative sputum culture during
6 active treatment.

7 A relapse was defined as a negative sputum
8 culture at the end of active treatment, with a
9 positive culture occurring during the follow-up
10 period.

11 Secondary efficacy parameters examined
12 included treatment success based on the results of
13 sputum cultures at the end of the intensive phase of
14 treatment, or two months, and at the end of the
15 continuation phase of treatment at six months.

16 In addition, the time to conversion was
17 also examined. Conversion was defined as the first of
18 two consecutive negative sputum cultures sustained
19 through active treatment.

20 Treatment success rates at the end of the
21 intensive and continuation phases of treatment and at
22 the end of the six-month follow-up period calculated
23 using the modified intent to treat, or ITT, population
24 are shown in this slide. Some patients had no culture
25 data available for these time points, for example,

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1 those who discontinued from the study for other than
2 efficacy reasons, including adverse events or their
3 own or the investigator's decision.

4 For this analysis, all missing results
5 which were balanced across treatment groups were
6 considered to be culture positive. Thus, all patients
7 who discontinued from the study for any reason were
8 treated as if they were treatment failures or
9 relapses, depending on when they left the trial.

10 This represents the worst case scenario
11 for calculation of absolute success rates in the
12 efficacy analysis.

13 The ITT analysis was performed on 286
14 rifapentine patients and 284 rifampin patients.
15 Success rates were similar in the two treatment arms
16 at the end of the intensive phase, at the end of the
17 continuation phase, and at the end of the six-month
18 follow-up, the primary efficacy parameter.

19 For treatment outcomes at the end of six
20 months of follow-up, a sustained rate for the
21 rifapentine arm was 70 percent and for the rifampin
22 arm, 71 percent, which met statistical criteria for
23 equivalence of the two treatments. The difference in
24 success rates was one percent, with 95 percent
25 confidence intervals of minus six to plus eight

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1 percent.

2 This same efficacy analysis was carried
3 out using three additional methods of handling missing
4 values. In a best case analysis, all missing values
5 were considered sputum negative.

6 A second analysis omitted all missing
7 values, and in a third iteration, only missing values
8 of those patients who were still ongoing but had not
9 yet reached the follow-up endpoint were omitted, with
10 all other missing values considered sputum positive.

11 Finally, the primary and additional
12 analyses were carried out on the protocol correct
13 population. Regardless of the method of handling
14 missing values or the population analyzed, the
15 conclusions were the same. The absolute magnitude of
16 the percent successes varied among the different
17 analyses and produced success rates similar to those
18 reported in earlier trials of anti-tuberculous drugs,
19 that is, success rates in the 90-plus percent range.

20 However, regardless of the analysis, the
21 rifapentine and rifampin groups had similar success
22 rates and had 95 percent confidence intervals that met
23 the statistical criteria for equivalence of the two
24 treatment groups. The upper limit of the confidence
25 intervals of the rifampin minus rifapentine success

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1 rate differences were generally less than ten percent.

2 This slide presents the data for
3 nonsuccesses in the ITT analysis at the six-month
4 follow-up endpoint. Note that the total number of
5 patients in each treatment are is less than the total
6 number of patients in the ITT population because ten
7 patients in each group did not reach the six-month
8 follow-up endpoint prior to the visit cutoff date.

9 The number of nonsuccesses in each
10 treatment arm was similar, with 75 in the rifapentine
11 group and 72 in the rifampin group.

12 Except for therapeutic failures, that is,
13 treatment failures and relapses, the reasons for
14 nonsuccess were balanced between the two treatment
15 groups. The most common reason for nonsuccess in both
16 groups was the patient choosing to discontinue the
17 trial.

18 This slide details the therapeutic
19 failures in ITT patients at the six-month follow-up
20 endpoint.

21 The 26 rifapentine patients and the 19
22 rifampin patients represent therapeutic failure rates
23 of 9.4 percent for rifapentine and 6.9 percent for
24 rifampin. The two and a half percent therapeutic
25 failure difference had a 95 percent confidence

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1 interval of minus two percent to seven percent.

2 Treatment failures were more frequent in
3 the rifampin arm, which had eight compared to one in
4 the rifapentine arm.

5 Relapses, however, were statistically
6 significantly more frequent in the rifapentine arm,
7 which had 25 compared to 11 in the rifampin arm. It
8 is noteworthy that these relapses were not associated
9 with the development of resistance to rifamycins.

10 The sole rifapentine treatment failure was
11 documented by a positive culture, as were five of the
12 rifampin treatment failures.

13 As part of our ongoing discussions with
14 the FDA, we further investigated possible explanations
15 for the relapse difference between the two treatments.
16 Analyses were carried out on a number of variables.
17 These analyses were not meant to mitigate the observed
18 differences in relapse between treatments. They are
19 post hoc exploratory analyses, not preplanned in the
20 protocol, of potential predictors of relapse that
21 might help us to better understand the outcomes of the
22 trial in terms of subpopulations and better define the
23 use of rifapentine as part of a multi-drug regimen.

24 Variables found not to be related to
25 relapse or treatment group differences included all

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1 but one demographic characteristic, which was gender:
2 body weight changes, baseline signs and symptoms,
3 baseline TB risk factors, baseline smears and
4 cultures, silicate exposure, and the pharmacokinetics
5 of rifapentine.

6 After multiple exploratory analyses,
7 several variables emerged as predictors of relapse
8 independent of treatment. These were male gender,
9 baseline severity of disease, and the strongest
10 predictor, a low number of doses of non-rifamycin
11 medications, that is, INH, PZA, and ethambutol, during
12 the intensive phase of treatment.

13 Coincidentally, all three factors were
14 more prevalent in the rifapentine arm, that is, the
15 rifapentine treatment group had a higher proportion of
16 males, greater baseline severity of pulmonary disease,
17 and higher intensive phase noncompliance with non-
18 rifamycin medications.

19 The slightly higher preponderance of males
20 in the rifapentine group was presented earlier and
21 will not be further discussed.

22 Although baseline signs and symptoms
23 showed only a slight trend toward higher frequency in
24 the rifapentine group, extent of pulmonary disease as
25 shown by baseline chest X-rays as further explored.

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1 Dr. David Lynch, a Board certified
2 radiologist with extensive experience in reading chest
3 X-rays from tuberculosis patients, conducted an
4 independent, blinded, quantitative evaluation of 83
5 percent of the baseline chest X-rays which were
6 available for evaluation.

7 A significant greater degree of cavitation
8 both in frequency of bilateral distribution and in
9 mean surface area of cavitation was found in the
10 rifapentine group. These findings suggest that the
11 patients enrolled in the rifapentine arm had
12 significantly more lung tissue destroyed by disease at
13 the time of study entry than in the rifampin group and
14 further suggests a greater bacterial load in the
15 rifapentine patients.

16 We do not believe that the slight
17 imbalances of gender and baseline severity disease are
18 enough to explain the relapse difference between
19 treatment arms. However, poor compliance with non-
20 rifamycin medications and its relationship to
21 conversion at the end of the intensive phase of
22 treatment appears to provide the most useful
23 information about the proposed use and future study of
24 rifapentine as part of a multi-drug, anti-tuberculous
25 regimen. Therefore, some of these analyses are not

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1 presented in greater detail.

2 Drug dosing in both intensive and
3 continuation phases was then examined looking first at
4 protocol defined noncompliance. In this and
5 subsequent analyses, as agreed with the FDA, all data
6 accumulated as of the visit cutoff date of July 8th,
7 1997, are included, that is, specifically including
8 data up to the 12-month follow-up endpoint from 68
9 percent of patients who had reached that milestone.

10 According to protocol, in the rifampin arm
11 of the intensive phase, patients could not take less
12 than 45 doses of the daily rifampin, INH, and PZA.
13 This usually meant 45 DOT doses, although for some
14 patients considered by the investigators to be
15 reliable enough to take their drugs on the weekends,
16 only 40 DOT doses were required.

17 In the rifapentine arm of the intensive
18 phase, the same daily dosing requirements apply to INH
19 and PZA, but patients could not take less than 17 DOT
20 doses of the twice weekly rifapentine.

21 In the continuation phase, compliant
22 patients could not take less than 32 DOT doses of
23 rifampin plus INH or less than 16 DOT doses of
24 rifapentine plus INH.

25 Finally, the protocol allowed only 14 days

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1 without receipt of any study drug.

2 Noncompliance with protocol defined
3 administration schedule was examined in the modified
4 ITT population excluding those patients who dropped
5 out of the study during the treatment phases.

6 In the intensive phase, protocol defined
7 noncompliance was significantly more frequent in the
8 rifapentine arm than in the rifampin arm. That is,
9 rifapentine patients were less compliant than rifampin
10 patients.

11 Noncompliance was similar in the two
12 treatment arms in the continuation phase.

13 In order to further explore why
14 noncompliance was greater in the rifapentine arm in
15 the intensive phase, noncompliance with the dosing of
16 all drugs separately was examined. This analysis
17 separates the drugs administered in the rifapentine
18 and rifampin treatment arms.

19 In the intensive phase, noncompliance with
20 rifapentine dosing was significantly less than
21 noncompliance with rifampin dosing. That is,
22 rifapentine patients were more compliant than rifampin
23 patients in taking the rifamycin portion of their
24 treatment.

25 However, noncompliance with INH and PZA

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1 dosing was greater in the rifapentine arm than in the
2 rifampin arm. Thus, the significantly greater overall
3 noncompliance in the rifapentine arm was due to
4 noncompliance with the dosing of the other treatment
5 drugs and not to noncompliance with rifapentine dosing
6 itself.

7 In the continuation phase, however, there
8 were no significant differences in noncompliance with
9 either rifamycin dosing or INH dosing between the two
10 arms.

11 In order to further explore intensive
12 phase non-rifamycin dosing, doses of INH, PZA, and EMB
13 ere analyzed separately. INH and PZA are combined for
14 these presentations since both drugs were administered
15 daily throughout the entire intensive phase, and the
16 patterns determined for each drug separately could be
17 virtually superimposed.

18 High and low dosing categories were
19 slightly different from protocol defined compliance in
20 these analyses and were based on the distribution of
21 the actual number of doses taken.

22 The high dosing group, which took greater
23 than 47 doses of NIH/PZA and greater than 41 doses of
24 EMB during the intensive phase, in this group relapse
25 rates were very low, approximately two percent with no

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1 differences between treatment groups. These relapse
2 rates represent a single patient in each treatment
3 group.

4 In one moderate dosing group, still taking
5 greater than 41 doses of EMB, but less than or equal
6 to 47 doses of INH/PZA, relapse rates were still low,
7 approximately five percent, and similar in the two
8 treatment groups.

9 Similarly, in the other moderate dosing
10 group where greater than 47 doses of INH/PZA were
11 administered with less than or equal to 41 doses of
12 EMB, the groups were still similar with relapse rates
13 of about four to six percent.

14 However, in the low dosing group receiving
15 both less than or equal to 47 doses of INH/PZA and
16 less than or equal to 41 doses of EMB, relapse rate in
17 the rifapentine arm was 23 percent, much higher than
18 the seven percent in the rifampin arm.

19 Thus, it appears that the number of
20 relapses increases as the number of non-rifamycin
21 intensive phase doses decreases for both treatment
22 arms, but the rifapentine arm is more sensitive to
23 this effect, especially in this low dosing group.

24 The relationship of relapses to time of
25 sputum conversion from positive to negative was also

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1 investigated. This slide presents the mean number of
2 days required for sputum culture conversion both for
3 patients who relapsed and those who did not in each
4 treatment group.

5 The addition to the database of those
6 patients who had reached their 12-month follow-up
7 endpoints decreased the number of rifapentine relapses
8 from 25 to 27, while rifampin relapses remained
9 unchanged at 11.

10 The 96-day mean time to sputum conversion
11 for the 27 rifapentine patients who relapsed was
12 significantly longer than the 62-day mean time to
13 conversion for the 11 rifampin patients who relapsed.

14 Also the mean time to sputum conversion
15 for the 27 rifapentine patients who relapsed was
16 significantly longer than the 55-day mean time to
17 conversion for the 225 rifapentine patients who did
18 not relapse.

19 This slide presents the relapse status of
20 patients by whether or not their sputum cultures had
21 converted to negative by the end of two months of
22 treatment, which is the end of the intensive phase.

23 For those patients whose sputum cultures
24 had converted to negative at the end of two months,
25 there was no significant difference between the six

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1 percent relapse rate for rifapentine and the four
2 percent relapse rate for rifampin.

3 However, for patients whose cultures
4 remained positive for more than two months, the 25
5 percent relapse rate in the rifapentine arm was
6 significantly greater than the six percent relapse
7 rate in the rifampin arm.

8 Relapse rates then appear to be related to
9 late sputum conversion, again, especially in the
10 rifapentine treatment arm.

11 The relation among relapses, intensive
12 phase, non-rifamycin dosing, and early or late sputum
13 conversion was then further explored. The data
14 illustrated in this analysis is the same as that shown
15 in Table 20 of the company's briefing document.

16 There were 252 rifapentine patients and
17 232 rifampin patients who entered follow-up. Within
18 the confines of protocol defined compliance, although
19 DOT dosing was required, patients actually took a
20 varying number of doses of non-rifamycin medications
21 in the intensive phase of treatment.

22 For these analyses patients were grouped
23 into three subgroups based on the actual receipt of
24 intensive phase, non-rifamycin medications of more or
25 less than 47 doses of INH/PZA and 41 doses of EMB as

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1 noted in an earlier analysis. These subgroups will
2 hereafter be referred to as the high, moderate, and
3 low dosing groups.

4 The high dosing group was comprised of
5 those who took greater than 47 doses of INH/PZA and
6 greater than 41 doses of EMB. The moderate dosing
7 group received greater than 47 doses of INH/PZA and
8 less than or equal to 41 doses of EMB or less than or
9 equal to 47 doses of INH/PZA and greater than 41 doses
10 of EMB, and the low dosing group were treated with
11 both less than or equal to 47 doses of INH/PZA and
12 less than or equal to 41 doses of EMB.

13 The N for each subgroup are shown in the
14 stacked bars and are similar for the two treatment
15 arms.

16 This next slide shows the proportion of
17 early and late sputum convertors in each non-rifamycin
18 dosing subgroup for rifapentine based on conversion
19 status at the end of the two-month intensive phase of
20 treatment.

21 The solid bars represent early convertors,
22 and the hatched bars late convertors in the high,
23 moderate, and low dosing groups. The proportion of
24 late convertors increased as the number of intensive
25 phase, non-rifamycin doses decreased from the high

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1 dosing group with ten percent to the low dosing group
2 with 37 percent.

3 The data for rifampin is added here in the
4 same format for solid and hatched bars. The trend is
5 very similar, though not as pronounced, with
6 increasing percent of late convertors with decreasing
7 number of non-rifamycin doses ranging from 14 percent
8 in the high dosing group to 24 percent in the low
9 dosing group.

10 In order to better understand the
11 relationship between conversion and relapse, the
12 proportion of relapses in early and late convertors in
13 each dosing subgroup was then explored in greater
14 detail.

15 The proportion of relapses in the early
16 convertors in each dosing subgroup for the rifapentine
17 arm are shown in this slide. Here the solid bars
18 represent patients who have not relapsed and the
19 cross-hatched bars represent patients who have
20 relapsed, again, in the high, moderate, and low dosing
21 groups.

22 As the number of intensive phase, non-
23 rifamycin doses decrease, the proportion of relapses
24 increased from zero percent to 13 percent.

25 This slide shows the same data for the

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1 rifampin treatment arm. Again, the hatched bars
2 represent the proportion of relapsers in each
3 subgroup. The pattern is the same as for rifapentine,
4 a trend to an increasing proportion of relapsers as
5 the number of non-rifamycin doses decreases from high
6 to the low dosing groups.

7 This slide shows the relapse data in the
8 same format for slow convertors or late convertors in
9 the rifapentine arm, that is, those who took more than
10 two months to convert. With the exception of the high
11 dosing group -- there was a very small sample size of
12 five patients with a single relapser -- there is a
13 marked increase in the percent of relapses with the
14 low dosing group, up to 39 percent.

15 In all dosing groups, the proportion of
16 relapsers was greater in the late convertors compared
17 to the early convertors.

18 This slide adds the corresponding data for
19 late convertors in the rifampin arm. Again, with the
20 exception of the high dosing group, with a small
21 sample size of eight and again with only a single
22 relapser, there is a small increase in the observed
23 percent of relapsers in the low dosing group.

24 However, the sample sizes are small, as
25 are the differences in percentage of relapsers. When

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1 compared to the early convertors there is no
2 difference in the relapse rates in contrast to the
3 rifapentine group.

4 In summary, the worst relapse result was
5 seen in the rifapentine group receiving the low number
6 of intensive phase, non-rifamycin doses with 13
7 percent and 39 percent relapsers in the early and late
8 convertors respectively.

9 It might be noted that 19 of the 27
10 rifapentine arm relapsers were in this low dosing arm.

11 Differences between the rifapentine and
12 rifampin arms were most striking for the low dosing
13 group, especially in the late convertors, with 39
14 percent relapses in rifapentine and only six percent
15 relapses for rifampin.

16 The fewest relapses occurred in the early
17 convertors in the high dosing group where, in fact,
18 there were no relapses in either treatment arm.

19 These exploratory analyzes indicate that
20 a low number of intensive phase, non-rifamycin doses
21 is related to both failure to convert sputum and to
22 relapse. This is seen particularly in the rifapentine
23 group with the lowest number of non-rifamycin doses in
24 the intensive phase. These patients were the least
25 likely to convert sputum by the end of intensive phase

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1 treatment and were the most likely to relapse during
2 follow-up.

3 These data suggest that deficient
4 intensive phase dosing of non-rifamycin medications
5 followed by once weekly continuation phase dosing may
6 not have been sufficient to prevent relapse in a
7 substantial fraction of the patients.

8 A possible suggestion would be to require
9 a minimum number of intensive phase, non-rifamycin
10 doses, that is, greater than 47 INH/PZA doses plus
11 greater than 41 EMB doses, and/or conversion of sputum
12 by the end of the two-month intensive phase to
13 initiate continuation phase dosing. Otherwise
14 intensive phase dosing should continue for another
15 month.

16 This is consistent with the results of
17 this study and the current ATS/CDC guidelines.

18 In conclusion, a 600 milligram dose of
19 rifapentine used in combination with other standard
20 anti-tuberculous drugs is an effective antibiotic for
21 the treatment of pulmonary tuberculosis, showing
22 equivalence of success rates to a combination
23 treatment regimen that included rifampin that is in
24 common use.

25 It is important to maintain adequate

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1 dosing with non-rifamycin medications during the
2 intensive phase of treatment to avoid a potential
3 increase in relapse.

4 Finally, I will present the summary of the
5 safety data from all Hoechst Marion Roussel trials in
6 the integrated summary of safety, not just the data
7 from Trial 8.

8 The next two slides summarize the safety
9 findings for rifapentine. First, the treatment
10 related adverse events were consistent with those
11 commonly seen with rifamycins and other anti-
12 tuberculous drugs.

13 Second, single doses of rifapentine up to
14 600 milligrams were safely administered to health
15 adult and pediatric subjects, to subjects with hepatic
16 impairment, and to subjects infected with HIV.

17 Third, patients with pulmonary
18 tuberculosis were safely treated with multiple 600
19 milligram doses for up to six months or with multiple
20 900 milligram doses for up to two months.

21 Finally, patients infected with
22 mycobacterium avian complex organisms were safely
23 treated with 300 to 450 milligrams per day of
24 rifapentine for up to 15 months.

25 This slide presents the exposure to study

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1 medication in the various trials. In the comparative
2 clinical Study 8, 361 patients received a median of 34
3 600 milligram doses of rifapentine.

4 In the clinical pharmacology and
5 pharmacokinetic studies, 228 subjects received single
6 and multiple doses of rifapentine ranging from 150 to
7 750 milligrams with a median of two doses per patient.

8 In the uncontrolled clinical trials, 61
9 patients received doses of rifapentine ranging from
10 300 to 900 milligrams with a median of 42 doses per
11 patient.

12 This slide presents the five most frequent
13 adverse events regardless of investigator judgment of
14 relationship to study drug in Study 8. It should be
15 noted that investigators were asked not to report
16 orange discoloration of the urine as an adverse event
17 since this occurrence was expected to result from the
18 use of rifapentine, as with other rifamycins.

19 The most common adverse event was
20 hyperuricemia, which occurred more frequently in the
21 rifapentine arm for reasons that are not apparently.
22 However, this hyperuricemia disappeared from both
23 treatment arms after the end of the intensive phase of
24 treatment, suggesting that it was due to PZA and EMB,
25 both of which are recognized to cause elevated serum

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1 uric acid levels.

2 In addition, symptoms that could be the
3 result of hyperuricemia, such as arthralgia and
4 arthritis, occurred with a similar frequency in both
5 treatment groups.

6 Pyuria and hematuria occurred at similar
7 incidences in both treatment groups, while proteinuria
8 occurred more frequently in the rifampin arm.

9 Thirty of the overdoses in the rifapentine
10 arm were unintentional excess doses administered with
11 doses of other anti-tuberculous drugs. Adverse events
12 were experienced by only two of the 30 patients who
13 inadvertently received rifapentine on a daily basis
14 for brief periods of time during the intensive phase
15 of treatment.

16 One developed mild itching, and the other
17 developed an elevated ALT, and both events resolved
18 without sequelae when the rifapentine dosing was
19 changed to twice weekly.

20 This slide presents the five most
21 frequently reported treatment related adverse events
22 in Study 8. Except for the hyperuricemia, the
23 incidence is balanced between the two treatment
24 groups. The treatment related adverse events are
25 among those known to occur with the use of anti-

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1 tuberculous antibiotics.

2 This slide presents the nature and
3 comparative incidence of serious adverse events in
4 Study 8. Deaths occurred at equal rates in the two
5 treatment arms, and none were considered related to
6 study drugs.

7 Except for overdoses, which are listed as
8 a serious adverse event by FDA definition and were
9 discussed previously, other serious adverse events
10 were balanced between the two treatment groups, and
11 few of them were considered to be treatment related.

12 This slide presents the incidence of
13 several important safety issues in all rifapentine
14 trials in the integrated summary of safety. There was
15 a higher incidence of serious adverse events in the
16 rifapentine arm, but the difference is due to the
17 higher incidence of overdosing which was discussed
18 earlier.

19 Discontinuations due to adverse events and
20 to laboratory abnormalities were balanced between the
21 two treatment groups. Most of the patients in the
22 uncontrolled clinical trials were individuals infected
23 with both HIV and mycobacterium avian complex.

24 The higher incidence of serious adverse
25 events encountered in this group compared to Trial 8

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1 is not surprising since HIV infected patients are
2 known to experience an increased number of adverse
3 events from multiple causes.

4 In addition, there were very few patients
5 in these uncontrolled trials, making the
6 interpretation of rates difficult.

7 The incidence of these important safety
8 issues and clinical pharmacology and PK studies was
9 very low.

10 In conclusion, the rifapentine trials
11 demonstrated that the safety profile of rifapentine
12 was similar to that of rifampin.

13 In addition, patients diagnosed with
14 pulmonary tuberculosis safely took 600 milligram doses
15 of rifapentine once or twice weekly for up to 26
16 weeks.

17 Finally, patients who inadvertently
18 received rifapentine on a daily basis did so without
19 serious adverse consequences.

20 Therefore, based on the results of the
21 comparative clinical trial of rifapentine, it is
22 possible to conclude that rifapentine, when used in
23 the regimen study, offers a new, effective, and
24 convenient way to treat pulmonary tuberculosis which
25 is equivalent in efficacy to a rifampin containing

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1 treatment regimen that is in common use.

2 Close attention should be paid to
3 intensive phase dosing with non-rifamycin medications
4 to avoid a potential increase in relapse.

5 In addition, rifapentine has an excellent
6 safety profile that is similar to that of other
7 rifamycin antibiotics.

8 Thank you.

9 The next presenter will be Dr. Michael
10 Iseman.

11 DR. ISEMAN: Ladies and gentlemen, good
12 morning.

13 I have been asked by Hoechst Marion
14 Roussel to provide my perspective on the clinical and
15 public health relevance of the new agent rifapentine.

16 Globally, as you've heard, the inability
17 to insure adequate anti-tuberculosis chemotherapy due
18 mainly to nonadherence with treatment has been the
19 major impediment to tuberculosis control. This
20 phenomenon has had several strongly adverse effects on
21 TB, notably higher rates of treatment failure and
22 acquired drug resistance.

23 These two factors combine to entail
24 extended or repeated courses of therapy, substantially
25 increased costs, prolonged infectiousness, excessive

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1 mortality, and perhaps most ominously, the potential
2 dilemma of transmittable, incurable tuberculosis.

3 Recently analyses have identified directly
4 observed therapy, or DOT, as the most efficient and
5 cost effective means of improving TB control. DOT has
6 been embraced as a treatment standard recently by the
7 American Thoracic Society and by the Centers for
8 Disease Control and Prevention, while DOTS, directly
9 observed therapy short course, a similar approach, has
10 been advocated as the global model by the World Health
11 Organization.

12 Directly observed therapy may be regarded
13 as the primary strategy to enhance TB control efforts.
14 Individual drugs may be seen as tools to help affect
15 this strategy.

16 I plan, therefore, to consider the various
17 elements of DOT in detail and then to explore the
18 current and potential contributions of rifapentine to
19 DOT programs.

20 Proven attributes of DOT include
21 substantial reductions in treatment failures.
22 Patients who take their medications are predictably
23 cured.

24 Diminished drug resistance. Although some
25 patients in every short course DOT regimen ever

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1 studied have had relapses, approximately 75 percent of
2 these relapses occur with fully susceptible strains.
3 Acquired multi-drug resistance is extremely rare.

4 Third, accelerated progression to a
5 noninfectious state. This appears to have a
6 significant effect in reducing the incidence of
7 tuberculosis in the community by halting recent
8 transmission and thereby limiting new disease.

9 And fourthly, cost effectiveness. Either
10 the Baltimore community based or the Denver Clinic
11 based DOT models show significant advantages in
12 economic modeling.

13 DOT is made feasible and economic through
14 two critical elements of modern regimens.

15 Short duration. Over the past 25 years,
16 we've witnessed the reduction of tuberculosis therapy
17 from 24 months down to the current level of six
18 months, and finally, intermittency, that is, the
19 ability to administer drugs twice or three times a
20 week in contradistinction to daily treatment.

21 Based on current in vitro studies, animal
22 models and the human trial experience you've heard
23 presented today, rifapentine offers potentially
24 significant advantages in both of these dimensions.

25 The results seen in a pivotal study are

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1 generally favorable. However, we must look at relapse
2 rates, the one troubling element in this trial. I
3 believe that the relatively high rates seen here
4 reflect several factors which I will subsequently
5 discuss in detail.

6 First of all, failure to deliver drugs
7 other than rifapentine in the initial first two months
8 of therapy resulted in diminished bactericidal
9 activity.

10 Secondly, the choice of ethambutol, not
11 streptomycin, as the fourth drug diminished the
12 efficacy of both arms of this trial.

13 Thirdly, a disproportionate extended
14 disease in patients in the rifapentine arm.

15 I will now discuss these issues and
16 consider their implications for the use of rifapentine
17 and the regimen used in this trial.

18 Diminished bactericidal activity.
19 Examining the apparent paradox of the slower
20 conversion rate of the rifapentine arm, 74 versus 79
21 percent, but contrasted to comparable rates of
22 achieved culture negativity at completion of six
23 months treatment, 99 percent in the rifapentine arm
24 versus 98 percent in the rifampin arm, followed by
25 higher relapse rates, 11 percent in the rifapentine

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1 arm compared with five percent in the rifampin arm, I
2 thought it appropriate and needed to consider these
3 data in terms of a modified version of Mitchison's
4 hypothetical treatment model.

5 In this model, there are either three or,
6 depending on your interpretation, four putative
7 subpopulations of tubercle bacilli. Variables of
8 these populations are believed to be either anatomic,
9 that is, the tissue within which they are located, or
10 metabolic state of their microbial metabolism
11 influenced by local factors.

12 The largest number of bacilli comprise
13 Population A represented by this pink oval, which are
14 characterized by rapid multiplication, thought to
15 reflect optimal growth factors, typically in the
16 caseous wall of a pulmonary cavity.

17 Drugs shown to be most active against
18 Population A in early bactericidal activity studies
19 are, in order of efficacy, isoniazid, clearly the most
20 potent drug in this arena, followed by streptomycin,
21 then the rifamycins, and finally ethambutol.

22 Population B is believed to represent more
23 slowly replicating bacilli existing in micro
24 environments less supportive of growth, presumably
25 mediated by local acidic conditions. Originally this

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1 was believed to represent microphage milieu. In fact,
2 now it appears to represent local tissue factors in
3 the wall of the cavity.

4 The drugs most active against population
5 B are believed to be pyrazinamide, playing a leading
6 role in this arena, followed by rifamycins, and then
7 isoniazid.

8 Population C, presumably the smallest
9 population, is believed to represent bacilli which
10 only replicate sporadically. Population C is believed
11 to be particularly vulnerability to the rifamycins.
12 In this model the rifamycins play a leading role in
13 elimination of Population C, followed by isoniazid.

14 Killing the bacilli represented in
15 Population A and B is done mainly through the effects
16 of isoniazid, PZA, and a rifamycin agent. This effect
17 is broadly regarded as bactericidal activity. As
18 indicated in this theoretical model, this phenomenon
19 is responsible for conversion of sputum to culture
20 negativity.

21 Depending on the size of these populations
22 and the potency of the drug regimen, the rate of
23 disappearance may be more rapid, as represented by the
24 steeply descending lines, or less rapid, the more
25 shallow descending lines, than usual.

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1 By contrast, the activity against the
2 sporadically replicating bacilli of Population C is
3 thought largely to reflect the unique contribution of
4 the rifamycin drugs. Mitchison deems this the
5 sterilizing effect and states that based on in vitro
6 studies, animal models, and human trials, rifamycins
7 play a unique role in killing these persistent
8 organisms.

9 If we assume at least the validity of
10 these diverse populations, this may well relate to the
11 discordant activity in the two phases, early intensive
12 and continuation of the rifapentine arm of Study 8.

13 Although it is not exactly concordant with
14 Mitchison's model, I interpret the results in this
15 manner. The diminished bactericidal activity from
16 missed doses of INH, PZA, and ethambutol led to
17 delayed sputum conversions in some patients. However,
18 the once weekly rifapentine-INH given over the last
19 four months was sufficiently potent that an equal
20 number of patients were culture negative at the end of
21 the six months of treatment, but there must have been
22 a population that was suppressed, but not killed due
23 to insufficient bactericidal activity. This
24 population of organisms then promoted the higher rates
25 of relapse in the months following treatment

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1 cessation.

2 The excellent results seen in those
3 patients in the rifapentine arm who did not miss early
4 doses of isoniazid, pyrazinamide, and ethambutol, data
5 previously shown by Dr. Gorodetzky supports this
6 interpretation. We should note that there was only
7 one relapse in each of these high dosing groups
8 consisting of 50 or more patients.

9 Overall, it is my strong impression that
10 the higher relapse rates in the rifapentine arm of
11 Trial 8 largely is due to features of the study
12 regimen, not intrinsic attributes of the drug
13 rifapentine.

14 Number two, ethambutol versus streptomycin
15 and relapse rates in short course therapy regimens.
16 The ideal of a 95 percent successful outcome with
17 short course chemotherapy was primarily derived from
18 regimens containing streptomycin as the fourth drug,
19 in addition to isoniazid, rifampin, and PZA.

20 In the white paper, an analysis of all of
21 the major short course trials which I submitted to
22 accompany the NDA, regimens which used ethambutol as
23 the fourth drug had higher, nine percent, relapse
24 rates than comparable streptomycin containing regimens
25 with five percent relapse rates.

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1 Thus, the relapse rate seen in either the
2 rifampin or the rifapentine arm of this trial are not
3 incongruous in relationship to previously published
4 trials.

5 Finally, a disproportionate burden of
6 disease. As Dr. Gorodetzky demonstrated, the patients
7 in the rifapentine arm of this trial, Protocol 8, had
8 several features historically associated with
9 unsuccessful outcome. These elements to some extent
10 may have also influenced the surplus of relapses among
11 the rifapentine group.

12 This current trial, while offering very
13 encouraging findings in terms of the equivalency of
14 once weekly rifapentine compared to twice weekly
15 rifampin in the continuation phase of treatment
16 highlights several issues. In addition to the
17 proposals made by Dr. Gorodetzky, I would suggest the
18 following.

19 Failure to achieve sputum conversion at
20 two months was a marker of the risk of relapse
21 particularly in the rifapentine arm. Thus, as
22 advocated in current ATS/CDC guidelines, clinicians
23 using the regimen employed in this trial might extend
24 the continuation phase of treatment for the initial
25 period for these, quote, late convertors.

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1 Extending the continuation phase until at
2 least three months after the last positive culture,
3 using the once weekly regimen, may, in fact, still
4 result in a net economy and increased efficiency for
5 TB control programs.

6 Secondly, the use of high dose
7 intermittent INH, PZA, and ethambutol during the
8 initial two months of therapy to accompany the twice
9 weekly rifapentine almost surely would have reduced
10 nonadherence, improved bactericidal activity, and
11 resulted in better performance than the regimen
12 studied.

13 While this is not explicitly demonstrated
14 in this study, I believe it is a wholly reasonable
15 extrapolation from the data in the aforementioned
16 white paper.

17 Animal model studies conducted by Michael
18 Cynamon in New York suggest that twice weekly
19 rifapentine is a more potent agent than rifampin in a
20 similar rhythm. This raises the possibility that a
21 rifapentine twice weekly continuation regimen might
22 allow us to reduce the overall duration of therapy
23 from our existing 26-week limit to the range of
24 perhaps 20 or 22 weeks.

25 This issue clearly should be addressed in

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1 the next generation of trials.

2 Fourthly, what is the optimal dose of
3 rifapentine? Given the high protein binding of the
4 rifamycins, higher doses may, in fact, enhance the
5 potency of rifapentine without increasing adverse drug
6 reactions. In vitro and animal model studies show
7 enhanced anti-tuberculosis activity with higher
8 concentrations of rifapentine, and this is consistent
9 with previous laboratory and clinical experience with
10 rifampin.

11 To summarize, the data presented today
12 show that rifapentine is a safe and effective drug for
13 the treatment of pulmonary tuberculosis. Demonstrated
14 equivalency between a 61 dose rifapentine containing
15 regimen and a 77 dose rifampin regimen is by itself an
16 important advance in TB control.

17 However, it is crucial to realize that it
18 took over 20 years since approval to identify all of
19 the options and the optimal usage for rifampin. I
20 anticipate that even more advantageous regimens
21 related to the previously discussed variables will
22 result from subsequent studies when this drug is
23 approved.

24 As the data indicate, the patients who
25 were adherent to this rifapentine regimen have

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1 exemplary results. To reiterate, the less favorable
2 results in this study reflect shortcomings of the
3 protocol, not of the drug.

4 In closing, I would suggest of all the
5 currently accessible pharmacologic agents, rifapentine
6 has the greatest potential for major contributions to
7 anti-tuberculosis chemotherapy and chemoprevention
8 programs.

9 Thank you, and now let me introduce Dr.
10 Elaine Waller.

11 DR. WALLER: You have now heard the
12 results of the clinical development program for
13 rifapentine for the treatment of pulmonary
14 tuberculosis. The primary property of rifapentine,
15 which distinguishes it from rifampin, is its longer
16 elimination half-life.

17 In clinical Protocol 8, rifapentine with
18 less frequent dosing than rifampin demonstrated
19 equivalent efficacy to a rifampin containing treatment
20 regimen in common use.

21 The safety profile of rifapentine was
22 found to be similar to that of rifampin and, thus,
23 rifapentine has a favorable benefit-risk profile.

24 Through exploratory analyses, we have
25 identified compliance with the non-rifapentine drug

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1 regimen to be a critical variable in determining the
2 time to conversion and relapse rate of patients on
3 rifapentine.

4 Dr. Iseman has provided a model to explain
5 this finding. We now better understand the critical
6 role of sufficient dosing of non-rifamycin drugs
7 during the intensive phase to treatment success, and
8 appropriate language can be built into the product
9 labeling to educate health care practitioners to the
10 importance of adequate dosing during this phase.

11 Dr. Iseman has provided his expert opinion
12 on the clinical interpretation of the rifapentine
13 results and has outlined the importance of this new
14 therapy to the strategy of directly observed therapy.

15 He also outlined further study of
16 rifapentine which could improve upon the proposed
17 recommended use.

18 Based on the clinical results available to
19 date and the supportive interpretation of expert
20 opinion, we ask this panel to find that rifapentine be
21 recommended for accelerated approval for the treatment
22 of pulmonary tuberculosis.

23 We are prepared to answer your questions.
24 In addition to Drs. Gorodetzky and Iseman, we have the
25 following people from Hoechst Marion Roussel prepared

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1 to respond:

2 Dr. Mark Eller, acting head, Global
3 Biodynamics;

4 Dr. Faruqi, Senior Director, Clinical
5 Research, Infectious Disease;

6 Dr. Parviz Hamedani, Vice President,
7 Infectious Diseases;

8 Dr. Michael Kenny, senior research
9 microbiologist;

10 And Dr. Stephen Ruberg, Vice President,
11 North American Biometrics and Data Management.

12 The following consultants are also
13 prepared to respond to questions:

14 Dr. Juzar Ali, associate professor of
15 pulmonary medicine, Louisiana State University Medical
16 Center;

17 Dr. Leonid Heifets, Director,
18 Microbacteriology Laboratory, National Jewish Medical
19 and Research Center for Immunology and Respiratory
20 Medicine, and professor, Department of Microbiology,
21 University of Colorado Health Sciences Center;

22 Dr. Gerry Mayer, Microbiology Consulting
23 Services and former Director of Clinical Microbiology
24 for a predecessor company to Hoechst Marion Roussel;

25 Dr. Lee Reichman, Executive Director, New

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1 Jersey Medical School, National Tuberculosis Center,
2 and professor of medicine and preventive medicine and
3 community health, New Jersey Medical School;

4 And Dr. John Sbarbaro, who is professor of
5 medicine and preventive medicine, University of
6 Colorado Health Sciences Center, and serves as an
7 advisor to the World Health Organization.

8 CHAIRMAN HAMMER: Thank you very much.

9 I'd like to open up the question period to
10 the sponsor to give the Committee members a chance to
11 ask relevant questions. I would ask the Committee
12 members to please prioritize your questions and
13 perhaps ask your two or three most pressing questions
14 initially in order to give the panel members a chance.
15 We'll have more time to complete any questioning later
16 this morning or early this afternoon.

17 So I will begin on my left with Dr. Bass.

18 DR. BASS: My first question has to do
19 with the design of the protocol and the HIV exclusion.
20 Was HIV status routinely determined on all of the
21 participants?

22 DR. GORODETZKY: Yes, Dr. Bass, it was
23 determined on all of the participants. It did not
24 necessarily get back very rapidly, but it was
25 determined on all of the participants in the trial.

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1 DR. BASS: And once the results were know,
2 HIV positive were excluded from the analysis?

3 DR. GORODETZKY: Not necessarily. There
4 were some patients. I believe there were four in the
5 rifapentine arm and nine in the rifampin arm whose
6 results came back sufficiently late that they made the
7 ITT criteria and were included in the efficacy
8 analysis. There was, I believe, only one relapse in
9 that group, and that was one of the four rifapentine
10 patients.

11 DR. BASS: All right. My second question
12 has to do with the post hoc analysis of the relapses,
13 and is it possible to bring your sides back up?

14 DR. GORODETZKY: Sure.

15 DR. BASS: If we could, Slide No. 39.

16 My interpretation of this is that in the
17 rifapentine arm during the intensive phase, it was
18 significantly greater nonadherence with the INH/PZA
19 component of the regimen; is that correct?

20 DR. GORODETZKY: That's correct.

21 DR. BASS: And now if we could see Slide
22 47 or let's -- yeah, 47. Here using perhaps slightly
23 different criteria for what nonadherence is and
24 including ethambutol in the regimens --

25 DR. GORODETZKY: Yes.

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1 DR. BASS: -- the bars look very similar.
2 Is this because of the inclusion of ethambutol or is
3 it a different definition of what nonadherence to INH
4 and pyrazinamide is?

5 DR. GORODETZKY: This particular slide
6 just shows the break-up into the three dosing groups
7 of high, moderate, and low. That just shows the
8 number in each of the groups.

9 The subsequent slides in this series,
10 however, do use that slightly different modification,
11 slightly different definition of dosing groups, but
12 they show consistent data, that there were greater
13 relapses in the patients who got decreased number of
14 intensive phase dosing.

15 Here the categories that we used were
16 based on actual number of doses received rather than
17 the protocol defined noncompliance. A lot of these
18 patients, even in the moderate and low dosing groups,
19 met the definition of protocol defined compliance, but
20 in fact, were among low dosing groups as we define
21 them here.

22 DR. BASS: I guess what I'm trying to
23 decide is whether the difference in these two is
24 mainly the inclusion of ethambutol or whether it's
25 mainly in a different definition of how much INH and

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1 pyrazinamide was taken.

2 DR. GORODETZKY: There is a difference in
3 the definition, but I don't think there's a difference
4 in the results of the two slides. There are two
5 different kinds of analyses.

6 This one breaks it down into additional
7 subgroups.

8 Can you bring up maybe Number 50 or 51?
9 The ones later in that sequence. Move beyond that.
10 Yeah, in fact, move two more so that we have all the
11 data on there.

12 What that shows is, again, high, medium,
13 and low dosing groups, rifapentine in the top group,
14 and for rifampin in the lower group, and it's broken
15 down there in addition to late convertors and early
16 convertors, and what we're seeing in the low dosing
17 groups for rifapentine, both in the early convertors
18 and the later convertors, you have a 13 percent
19 relapse rate in the early convertor low dosing group
20 and a 39 percent relapse rate in the late convertor
21 low dosing group.

22 Now, that compares to the rifampin which
23 in the low dosing group showed eight percent relapse
24 rate for early convertors and six percent relapse rate
25 for low convertors. That's consistent with the first

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1 slide we showed, which showed more relapsers in the
2 rifapentine patients who took low numbers of non-
3 rifamycin doses compared to the rifampin group that
4 took low doses.

5 DR. BASS: Yeah, I understand that very
6 well. Maybe I'm not expressing myself well, but I'm
7 trying to decide whether the difference in the two
8 pieces of information is due mainly to the inclusion
9 of ethambutol or to a different definition of what
10 nonadherence to the INH and rifampin part of the
11 regimen is.

12 And it seems that it's even possible that
13 nonadherence to ethambutol could have been influenced
14 by your protocol since once the susceptibility results
15 were known, that drug could have been discontinued and
16 resulted in artificial nonadherence.

17 DR. GORODETZKY: Well, it's true that it
18 was discontinued, but for many of those patients, by
19 the time the resistance data was back on the initial
20 isolates, we were well beyond the two-month intensive
21 phase.

22 Steve, do you want to try to answer that
23 question?

24 DR. RUBERG: Steve Ruberg from Hoechst
25 Marion Roussel.

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1 I think, Dr. Bass, Slide 39 is based on
2 the protocol definition of compliance, which includes
3 directly observed therapy. When we saw the
4 noncompliance issue arising, we did more exploratory
5 analyses, and Slide 47 represents all doses taken by
6 the patient. We wanted to include all of that
7 information in terms of our exploratory analyses.

8 And so we included or counted doses that
9 were not part of directly observed therapy. So there
10 is a slightly different definition in going from one
11 to the other related to the directly observed therapy,
12 which is part of protocol defined compliance. Okay?

13 DR. BASS: Yeah, I understand that.

14 CHAIRMAN HAMMER: Dr. Feinberg has a
15 clarification.

16 DR. FEINBERG: But as I understand it from
17 the briefing book you gave us, compliance defined by
18 the protocol was actually different for the two
19 different arms, and tell me if I'm interpreting this
20 correctly.

21 In the rifampin arm -- no, it just says in
22 the intensive phase dosing you had to receive
23 essentially three-quarters of the scheduled doses, 45
24 of 60, and then patients in the rifapentine
25 combination group were required to receive all 17

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1 scheduled doses by DOT.

2 I don't know if I'm interpreting that
3 correctly, but it seemed as if there's different
4 criteria for the two different arms.

5 DR. GORODETZKY: Yes, there were, but the
6 criteria for the non-rifamycin doses in the intensive
7 phase was identical. You remember in the rifapentine
8 arm, it was twice a week rifapentine, but daily INH,
9 PZA and ethambutol. So that 40, 40, five for the INH-
10 PZA, ethambutol is identical in both treatment arms.

11 DR. FEINBERG: For both treatments.

12 DR. GORODETZKY: And, in fact, that's what
13 allowed us to do the analysis in the intensive phase,
14 separating out the non-rifamycin doses from the
15 rifamycin doses.

16 CHAIRMAN HAMMER: Let's try to stay in
17 sequence.

18 Dr. Bass, are you --

19 DR. BASS: I'll pass.

20 CHAIRMAN HAMMER: Dr. Hopewell.

21 DR. HOPEWELL: In the presentations and
22 the briefing book, you've been very careful to say
23 pulmonary tuberculosis. Did you exclude patients with
24 extra pulmonary sites of disease specifically? And if
25 you didn't, are there any data on patients with extra

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1 pulmonary sites of disease?

2 DR. GORODETZKY: Yes, we did exclude
3 patients with extra pulmonary tuberculosis, and, no,
4 I don't believe we have any data on extra pulmonary
5 tuberculosis.

6 DR. HOPEWELL: And so you went through and
7 systematically checked urines, checked lymph nodes,
8 checked other things to be certain that there weren't
9 extra pulmonary sites of disease as well as pulmonary?

10 DR. GORODETZKY: Yes, sir. That was done
11 during baseline, yes.

12 DR. HOPEWELL: It's one of the sort of
13 intriguing things that is seemingly inexplicable, is
14 the amount of abnormal urinalysis results, a lot of
15 hematuria, a lot of proteinuria, pyuria.

16 DR. GORODETZKY: Yes, sir, they were.
17 They were balanced between the two groups. We don't
18 feel they were related to the treatment.

19 DR. HOPEWELL: No.

20 DR. GORODETZKY: But they were probably
21 related to the conditions specifically in South Africa
22 where we had more than 90 percent of our patients. We
23 can provide some more discussion of that.

24 DR. HOPEWELL: So at this point, maybe I'm
25 sort of jumping ahead, and I certainly don't know the

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1 regulations that well. The labeling would have to say
2 that extra pulmonary tuberculosis must be excluded
3 before A rifapentine regimen could be used?

4 DR. GORODETZKY: Well, I think, again,
5 this is a more regulatory issue, but I would think
6 that it would be indicated for pulmonary tuberculosis,
7 which is where we have our data, yes, sir.

8 DR. HOPEWELL: Okay. The second question.
9 The severity of disease estimation was predominantly
10 based on the differences in radiographic scores
11 between the two groups.

12 DR. GORODETZKY: Primarily, yes. We did
13 look at signs and symptoms. They were essentially
14 balanced between the two groups. There was a slight
15 trend towards increased frequency in the rifapentine
16 group, but the only statistically significant
17 differences we found was in the quantitative
18 evaluation of the baseline X-rays, and that was
19 specifically in cavitation.

20 DR. HOPEWELL: And so two sort of
21 questions that come from that. Was there any sort of
22 assessment of immunologic status, even a tuberculin
23 skin test, to know whether or not there were any
24 differences in what might be viewed as host
25 responsiveness to the disease between the two groups?

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1 DR. GORODETZKY: I don't believe there was
2 anything specifically aimed at immunologic status.
3 There was a whole host of the usual clinical
4 chemistries and those kinds of things done and a full
5 physical exam.

6 DR. HOPEWELL: Right.

7 DR. GORODETZKY: But, Mario, was there
8 anything specific? I didn't think so.

9 DR. HOPEWELL: And similarly, was there
10 any quantitative bacteriology done early in the course
11 to see if -- I mean the prevalative positive smears
12 was the same in both groups, but were actually
13 populations evaluated and were they similar in both
14 groups?

15 I know there were some EBA data presented
16 in the briefing book, but I don't think any of that
17 came.

18 DR. GORODETZKY: The bacteriology was
19 quantitative in that there were counts, and there were
20 also smears done, and I believe those were balanced
21 between the two groups, although the pulmonary X-rays
22 would indicate the possibility of a greater bacterial
23 load in those patients with the more severe cavities.
24 No, but I don't believe that showed up in the bacteriology.

25 DR. HOPEWELL: The scoring of X --

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1 DR. GORODETZKY: -- balance between the
2 two groups.

3 DR. HOPEWELL: The scoring of the X-rays
4 is a notoriously difficult thing to do.

5 DR. GORODETZKY: And, in fact, in this
6 case there was a new methodology developed because
7 there was not one in existence, and Dr. Lynch invented
8 one for this trial.

9 DR. HOPEWELL: And finally, although this
10 may be in the protocol and I missed it, were the drugs
11 dosed with food or fasting?

12 DR. GORODETZKY: The drugs were dosed in
13 the morning. It was not specified -- early in the
14 morning -- and it was not specified whether they
15 should be dosed with or without food.

16 We did question the patients about whether
17 they had eaten in the last hour or intended to eat in
18 the next two hours. Got a lot of positive responses
19 in both groups for that, but the pharmacokinetic data
20 that I showed showed fasting data, and we felt that
21 the pharmacokinetics we could achieve with especially
22 the blood levels out 72 hours were sufficiently good
23 in the fasting state that we did not have to specify
24 food conditions.

25 Also, specifying food conditions would

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1 have a differential effect potentially on the INH. So
2 we did not specify in this case.

3 DR. HOPEWELL: That's all. Thanks.

4 CHAIRMAN HAMMER: Thank you.

5 Dr. Snider.

6 DR. SNIDER: I think the sponsor has made
7 an argument that the difference in relapse in the two
8 regimens is primarily related to nonadherence with
9 non-rifapentine drugs in the initial phase of therapy,
10 perhaps also to a lesser extent due to baseline
11 severity of disease in male gender, and I think the
12 kinds of univariate approaches that have been taken to
13 the presentation have been helpful in dissecting that
14 apart.

15 But my question is whether any
16 multivariate analysis has been done to see if you take
17 all of those things into account into some kind of
18 multivariate model whether you can show equivalence in
19 the relapse.

20 DR. GORODETZKY: I'll call on my
21 statistical colleagues.

22 DR. RUBERG: As part of our exploratory
23 analysis, we did not do formal statistical analysis of
24 the multivariate approach, although descriptively I
25 believe it's in Slide 53 where you had the complete

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1 conversion and nonconversion and relapse rates. In
2 that sense, descriptively we are showing several
3 different variables on the page at one time.

4 There are two treatment groups. There is
5 conversion status, conversion by two months or not two
6 months. There are different compliance groups
7 depicted there.

8 So in a sense this is a pictorial
9 description of a multivariate approach, and as we
10 pointed out in the presentation, there are some
11 similar patterns across the treatment groups, but
12 there are some distinct differences still in the
13 treatment groups, and I think Dr. Gorodetzky
14 mentioned, for example, the high relapse rates in the
15 low compliance groups on rifapentine exist even when
16 accounting for these other variables or breaking out
17 these other variables. It's still higher, the 13 and
18 39 percent. It could be eight and six percent on the
19 bars that are on the far right side, representing the
20 low dosing group with the non-rifamycin medications.

21 DR. SNIDER: Okay. The second question is
22 that Mike Iseman and no one else mentioned once a week
23 isoniazid in the continuation phase and what
24 contribution that might make. Although one could,
25 indeed, argue about the nonadherence in the early

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1 phase being very important, the question arises as to
2 whether one might overcome that with twice a week
3 therapy, and I think you suggested that, but it seems
4 to me that it may be more important not for the
5 rifapentine, but for the fact that you don't have a
6 companion drug that is as good as rifapentine for once
7 a week therapy.

8 DR. ISEMAN: Certainly that's a very
9 critical point, Dr. Snider. The threat of giving a
10 long acting drug that has therapeutic activity for 72
11 hours in contrast with even at 900 milligrams INH
12 would not persist, you would have then unbalanced
13 therapy, in effect, possible monotherapy, which either
14 could create drug resistance or conceivably lead to
15 reduced efficacy.

16 And I think the continuation arm of once
17 weekly therapy was sufficient to keep the cultures
18 negative, but in contrast to the rifampin arm which
19 noncompliance early on didn't lead to a greater risk,
20 but twice weekly INH-rifampin was more effective in
21 mopping up those persistent organisms.

22 I interpret the data to say that if the
23 front end of the therapy is really loaded to reduce
24 these putative populations that are the ones that put
25 a patient at risk of reactivation, once weekly is

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1 adequate, but if it's not done weekly, it's probably
2 not sufficient.

3 DR. SNIDER: And finally, the follow-up
4 question about pharmacokinetics or interactions
5 between the drugs that are being given with regard to
6 either absorption or I wouldn't expect a lot of
7 metabolic things going on, but it's conceivable.

8 What do we know about the co-
9 administration of rifapentine with the other drugs in
10 this regimen? Is there any impact?

11 You know, it just raises questions not
12 only relative to the efficacy, but this weird
13 hyperuricemia and so forth.

14 DR. ISEMAN: I think there's some evidence
15 that rifampin given day is a very potent inducer. It
16 may change the distribution of PZA and, therefore,
17 actually partly attenuate the hyperuricemia. I looked
18 at the relatively higher hyperuricemia among the
19 rifapentine group. My inference from that data was
20 that rifapentine didn't have that same attenuating
21 effect. Perhaps it's because it's less active in
22 elimination of modifying the renal handling of
23 ureates.

24 I think it was a causal relationship, but
25 I don't think it's clinically significant.

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1 DR. SNIDER: That's all.

2 CHAIRMAN HAMMER: Thank you.

3 Dr. Bertino.

4 DR. BERTINO: Could you clarify for me how
5 many patients in this trial were HIV positive?

6 DR. GORODETZKY: There were 13 patients
7 who were HIV positive in the trial.

8 DR. BERTINO: Okay. Thanks.

9 On page 207 of the briefing book under
10 adverse events, when a statistical analysis was done
11 on overall adverse events, did females have a greater
12 statistically significant increase in AEs over men?

13 DR. GORODETZKY: I'll turn to my
14 colleagues for that.

15 DR. RUBERG: We did not do a formal
16 statistical analysis of adverse event to generate P
17 values for differences between various subgroups or
18 across the adverse events.

19 DR. BERTINO: Okay, and you probably
20 didn't do a multivariate analysis on any of it.

21 DR. RUBERG: No, we did not.

22 DR. BERTINO: Okay. Is there any plans to
23 look at other than indinavir? I mean that's a fairly
24 significant drug interaction. Since we can't do
25 therapeutic drug monitoring of indinavir, it would

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1 seem that the combination with rifapentine essentially
2 would make that drug of no use in HIV infected
3 patients because of the potential for HIV resistance.

4 DR. GORODETZKY: In terms of potential
5 other studies, none planned at the moment. Certainly
6 other studies will be done.

7 In terms of the potential use of
8 rifapentine with indinavir, as we showed, it falls in
9 the middle with regard to reducing the Cmax for
10 indinavir.

11 Rifapentine is an enzyme inducer. It did
12 reduce the Cmax of indinavir to 55 percent compared to
13 the 87 percent that rifampin does and the 22 percent
14 that rifabutin does. So it's right in the middle.

15 Whether it will prove to be useful with
16 indinavir we really don't know at this point. It's
17 possible, but we just don't know.

18 DR. BERTINO: So if Cmax was reduced,
19 presumably area under the curve was reduced. Do we
20 know --

21 DR. GORODETZKY: Area under the curve?

22 DR. BERTINO: -- proportionally how much?

23 DR. GORODETZKY: Would that also be about
24 55 percent, Mark?

25 DR. ELLER: I think it was approximately

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1 70 percent.

2 DR. GORODETZKY: Seventy percent.

3 DR. BERTINO: All right. So a big
4 reduction --

5 DR. GORODETZKY: Yeah, isn't too much.

6 DR. BERTINO: Well, you know, I'm just
7 wondering, you know, if the FDA eventually approves
8 this drug, if the recommendation should be not to use
9 concurrent indinavir with this regimen.

10 DR. GORODETZKY: I think we're going to
11 discuss that in a little more detail further on, but
12 just as a preliminary answer, I think that at the
13 moment we have very little data about the use of
14 rifapentine in HIV positive patients with or without
15 any other drugs.

16 I think given that limited amount of data,
17 there would certainly have to be a great deal of
18 caution in any combined use right now of rifapentine
19 with --

20 CHAIRMAN HAMMER: That's the current
21 recommendation for rifampin, not to use it.

22 DR. BERTINO: Okay. Thanks.

23 CHAIRMAN HAMMER: And it's likely --

24 DR. GORODETZKY: Again, we have very
25 little data at the moment. Certainly a great deal of

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1 caution at least.

2 CHAIRMAN HAMMER: Thank you.

3 Dr. D'Agostino.

4 DR. D'AGOSTINO: I'd like to ask some of
5 the questions or a couple of questions on the actual
6 analyses that led the statement that they're
7 equivalent treatments.

8 When you have an equivalency analysis and
9 you assign subjects that you don't really have
10 complete information, when you assign them the same
11 way in both groups, you tend to make the two groups
12 look very similar. You know, for example, if there
13 was no culture data on any subjects, you would say
14 that both groups were identical.

15 And I'm concerned that in the definition
16 or in the analyses the ways you tried to address the
17 missing data or the no culture is going to tend to
18 make the groups look similar. So could you tell me
19 how many subjects out of the 286 and 284 -- how many
20 subjects actually didn't have culture data available
21 in that equivalency analysis?

22 If I understand correctly, you called them
23 all positive culture. So you made them nonsuccesses.

24 DR. RUBERG: We're getting the number.
25 We're going to try and derive the number specifically

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1 to your question about how many had missing values.

2 But perhaps in the meantime I could show
3 Slide E-162 where we show confidence intervals looking
4 at protocol correct patients who had --

5 DR. D'AGOSTINO: That has a problem. Show
6 it. I think it would be informative, but that has a
7 problem, too, because that's the ones that you have
8 all of the information on. It's the group that you
9 don't have information on that is, I think, where the
10 balance hangs one way or the other.

11 How did this come out? Actually this
12 would be --

13 DR. RUBERG: Right. The missing values
14 were balanced across the treatment groups, and when we
15 did have them, we wanted to handle them a similar way
16 in different analyses for each of the treatment
17 groups, rifampin and rifapentine, and here are four
18 different analysis approaches, as mentioned by Dr.
19 Gorodetzky in the presentation, regarding the handling
20 of missing values and the confidence intervals for the
21 intent to treat and the protocol correct populations.

22 So you can see that they're very
23 consistent. Estimate of the difference is given by
24 the colored dots, green for intent to treat and orange
25 for protocol correct, as well as width of the

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1 confidence interval.

2 DR. D'AGOSTINO: And if you wanted to show
3 one drug was superior to the other, that would be
4 exactly what I would suggest you would do, that you'd
5 handle them in the same way because that way you would
6 diminish the difference.

7 Here you want to show equivalency. So
8 somehow you want to handle the missing data in an
9 opposite fashion. So you say what's the potential for
10 the maximum separation for these two groups. Do you
11 see the point I'm making?

12 DR. RUBERG: Yeah, I understand the point
13 in the sense to intentionally induce a difference or
14 a bias between the treatments based on the missing
15 values to see how different they could be.

16 DR. D'AGOSTINO: Yeah. What you've done
17 here, in the first one you say we've made it worse.
18 You made it worse in the sense that the success rate
19 is the lowest possible.

20 DR. RUBERG: Correct.

21 DR. D'AGOSTINO: But you made it the
22 lowest possible in both groups.

23 DR. RUBERG: Correct.

24 DR. D'AGOSTINO: Therefore making the two
25 groups look very similar, and I think it would be

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1 interesting somewhere if you can't pull it right out
2 to see that number because if it's a significant
3 portion of the data, I think there's a concern. I
4 think if it's not a significant portion of the data,
5 it might not be a concern.

6 DR. RUBERG: Right. That's something that
7 we can notes, perhaps investigate, but in the intent
8 to treat --

9 DR. D'AGOSTINO: Well, can you pull it out
10 before the morning is over?

11 DR. RUBERG: Okay. We'll see what we can
12 do.

13 DR. D'AGOSTINO: I think we should know
14 what it is.

15 CHAIRMAN HAMMER: Or you can give it --

16 DR. RUBERG: We'll do the best we can.

17 CHAIRMAN HAMMER: -- early this afternoon.

18 DR. D'AGOSTINO: Yeah. The other question
19 then, all of these other analyses that followed were
20 always the intent to treat analyses from the intent to
21 treat population, all of the other analyses in terms
22 of groups and divisions?

23 DR. RUBERG: What was presented in Dr.
24 Gorodetzky's presentation was based on that, yes.

25 DR. D'AGOSTINO: Then just one last

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1 question in terms of how you interpret the study and
2 how you pull out results from the study. I understand
3 the compliance, or I think this question in terms of
4 beating the data to death by looking at all of these
5 sub-analyses, though I think it's appropriate for you
6 to do that, but how do I disentangle the package that
7 I have in the RPT group, a bigger noncompliance? How
8 do I disentangle that?

9 I mean you can tell me that's because of
10 other drugs, but it's still part of the treatment. So
11 how do I feel comfortable about saying that I
12 shouldn't worry about it in interpreting the trials?

13 DR. RUBERG: I'm not exactly sure the
14 question is how we're distinguishing the non-
15 rifamycin?

16 DR. D'AGOSTINO: Well, you say the
17 noncompliance doesn't have to do with the RPT itself.
18 It has to do with the other drugs, but I don't know
19 how to separate that in terms of interpreting the
20 trials. It's a regimen that you gave as opposed to a
21 particular drug.

22 DR. RUBERG: There's definitely
23 confounding between the regimen and trying to sort
24 these matters out, and that also happens in the
25 continuation phase.

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1 We did look at compliance with rifapentine
2 and rifampin, and as one might expect, if you got less
3 rifapentine or less rifampin, the failure rate or the
4 relapse rates were also higher, but the differences
5 were not that dramatic.

6 Where we saw the most dramatic difference
7 was in the group that got low dosing on the INH, PZA,
8 and the ethambutol, is where we saw this very wide
9 separation in the relapse rates, and we thought was
10 most predictive or descriptive of the difference.

11 DR. D'AGOSTINO: Thank you.

12 CHAIRMAN HAMMER: Dr. Self.

13 DR. SELF: I'd like to continue a bit on
14 that theme of missing data and the challenges of doing
15 an equivalence trial.

16 This is also an unblinded trial, and for
17 the reasons that were just described in looking at
18 equivalence, it actually motivates, I think, looking
19 a little more carefully at the subgroups as well as
20 worrying about what data are not there.

21 And in one of the slides describing the
22 various reasons for therapeutic failure, the treatment
23 failure is broken down into two categories: culture
24 defined failure, but then there's this category
25 "investigator defined failure." There were three of

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1 these in the comparison arm and none of these in the
2 rifapentine arm.

3 I wonder if somebody could describe what
4 investigator defined failure was.

5 DR. GORODETZKY: There were, indeed --
6 your recollection is quite correct -- there were three
7 of the eight in the rifampin arm. Five were confirmed
8 by culture and three were investigator defined.

9 And as I understood it, it was simply the
10 investigator -- in some cases the patient just left
11 the trial, and the investigator felt that perhaps
12 there signs and symptoms of relapse or recurrence,
13 whether it was during treatment as treatment failure
14 or relapse inflator, but never got a culture to
15 confirm them, and the only explanation that we would
16 have for that would be to call them investigator.

17 They were not culturally -- we broke them
18 into just simply two groups, those that were confirmed
19 by sputum culture and those that were not. Those that
20 were not we considered investigator defined.

21 I know that's not a terribly satisfactory
22 to you. Is there anything further than that, Mike?

23 That's basically all we have.

24 DR. SELF: So how would they be
25 distinguished from choice to discontinue by a patient

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1 investigator which got left on the previous page, not
2 included in the therapeutic failure category?

3 DR. GORODETZKY: Choice to discontinue was
4 not necessarily because they felt there was -- anyone
5 felt there was a reoccurrence of TB. It was a patient
6 who no longer wanted to be in the trial, a patient who
7 may have gone to jail. There were a variety of
8 reasons, but they were clearly distinguished by the
9 response of the investigator on the case report form
10 as the patient chose to leave the trial, not related
11 to the potential recurrence of the disease.

12 DR. SELF: I have one other question, the
13 specific one about numbers. There were 722 that were
14 enrolled and randomized, and then we lose 152 right
15 away to get to what's described as an intent to treat
16 group. There is a statement that most of those were
17 due to negative culture at baseline. What were the
18 rest? How many were not in that?

19 DR. GORODETZKY: We can give you the
20 specific reasons why they dropped out. We'll call up
21 that slide for you.

22 The two major reasons were negative
23 culture and a culture found to be resistant, and of
24 course, those were found after the patients had
25 already been admitted to the trial. So they were then

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1 dropped in making up the intent to treat. Those were
2 by far the two largest.

3 But we do have the full listing of those
4 150. You can see that in the rifapentine group there
5 are only seven out of the 75 who are not in those
6 other two categories.

7 DR. SELF: Thank you.

8 CHAIRMAN HAMMER: Dr. Feinberg.

9 DR. FEINBERG: I have one comment and then
10 two questions. I guess I'm concerned. My comment is
11 that adding up the numbers on page 43 of the briefing
12 book, it looks to me that about 299 of these 722
13 patients discontinued the study at some point for
14 something that looks to me like a 40 percent
15 cumulative dropout rate, and I guess I'm concerned
16 that the, you know, results and interpretation of the
17 results will suffer from a dropout rate that's that
18 substantial.

19 And here are my two questions. You stated
20 that more than or at least 90 percent of the patients
21 were enrolled in South Africa, and I guess my question
22 is, you know, why were not more centers and more
23 patients enrolled in the United States. One would
24 like, of course, to feel that these results are
25 generalizable to a U.S. population.

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1 DR. GORODETZKY: I believe that the issues
2 were practical availability of patients. There is a
3 trial already ongoing in the U.S. in TB patients by
4 the CDC, and in terms of availability to get
5 reasonable entry rights, patients were enrolled
6 primarily in South Africa.

7 Now, we have done comparisons between the
8 results among North American and South African
9 patients, and the results are essentially the same,
10 although the numbers are very small in the U.S., U.S.
11 and Canada.

12 The nature of the patient populations was
13 very slightly different. The South African patients
14 were somewhat sicker patients. They were a slightly
15 higher proportion of females in North America than in
16 South Africa, although it was still predominantly male
17 even in North America. The patients in North America
18 weighed a little more than the patients in South
19 Africa.

20 All of these things are consistent with
21 perhaps a lesser intensity of disease in North America
22 than South Africa. They were, however, for all of
23 these factors balanced across treatments, and when you
24 look separately at efficacy in the North American
25 patients versus the south African patients, again,

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1 there are no significant differences. They're
2 essentially equivalent in success rates in both cases.

3 DR. FEINBERG: All right. Although those
4 numbers, of course, are very small.

5 DR. GORODETZKY: The numbers are very
6 small, and when you start subcategorizing they get
7 even smaller.

8 DR. FEINBERG: Okay, and then my second
9 question is for Dr. Iseman. Could you please restate
10 the hypothesis that you felt explained the difference
11 in sputum conversion in two months versus the culture
12 negativity rate at six months and then the subsequent
13 relapse rate?

14 DR. ISEMAN: Briefly stated, whether the
15 patients converted early or late, the continuation
16 arm, either the rifapentine or the rifampin arm, were
17 sufficient to keep the cultures negative through the
18 six months and termination of therapy, but because of
19 the late conversion from the absence of early
20 bactericidal activity, one of those putative
21 populations was probably represented in higher numbers
22 than had been the rifapentine arm, and once weekly,
23 rifapentine and INH, wasn't sufficient to eliminate
24 those persisting organisms, and they presumably then
25 become the vectors for reactivation post treatment.

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1 Was that coherent?

2 If I might take the opportunity to comment
3 about your observation about the dropout rates, what
4 you've just described is the world TB chemotherapy
5 trials. It's very frustrating. One of the reasons
6 it's very difficult to conduct, and I point out in the
7 United States and U.S. Public Health Service Trial 21
8 that embraced a six-month arm and a nine-month arm, in
9 the six-month arm there was 38.6 percent of the
10 patients lost to protocol and there were 50 percent in
11 the nine-month protocol. So that's pretty much par
12 for the course.

13 CHAIRMAN HAMMER: Dr. Hamilton.

14 DR. HAMILTON: I'd like to follow up on
15 the question just posed by Dr. Feinberg concerning the
16 applicability of the population studied to a more
17 generalized world population, and in doing so ask my
18 consultants here and those in the audience who are
19 substantially more knowledgeable about this than I
20 whether there are predictable differences in
21 metabolism of anti-tuberculous drugs by race or
22 ethnicity.

23 Somewhere deep in the cobwebs here there
24 is this notion of acetylation of INH as being
25 different, and I'm wondering if there are any efficacy

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1 or safety issues that might be further addressed in
2 this regard.

3 DR. SNIDER: I mean, I think that's a
4 particularly important point with regard, again, to
5 the less frequent dosing of isoniazid, you know, in
6 the continuation phase because the rapid acetylators
7 are going to have levels above the MIC for a
8 significantly shorter period of time.

9 DR. ELLER: In terms of the rifapentine
10 PK, we did a population pharmacokinetic analysis of
11 the results for Protocol 8 and did not find
12 demographic features relating to race to influence the
13 pharmacokinetics of rifapentine.

14 Acetylator status, there may be slight
15 variations in Asian populations, but basically it's
16 almost a 50-50 split.

17 DR. SNIDER: I think in Asians it's like
18 90-10, which is --

19 DR. ELLER: Right. In Asians it's
20 different, but in Africans and Caucasians it's closer.

21 CHAIRMAN HAMMER: Would you please state
22 your name for the transcript?

23 DR. ELLER: Yes, Mark Eller, Hoechst
24 Marion Roussel.

25 DR. HAMILTON: The second point, mention

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1 was made by Dr. Gorodetzky, I think, concerning
2 briefly the efficacy of rifapentine to treat MAC. I
3 was not clear whether there were formal studies in
4 that regard, whether we can count on it, whether we
5 have MICs that are useful here.

6 We're talking about enrolling patients in
7 this study prior to culture positivity, I think; is
8 that right? They're initiated on treatment expecting
9 the culture to become positive. Are we exposing those
10 who have MAC pulmonary disease to an inadequate
11 regimen early on?

12 I'd like some reassurance there.

13 DR. GORODETZKY: Well, there were trials
14 initiated in MAC. However, they were discontinued.
15 The patients were not available during the changing
16 demographics of the disease, and the only reason those
17 patients were included in the presentation was for
18 safety data, not for efficacy data.

19 We are making no claims for efficacy, and
20 certainly if you were going to treat for MAC, we would
21 not have any data to recommend rifapentine at this
22 time.

23 DR. HAMILTON: What is the sensitivity, or
24 are we believing those these days?

25 DR. KENNY: I can give you the range of

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1 MICs for --

2 CHAIRMAN HAMMER: Please come to the
3 microphone.

4 DR. KENNY: Mike Kenny, Hoechst Marion
5 Roussel.

6 The MIC range for rifapentine from the
7 published literature is about .6, 32 micrograms per
8 mL.

9 DR. HAMILTON: And finally, probably it
10 was said, but I missed it. How many cultures were
11 actually take at these follow-up points? Was it one
12 or two or three? What?

13 DR. GORODETZKY: There were a variety of
14 numbers of cultures taken throughout the treatment
15 period. During the follow-up period, there was one
16 culture taken at each of the visits unless there was
17 a suspicion that there might be relapse, and then a
18 second culture was taken.

19 So there were essentially single cultures
20 at each of the follow-up time points.

21 DR. HAMILTON: I'd like to ask the
22 consultants then is that of any concern to you who
23 have some greater knowledge about the reproducibility
24 and consistency of findings.

25 DR. BASS: I would say in the absence of

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1 clinical suspicion of relapse, the, you know, prior
2 probability would be so low that getting additional
3 cultures would not be very productive.

4 CHAIRMAN HAMMER: Dr. Pomerantz.

5 DR. POMERANTZ: First of all, I was
6 thinking, gosh, wouldn't it have been simple if there
7 wasn't this relapse difference, but unfortunately
8 there is, and obviously that's going to be the main
9 point of questions, as you've heard, even though Dr.
10 Iseman has given his usual very erudite statements and
11 has convinced at least some of us of the reasons for
12 this relapse change.

13 But let me just ask a few other ones. One
14 of the things that was not clear to me until it was
15 brought out is there really were HIV infected
16 individuals in these groups, albeit low, but certainly
17 enough to have an effect.

18 Since it is South Africa, was HIV II as
19 well as I looked for?

20 DR. GORODETZKY: The answer is no.

21 DR. POMERANTZ: It was not. That's a
22 problem because even though it's not the major area,
23 there still is a group of HIV II infected individuals
24 in South Africa that could get through your screen.

25 As you know, the third generation ELISAS

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1 in the United States pick up HIV II. So are you sure
2 that it wasn't picked up without knowing, you know?

3 DR. STALLARD: Mya Stallard (phonetic)
4 with Hoechst Marion Roussel.

5 They were supposed to do an ELISA, and if
6 that was suspicious, they were supposed to follow up
7 with a Western Blot.

8 DR. POMERANTZ: Yeah, but what ELISA did
9 they use in South Africa?

10 DR. STALLARD: My understanding, it was
11 the same ELISA that was used in the United States.

12 DR. POMERANTZ: Are you sure?

13 DR. STALLARD: That was my understanding.

14 DR. POMERANTZ: Okay. Because that's not
15 always the case, and that's one of the problems,
16 because only the third generation ELISAs pick up HIV
17 II and only some of those do that, and that can be
18 missed very easily on the others.

19 So you might not know what your HIV status
20 is there.

21 The second thing is in the ones that you
22 did pick up, do you have a good indication of the
23 state of disease, viral RNA levels in those patients,
24 to make sure that you don't have those confounding
25 variables separating the two groups?

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1 DR. GORODETZKY: No, there was no
2 additional work done on those. Once it was found that
3 they were HIV positive, that was all that was done,
4 and usually that information was found late, and
5 that's why, indeed, it was an exclusion criteria for
6 the study, and those few got in because they were
7 late.

8 And, in fact, as I said, only one of those
9 patients relapsed.

10 DR. POMERANTZ: Right. Okay.

11 DR. GORODETZKY: And that was not with a
12 resistant organism.

13 DR. POMERANTZ: Okay. Thank you.

14 The other question I have is when you look
15 at the data on cavities, which is on page 50 of the
16 book that was provided to us, it was somewhat
17 difficult to understand when you first look at the
18 table, which is Table 8, because it is written down
19 that a P value of .032 is found in the cavitation
20 area, and that's really, as I found out just in
21 rereading this and listening to you talk, is only for
22 bilateral cavities.

23 If you look at total cavitation, not just
24 the surface area, but just the number of patients that
25 had cavities, they're the same. So I just wanted to

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1 point that out to this committee because I wasn't
2 clear about that, and the packet is somewhat difficult
3 to understand, maybe even not quite the best way of
4 representing this data, because that makes it less
5 convincing to me at least that it was the cavitation
6 difference here.

7 And the other thing that came up that Dr.
8 Iseman talked about is that you had one radiologist
9 reading these films, no confirmation from another
10 radiologist, in the fact that it's hard enough to
11 quantitate these, and then at the same time using a
12 not validated in the literature way of evaluating
13 them. At least it seems that it was invented by Dr.
14 Lynch, as was said.

15 Wouldn't it have been better to at least
16 look at it with another radiologist?

17 DR. ISEMAN: We struggled with this issue
18 as we tried to, from my perspective, not to make
19 apologies, but to understand why the disparate results
20 evolved.

21 Dr. Lynch has actually practiced
22 quantitative analysis of our patients with
23 microbacterium avium (phonetic) lung disease and
24 developed a system which, I think, by zone and
25 intensity of infiltrate and extent of cavitation has

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1 some clinical applicability and took that and modified
2 it in an effort to assess the extent of disease.

3 He found, as well, although it didn't
4 predict relapse, that there was increased areas of
5 pneumonic consolidation among the patients in the
6 rifapentine arm, but it was an effort to understand
7 the differences.

8 To have two individuals read it would have
9 been really extraordinary. He had to go there and
10 read hundreds of X-rays, and I think the fact that he
11 read them blinded gave me some comfort as to the
12 utility of the results.

13 DR. POMERANTZ: Thank you.

14 CHAIRMAN HAMMER: Dr. Lipsky.

15 DR. GORODETZKY: I would like to amplify
16 just slightly perhaps a clarification with regard to
17 the Table 8 on page 50 that it lists two P values of
18 .032. It's coincidental that those are the same.
19 They are different.

20 DR. POMERANTZ: Oh, I understand.

21 DR. GORODETZKY: The first P value does
22 reflect the difference in the distribution among
23 nonunilateral and bilateral, and there was a
24 significant difference between the rifapentine and the
25 rifampin group. As you can see in the percentages,

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1 for unilateral it's at 52 versus 40 percent, and for
2 bilateral there's a 43 versus a 53 or 54, and that was
3 sufficient for that P value.

4 DR. POMERANTZ: But when I read that
5 table, if I didn't read the text carefully and I just
6 looked at the table, it would look to me that the P
7 value is different in total cavitation, instead of
8 stating it that it is the difference between
9 unilateral and bilateral because there is no
10 difference in the people that have cavity, just
11 cavitation.

12 DR. GORODETZKY: Oh, no. You're quite
13 right. It's the difference in the distribution of
14 those values.

15 DR. POMERANTZ: I'd just rewrite that
16 table. That's all.

17 DR. GORODETZKY: Okay. that's really what
18 I wanted to clarify, and I apologize for the
19 confusion.

20 CHAIRMAN HAMMER: Dr. Lipsky.

21 DR. LIPSKY: It appears that the
22 background for developing a once weekly dosing with
23 this drug was based on its long half-life in some
24 early clinical pharmacology studies. In the
25 background book, you referred to early bactericidal

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1 activity in a study that was done it looks like in the
2 initial treatment, prior to other treatment, and you
3 referred to a synopsis and a page which I can't find,
4 at least the data on that.

5 Do any of you have, you know, any of that
6 data that looks at -- and perhaps if you don't have
7 the -- do you have this book in front of you or do you
8 want me to read it?

9 I'll read it. "In an open label, parallel
10 groups, active control, clinical pharmacology studies,
11 patients were randomized to one of three comparative
12 dosing, 600 milligrams of rifapentine on day one only,
13 200 milligrams of isoniazid on days one and two, and
14 600 milligrams of rifampin on days one and two, and
15 the study showed that this mean number of . . . units
16 of sputum for patients receiving . . . were
17 significantly decreased from baseline."

18 Do you have that data? And then you go on
19 saying from this data we can develop this. You know,
20 the dosing came forward. Do any of you know what I'm
21 talking about or reading?

22 Because going through the book I can't
23 find --

24 PARTICIPANT: What page are you --

25 DR. LIPSKY: I'm reading on page 28 in the

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1 beginning.

2 And perhaps while you're doing that, for
3 the relapses, it appears that we've made a lot of
4 discussion on rifapentine. What about the once weekly
5 isoniazid? How are you interpreting that? I mean
6 where's the problem here?

7 DR. GORODETZKY: I think again, and
8 perhaps we're reiterating here, that if in the initial
9 intensive phase of treatment the treatment with the
10 non-rifamycin medications is not sufficient to hit the
11 bacterial infection hard, that is, to do a full
12 eradication, then perhaps once a week rifapentine and
13 INH -- and we can't separate the two because they were
14 both given together -- is insufficient, and that was
15 the suggestion.

16 And the counterbalance to that is in the
17 group of patients who are in the high dosing group,
18 who took a large number of the doses of INH, PZA, and
19 EMB, the relapse rates were very low, and in that
20 group there was only a single relapser. So we felt
21 that in that group when they took a lot of the non-
22 rifamycin medications early there was sufficient
23 bactericidal activity that once a week rifapentine and
24 INH was sufficient in the four months of continuation.

25 Now, again, I'm reiterating what we had

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1 already said.

2 DR. LIPSKY: I realize, but the problem in
3 the once a week administration you believe is with the
4 INH or -- I realize you're giving two drugs, and it
5 may be impossible.

6 DR. GORODETZKY: That's right.

7 DR. LIPSKY: But isn't it more logically
8 to be with the INH?

9 DR. GORODETZKY: It very well may be, but
10 we can't separate them because they were given
11 together.

12 DR. LIPSKY: I mean, still you're giving
13 a drug that has a half-life of three hours --

14 DR. GORODETZKY: Sure, yeah.

15 DR. LIPSKY: -- and the pharmacodynamics
16 are a little bit --

17 DR. GORODETZKY: I think stated in the
18 generality if you have not done sufficient eradication
19 in the first two months in your intensive phase, then
20 once a week combination with rifapentine and INH --
21 and it may, indeed, be the INH -- is not sufficient.
22 There's no way to separate those out.

23 In rifapentine we don't claim a seven-day
24 half-life on that one either. What we're claiming is
25 at 72 hours we are above the MIC.

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1 DR. LIPSKY: Right.

2 DR. GORODETZKY: So I don't know which
3 drug it is. It's more likely to be INH, which has the
4 shorter half-life.

5 DR. LIPSKY: I realize with resistance and
6 what we understand about tuberculosis you can't do the
7 study.

8 DR. GORODETZKY: Sure.

9 DR. LIPSKY: But you'd wonder if what
10 happens if we didn't have a rifamycin at all in this
11 study.

12 DR. GORODETZKY: Yeah, and I don't --

13 DR. LIPSKY: I mean what would happen?

14 DR. GORODETZKY: Yeah.

15 CHAIRMAN HAMMER: I think Dr. Feinberg
16 wanted to ask a clarifying question.

17 DR. LIPSKY: But still I wonder is there
18 an answer to -- it looks like you've got some
19 interesting data early on on what happened.

20 DR. GORODETZKY: Yes, we're getting that.
21 In fact, it's Protocol 6, and we do have some back-up
22 slides on that. We can show you the data on the early
23 bactericidal activity study.

24 CHAIRMAN HAMMER: Go ahead, Judith.

25 DR. GORODETZKY: And in the briefing book

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1 I'm told it's on page 319.

2 DR. KEUNG: Anther Keung from Hoechst
3 Marion Roussel.

4 We had done an early bactericidal activity
5 study in South Africa, and the dose of rifapentine
6 given was 600 milligram dose on day one and rifampin
7 as a comparison drug was given, a 600 milligram dose,
8 on both day one and day two due to the shorter half-
9 life of rifampin.

10 And we also had an INH group into the
11 study as a positive control.

12 Next slide, please.

13 And the results of this study showed that
14 rifapentine decrease the coniforming (phonetic) of
15 bacilli after a single dose about 0.23, which is
16 comparable of rifampin when it's given on both day one
17 and day two.

18 When followed by INH, which is decreased
19 by 0.45 and is in a log scale, and we do a statistical
20 analysis on this study among those three groups, we
21 find that there was no statistical significant
22 difference between all those three, and as you can see
23 the number of the subject relatively small in the
24 study.

25 DR. LIPSKY: Thank you.

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1 DR. ISEMAN: Thank you.

2 It is a very important question -- this is
3 Mike Iseman -- about the activity of isoniazid,
4 particularly in relation to acetylation phenotype. In
5 the Madras, India, studies the patients were initially
6 treated in the hospital with INH, streptomycin and PAS
7 in the days when this study was done and then
8 discharged to follow up with intermittent therapy.

9 Individuals receiving once weekly
10 isoniazid PAS, a very weak drug, did quite well unless
11 they were rapid acetylators of INH, in which case the
12 regimen fell short of its intended purpose.

13 So it's certainly possible that it's the
14 half-life of INH that influences the adequacy of the
15 once weekly administration.

16 DR. LIPSKY: Thank you.

17 And just for the record, it's interesting
18 you've talked about the cobwebs, but I believe with
19 isoniazid that it was the very first drug in which a
20 genetic polymorphism was shown to occur with
21 metabolism in the classic study by Kuzick (phonetic).

22 CHAIRMAN HAMMER: Just a brief question.
23 We're dealing with the six-month follow-up data
24 because we're dealing with accelerated approval issues
25 today, but if I recall correctly, 68 percent of the

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1 subjects were followed through 12 months.

2 I may have missed it, but could we just go
3 over the 12-month follow-up data?

4 DR. GORODETZKY: The 12-month data, the
5 pertinent issue was that there were two additional
6 rifapentine relapses, which brought the numbers from
7 25 up to 27 when we included that 68 percent of
8 patients.

9 CHAIRMAN HAMMER: Thank you.

10 And just the last question. The
11 population PK was done in Protocol 8?

12 DR. GORODETZKY: Yes, it was.

13 CHAIRMAN HAMMER: So the timing of that,
14 was that done pre-dose, post dose? What did it tell
15 us about the PK profile in this study in the
16 populations we've been discussing at the end of the
17 dosing interval?

18 DR. ELLER: If you could bring up Slide K-
19 19.

20 This slide shows the protocol design for
21 the population PK component of Protocol 8, and
22 basically we took -- tried to get six samples per
23 patient, two each, on days one to three, 56 to 58, and
24 175 to 77, so both in the intensive phase and in the
25 continuation phase, and go them on 280 males and 70

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1 females.

2 In terms of the overall results, the
3 clearance values were 2.4 liters per hour for these
4 groups compared to 2.1 in normal healthy subjects. So
5 it was very representative, very close.

6 CHAIRMAN HAMMER: Dr. Bertino.

7 DR. BERTINO: when you looked at that, you
8 had -- could you bring that slide back up, please?

9 Any difference between men and women to
10 try to explain the male failures?

11 DR. ELLER: We looked at that as well, and
12 that's --

13 DR. BERTINO: Were there relapses?

14 DR. ELLER: Let's go to Slide K-22. No,
15 K-22, K-22.

16 CHAIRMAN HAMMER: Also, while that's
17 coming up, was rifapentine measured or all drugs in
18 the regimen measured?

19 DR. ELLER: Just rifapentine.

20 This slide compares the results of the
21 clearance values in liters per hour for men and women
22 for both the healthy subjects and the special -- from
23 the healthy subjects in bioavailability studies and in
24 the focused studies we did in women, Protocol 12, and
25 that which we obtained from Protocol 8 from the

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1 population PK analysis, and you can see for men it was
2 2.3 versus 2.5 in the TB patients, and for females,
3 1.9 versus 1.7.

4 So, again, a fairly close relationship
5 between healthy subjects and TB patients. However,
6 the spread was a little bit more in the TB patients
7 than what we saw in normals.

8 DR. BERTINO: But there's a big
9 difference, sex difference, between men and women in
10 your TB patients.

11 DR. ELLER: Yes. The difference is more
12 pronounced in the TB patients than in the normal
13 healthy subjects. That is correct.

14 DR. BERTINO: Was that statistically
15 analyzed?

16 DR. ELLER: That did pop out in the
17 population pharmacokinetic analysis as we do some of
18 the objective function or being statistically
19 significant. That's correct.

20 DR. BERTINO: So a potential explanation
21 for the efficacy differences in men could be a
22 pharmacokinetic difference.

23 DR. ELLER: Well in terms of relapse, we
24 did look at the kinetics in terms of relapse and non-
25 relapse, and the clearance values for relapse patients

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1 were 2.4 versus 2.3 in success, and in fact, we have
2 a histogram of those, K-25.

3 So this is a histogram of frequency in
4 terms of absolute number of patients versus clearance
5 values, and the successes are shown in yellow and the
6 relapses in red, and the centers of the distribution,
7 again, were 2.4 and 2.1, and you can see that the
8 range of values for the successes is broader than the
9 range of values for those who relapse.

10 So I don't think it's kinetics per se or
11 any potential predecessor factor that could have
12 affected kinetics that's responsible for the relapses.

13 CHAIRMAN HAMMER: In the continuation
14 phase, what days were sampled during the population
15 PK?

16 DR. ELLER: That was back on K-19. I
17 don't remember it off the top of my head.

18 Fifty-six to 58 and 175 to 77.

19 CHAIRMAN HAMMER: Okay. Thank you.

20 We're running a little behind. I think
21 it's well timed for a break. We'll take a 15-minute
22 break and try to reconvene at 10:45.

23 (Whereupon, the foregoing matter went off
24 the record at 10:29 a.m. and went back on
25 the record at 10:52 a.m.)

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1 CHAIRMAN HAMMER: We're running somewhat
2 behind, but I think we'll be able to catch up
3 throughout the day.

4 The next item on the agenda is the FDA
5 presentation, and Dr. Joyce Korvick will lead that
6 off.

7 DR. KORVICK: Thank you, Dr. Hammer.

8 I'll just wait for one more second for
9 some of the Committee members to come back into the
10 room.

11 May I have the first slide, Brenda?

12 Okay. I will just use a moment of your
13 time to present the members of the primary review
14 team, which included myself, Dr. Mann doing the
15 clinical review. Marianne Mann did the safety review
16 of this application; Dr. Hammerstrom, biostatistics;
17 Brenda Atkins, our project manager; Dr. Gosey,
18 microbiology; Dr. Kumi, biopharmaceutics; Dr.
19 McMaster, toxicology; and Dr. Smith, chemistry.

20 Next slide. That's the one, and if you
21 blank the screen, it'll look better up here. F-5.

22 All right. I'm going to proceed with a
23 brief introduction and give a clinical presentation,
24 which will focus on study design, patient
25 distribution, and focus also on the outcomes of those

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1 18 HIV patients that were discussed a little bit
2 earlier.

3 Dr. Hammerstrom will present the
4 statistical observations, and I will come back to make
5 some summaries and introduce the questions to the
6 Committee.

7 Next slide.

8 The applicant has submitted the following
9 proposed indication for rifapentine: the treatment of
10 pulmonary tuberculosis used in conjunction with at
11 least one other anti-tuberculosis drug to which the
12 isolate is susceptible.

13 Additional wording in the draft label
14 describes the regimen utilized in the Study 8.

15 Next slide, please.

16 A copy of the accelerated approval
17 regulations have been provided to you in your FDA
18 background materials.

19 As the applicant has already described,
20 rifapentine is being considered for approval under
21 these regulations. The unmet need that would
22 potentially be filled by rifapentine is for fewer
23 doses of anti-tuberculosis therapeutic drugs in order
24 to facilitate compliance with directly observed
25 therapy.

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1 The proposed regimen reduces the number of
2 visits in the continuation phase by half.

3 An agreement was reached with the
4 applicant that the accelerated approval could be based
5 on six-month follow-up outcomes, which in this case
6 were postulated at the time of design to be similar.

7 In addition, several studies in the
8 literature have documented that the majority of the
9 relapses would have occurred during the first three to
10 six months in the follow-up therapy.

11 In Study 8, all patients were scheduled
12 for additional follow-up at 12, 18, and 24 months.

13 Referring to the accelerated approval
14 regulations, there are provisions for requests from
15 the FDA for the company to provide additional research
16 focusing on unanswered questions. As you consider the
17 data today, please consider what recommendations you
18 would make in this regard.

19 Next slide.

20 The next two slides review treatment and
21 outcome design issues. In the first 180 days,
22 treatment was given with either rifampin or
23 rifapentine containing regimens.

24 Again, it is useful to point out in the
25 first 60 days both arms required daily administration

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1 of the companion drugs, but only twice a week
2 rifapentine, and then daily rifampin.

3 One should recall the applicant's
4 discussion of compliance focused on the induction
5 phase where companion regimens were similar, where the
6 difference, again, was in the rifapentine and rifampin
7 dosing.

8 One should also note that in the
9 consolidation phase, INH was being given once per week
10 in the rifapentine arm compared to rifampin. While
11 compliance was not an issue in the continuation phase,
12 the adequacy of once per week dosing of INH might also
13 be an issue.

14 Next slide.

15 Sputum culture status was used as a
16 primary outcome variable on Study 8. In the FDA
17 review of the applicant's data, protocol definitions
18 were applied. Slight variations in the data presented
19 by us are due to the slightly different classification
20 of outcomes.

21 Overall the FDA classifications did not
22 qualitatively change the conclusions reached by the
23 applicant, that is, similar conversion rates at the
24 end of therapy and increased relapse rates in the
25 rifapentine arm in follow-up.

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1 This slide reviews for you the treatment
2 and follow-up time sequences, as well as the outcome
3 terminology used by the FDA. Focusing on the outcome
4 definition at the end of the induction phase, examples
5 of various definitions counting success are given. A
6 categorical definition where sputum cultures are
7 either positive or negative at 60 days, or a
8 physiologic definition could be applied where the
9 patient had to have at least two consecutive negative
10 sputum cultures which were sustained through day 60.

11 The differences are seen more clearly in
12 the continuation phase. Conversion requires two
13 consecutive negative cultures which were sustained
14 through day 180 of treatment.

15 Time to conversion was counted from the
16 first day of a string of negative sputums leading up
17 to day 180, not counting early negatives.

18 There were a number of patients who had
19 two negative cultures by day 60, had a couple of
20 intervening positive sputum cultures, but then had two
21 sustained negatives up to day 180. The earlier day of
22 one or two negative cultures were not considered the
23 beginning of the conversion time by the FDA, only the
24 beginning of that string that led up to 180.

25 Finally, relapses were counted as any

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1 positive sputum culture for tuberculosis. If a
2 patient had a positive culture followed by several
3 documented negative cultures, they would not be
4 counted as relapses. Where no follow-up cultures were
5 available, the patient was counted as a relapse.

6 Next slide.

7 This gives you an accounting of the
8 patients and the distribution. As the applicant has
9 told you, there were 361 patients in both arms that
10 received at least one dose. They were randomized and
11 received at least one dose of study therapy. The
12 applicant dropped 77 and 75 patients in both groups --
13 I should say excluded them from the analysis -- and
14 the reasons were given below. These are mostly based
15 on inclusion and exclusion criteria.

16 From the analysis we also excluded an
17 additional 14 and 17 patients in each arm. Nine and
18 14 were HIV positive patients, and I will be
19 discussing the outcomes separately as to not confuse
20 the issue here. So in our analysis recall that we're
21 only using the documented negative HIV positives with
22 the caveats spoken to earlier regarding the test.

23 And again, resistance at baseline. Some
24 of these patients, six and three, their data for
25 resistance wasn't available early, and they were

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1 included in the ITT analysis of the sponsor, but we
2 chose to include them for consistency.

3 So in the end, the FDA analysis, modified
4 intent to treat, would include 270 in the rifampin arm
5 and 279 in the rifapentine arm.

6 Next slide.

7 What were the outcomes of these 270/279
8 patients by the end of 180 days of treatment? Thirty-
9 eight and 30 were lost to follow-up during the
10 induction phase. A total of 232 and 249 actually
11 reached the end of the treatment phase and had
12 cultures that were available for evaluation.

13 Of these that reached the end of the
14 treatment phase, nine and four were known not to
15 convert. That is, they continued to have positive
16 sputum cultures at that time.

17 Two hundred twenty-three and 245 converted
18 at that date.

19 Next slide.

20 Before looking at the outcomes in the
21 follow-up phase, let's consider for a moment the data
22 available for patients who were lost to follow-up
23 early in therapy, as you recall, 38 and 30.

24 Available sputum data shows us that in the
25 last visit or the last two visits a lot of patients

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1 were having negative cultures. However, because we
2 don't have follow-up data, we don't know if they
3 sustained these through 180 days. So these would be
4 unknown outcomes.

5 There were a number of patients, 15, 19 --
6 and nine in the rifapentine arm, who at their last
7 visit had still positive sputum cultures. This last
8 visit for both groups occurred primarily during the
9 first two months of treatment.

10 Next slide.

11 In order to be eligible to relapse --
12 we're now talking about the outcomes of the converters
13 -- in order to be eligible to relapse, you had to
14 convert at 180 days as per a previously discussed
15 definition. There were 212 in the rifampin group and
16 219 in the rifapentine that were documented not to
17 relapse, and there were 11 and 26 given the FDA
18 classifications that did relapse any time in the
19 follow-up period.

20 Of the converters, what kind of data do we
21 have? There were 24 and 28 patients who were followed
22 for less than six months in follow-up phase. Sixty-
23 two and 65 had follow-up to about six months, and 126
24 in each group were followed up through 12 months.

25 So that gives you a feeling for how these

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1 patients were distributed for the amount of follow-up
2 of the 223 and 245 patients. Dr. Hammerstrom will be
3 presenting some KMs later, Kaplan-Meiers.

4 Next slide.

5 Considering the patients who converted and
6 relapsed in the follow-up period, they are listed
7 here. These are cumulative relapses, and one can see
8 that the majority of relapses did occur in the first
9 six months.

10 However, it's interesting to note that a
11 substantial proportion of relapses occurred in the
12 rifapentine arm after six months of follow-up.

13 Next slide.

14 This slide shows the outcomes for the 13
15 HIV positive patients. As you can see, one in nine
16 and four -- one in the rifampin withdrew in the early
17 induction phase, none in rifapentine. There were
18 eight converters in the rifampin with no relapse, and
19 one in the rifapentine arm. There were two patients
20 that converted in the continuation phase in the
21 rifapentine arm but have no follow-up during the
22 follow-up period. So we cannot know whether these
23 patients would have relapsed or not.

24 Finally, for relapses there were none in
25 the rifampin group, and there was one in the

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1 rifapentine group.

2 Dr. Schluger will be presenting recently
3 published data regarding HIV positive patients and
4 tuberculosis treated with rifapentine following this
5 presentation, which do not include this study data.

6 Next slide.

7 Let's discuss the development of
8 resistance to rifampin. I'm using rifampin here
9 because those breakpoints are established by the
10 MCCLS. We're all aware that there is cross-resistance
11 between rifapentine and rifampin.

12 Of the converters, one patient in each
13 treatment group relapsed with an isolate resistant to
14 rifampin. The RFLP data were available for the
15 patient in the rifapentine arm, and it was reported by
16 the applicant to us that they did not match the
17 baseline strain. Therefore, it would suggest to us
18 that this represented perhaps a new infection and not
19 the development of a rifampin resistant isolate.

20 For the rifampin patient, there were no
21 RFLP results available for sputum cultures.

22 The patients who failed to convert, the
23 documented failed to convert during the treatment
24 period, did not develop rifapentine resistance. It is
25 also of interest that we did not find the development

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1 of isoniazid resistance even though these groups were
2 supposedly more noncompliant.

3 Next slide.

4 The applicant reviewed the impact of these
5 characteristics on outcome. FDA will consider the
6 first three: baseline chest X-ray, time to
7 conversion, and compliance with therapy.

8 Dr. Hammerstrom will now give you the
9 statistical report.

10 DR. HAMMERSTROM: Next slide, please.

11 My talk will focus on three issues. First
12 I will show that conversion rates are essentially the
13 same, while taking loss of follow-up into account.

14 Secondly, I will discuss the higher
15 relapse rates for rifapentine and describe the timing
16 of the relapses.

17 Third, I will share that the risk of
18 relapse with rifapentine remains higher even when
19 taking into account factors which may be related to
20 outcome.

21 Next slide, please.

22 This slide shows the results at the end of
23 the treatment period. First are those subjects who
24 are lost to follow-up before the end of the treatment,
25 38 and 30.

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1 Second, those who reached the end of
2 treatment still positive were more or less counted as
3 failures, nine and four.

4 And third, those who converted to negative
5 cultures by the end of treatment.

6 As one can see, there are comparable
7 percentages in each of these responses, in each of the
8 response categories in each arm.

9 One should also note that there are more
10 loss to follow-up than there are observed to have
11 failed at the end of treatment. Also notice that the
12 five percent difference in conversion rate consists of
13 a two percent difference in observed failure rates and
14 a three percent difference in loss to follow-up.

15 Next slide, please.

16 This slide adds information about relapses
17 occurring at any time during follow-up for those who
18 did convert. One again notes that the percent
19 converted and the percent converted and not relapsed
20 are comparable in the two arms, but that the rifampin
21 changes from being five percent worse than
22 rifapentine, 83 percent versus 88 percent with respect
23 to conversion, to being one percent better, 79 percent
24 versus 78 percent, with respect to conversion without
25 relapse.

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1 Thus, the difference in conversion rates
2 is balanced by a difference in the relapse rates.

3 Next slide, please.

4 This slide repeats the conversion rate and
5 a rate of relapse pre-follow-up shown previously. It
6 also gives the confidence intervals for the
7 difference, rifapentine minus rifampin, and the ratio,
8 rifapentine over rifampin, of these two rates.

9 First I will discuss the conversion rates.
10 Notice that the confidence interval, minus one percent
11 to 12 percent, for the difference in conversion rates
12 includes zero and goes up to 12 percent better for
13 rifapentine. The ratio of the rates is slightly
14 greater than one.

15 As one can see, the interval generally
16 favors rifapentine with respect to conversion at end
17 of treatment.

18 Now I will discuss the rates of relapse
19 pre-follow-up. When the relapses during follow-up are
20 taken into account, the difference between the arms
21 disappears, becoming negative one percent. This
22 results from a higher relapse rate on the rifapentine
23 arm, as will be discussed later.

24 When we are comparing an experimental drug
25 to an active control, we generally focus on the lower

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1 found of the confidence interval. The lower bound for
2 the difference indicates that rifapentine could be as
3 much as seven percent worse in absolute terms. The
4 lower bound for the ratio indicates it could be as
5 much as eight percent worse in relative terms.

6 One should recall that there's no formal
7 definition of clinical equivalence for tuberculosis
8 treatments. So the minus seven percent and the .92
9 don't necessarily constitute regulatory definitions of
10 having achieved equivalence.

11 Next slide, please.

12 One important question is: is there any
13 difference in the times to conversion between the
14 treatment arms? This slide gives the Kaplan-Meier
15 curves for time to conversion. One can see that there
16 is no meaningful difference between the arms. The two
17 curves lie almost on top of each other.

18 In this analysis we classified subjects
19 who were lost to follow-up during treatment as
20 follows. If the final culture is positive, they were
21 treated as having been observed out to day 180 and
22 being a failure.

23 If the final one culture was negative and
24 the previous culture positive, they were considered as
25 censored at that time.

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1 If the final two cultures ere negative,
2 they were treated as actually having been observed to
3 convert at that time.

4 Other permutations on how you treat the
5 loss to follow-up have been tried. The curves
6 continue to look like this regardless of pretty much
7 however you treat loss to follow-up.

8 Next slide, please.

9 Recall that there was an observed
10 difference in the relapse rate between the two arms.
11 This slide shows the relapse rates in the two arms
12 expressed as percentages of the number converted:
13 five percent of the 223 rifampin and 11 percent of
14 this 245 rifapentine.

15 Next slide, please.

16 This slide adds the 95 percent confidence
17 interval for the difference in the relapse rates and
18 for the relative risk or relapse. One can see that
19 the confidence intervals, two percent to ten percent,
20 or 1.1 to 4.3, show that the relapse rates are
21 statistically significantly different. The difference
22 does not include zero, and the relative risk does not
23 include one in the confidence intervals.

24 The relative risk is estimated to be
25 greater than two, with a 95 percent confidence that

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1 shows that it might be as much as four times higher
2 for those subjects who converted by the end of
3 treatment.

4 Next slide, please.

5 This slide shows the number of relapses in
6 various post treatment periods, zero to three months,
7 four to seven months, and greater than or equal to
8 eight months. One should notice that there are five,
9 five, and one rifampin releases -- relapses in the
10 successive periods compared to ten, nine, and seven
11 rifapentine relapses.

12 Counts here differ slightly from the
13 applicant's results because of slight differences in
14 the borders between the time periods and in the number
15 of patients included in the ITT analysis.

16 Next slide, please.

17 This slide shows similar information as
18 the previous slide, but in graphical form. These are
19 the Kaplan-Meier curves, time to relapse. In this
20 display one sees even more clearly that the curves are
21 still diverging at the end of the longest follow-up.

22 Recall that there is not complete follow-
23 up through 12-month post treatment. These curves are
24 statistically significantly different when measured by
25 the log rank test.

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1 Next slide, please.

2 Several factors were suggested by the
3 applicant's analyses to be related to the risk of
4 relapse. I will discuss the following factors:
5 sputum status at day 60, baseline chest X-ray, and
6 compliance with companion drugs during the intensive
7 phase.

8 As mentioned in Dr. Korvick's talk, sputum
9 status at day 60 has been defined in three different
10 ways.

11 First, converted at day 60, which means a
12 sequence of unbroken negative cultures began on or
13 before day 60 and were followed all the way out to day
14 180. That means that you cannot tell at day 60
15 whether someone has converted at that day or not
16 because some of the people who had a positive culture
17 on day 60 had an isolated negative on day 90 or day
18 120 and would not be considered as converting at day
19 60.

20 Second, there were two -- one could
21 require two negatives by day 60 without using
22 information recorded after day 60.

23 And third, one could look at simply
24 whether or not the day 60 visit was negative
25 regardless of earlier or later results.

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1 Next slide, please.

2 Using our definition of day 60 status
3 based on conversion at day 60, which means no later
4 positives after day 60, we observe, first, that the
5 risk of ultimate relapse is higher for subjects not
6 converted by day 60. In rifampin it goes from five
7 percent to six percent. In rifapentine it goes from
8 seven percent to 19 percent.

9 Second, looking across the rows, one sees
10 that the risk of relapse is higher for rifapentine
11 both among day 60 convertors, seven percent versus
12 five percent, and for nonconvertors, 19 percent versus
13 six percent.

14 Note that the relative risk of rifapentine
15 to rifampin is somewhat lower in the early convertors,
16 1.6 versus 3.4 in the nonconvertors. Using a Breslav-
17 Day test for heterogeneity of the relative risks, this
18 was not a statistically significant difference.

19 Next slide, please.

20 Using our criterion of two negative visits
21 by day 60 without regard to what happens at subsequent
22 visits, we see the same pattern. First, going down
23 the columns, the risk of ultimate relapse is higher
24 for subjects without two negative visits by day 60,
25 seven percent versus two percent in rifampin and 13

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1 percent versus seven percent in rifapentine.

2 Second, going across the rows, the risk of
3 relapse is higher for rifapentine both among subjects
4 with two negatives by day 60, seven percent versus two
5 percent, and for subjects without two negatives by day
6 60, 13 percent versus seven percent.

7 It's also worth noting that the pattern
8 seen in the relative risks of the previous slide have
9 been reversed here. The relative risk of rifapentine
10 to rifampin is higher for subjects with earlier
11 negative cultures. It's three if you add two negative
12 cultures by day 60 as opposed to 1.9 if you had fewer
13 than two negatives by day 60.

14 Again, by Breslav-Day tests, these are not
15 statistically significant differences.

16 Next slide, please.

17 Finally, using just the day 60 culture
18 results, we see the familiar pattern. First, looking
19 down the columns, the risk of ultimate relapse is
20 higher for subjects with positive culture on day 60,
21 nine percent versus four percent of rifampin and 18
22 percent versus nine percent on rifapentine.

23 Second, the risk of relapse is higher for
24 rifapentine both among subjects with negative culture
25 on day 60 and among subjects with positive culture on

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1 day 60, nine percent versus four percent for subjects
2 with negative culture, 18 percent versus nine percent
3 for subjects with positive culture.

4 Notice also that the relative risks in
5 this case are identical in the two strata.

6 These last three slides have all shown
7 that early conversion regardless of exactly how
8 measured is associated with a lower risk of ultimate
9 relapse, but that the risk of later relapse is higher
10 with rifapentine than with rifampin for each of the
11 subgroups, regardless of exactly how you subdivide it.

12 Next slide, please.

13 We now turn to the relationship of
14 baseline chest X-ray to risk of ultimate relapse. The
15 three rows of the table correspond to progressively
16 worse X-rays: no cavities, unilateral cavitation, and
17 bilateral cavitation.

18 The numbers in this table are based on the
19 applicant's numbers for relapses since the FDA
20 computer file did not include the baseline chest X-
21 ray. Therefore, that number of relapses, if you add
22 them all up, will not quite be -- will differ by one
23 from what it's been in previous slides.

24 We see that the relative risk of
25 rifapentine to rifampin varies from approximately one

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1 and a half to approximately three, depending on which
2 subgroup one is looking at. The subjects with
3 bilateral cavitation have higher relative risk,
4 although these relative risks -- there are three as
5 opposed to one and a half -- although these relative
6 risks were not statistically significantly different
7 among the subgroups.

8 One should also notice that approximately
9 60 percent of the subjects in this study had bilateral
10 cavitation. Only about 40 percent have no cavitation
11 or unilateral cavitation.

12 Next slide, please.

13 Finally, if we look at relapse rates
14 stratified by compliance with the other drugs in the
15 regimen, the definitions for compliance here are the
16 same as with respect to the number of doses that
17 separates low from high, are the same as those used by
18 the sponsor.

19 The first row contains subjects who are
20 poor compliers both in INH, PZA, and on ethambutol.
21 This is based on the applicant's classification.

22 The second row contains subjects who were
23 poor compliers to INH/PZA but good compliers with
24 respect to ethambutol.

25 The third row contains those who were good

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1 compliers with INH but poor compliers with ethambutol.

2 And the last row contains subjects who
3 were good compliers on all drugs.

4 Once again, the relative risks of ultimate
5 relapse are always higher than one, regardless of
6 which subgroup one is looking at.

7 The table shows that the relative risk is
8 highest in the subgroup with poor compliers on both
9 INH/PZA and ethambutol, seven percent and 23 percent
10 for the risks in each arm for overall relative risk of
11 3.2.

12 It also shows that rifapentine subjects
13 outnumber rifampin subjects in that arm by 84 to 70.
14 However, in the group with the lowest relative risks,
15 those -- that's this group -- poor INH/PZA compliers
16 and good ethambutol compliers, the relative risk is
17 1.1.

18 Rifapentine subjects also outnumber
19 rifampin subjects in this subgroup, 71 to 58. Thus,
20 it appears that the elevated relative risk is not
21 entirely explicable by confounding with level of
22 compliance, even if one were to ignore the fundamental
23 point that making causality determinations on the
24 basis of compliance is problematic because compliance
25 is not a baseline characteristic.

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1 We do not know if patients are
2 noncompliant because of problems with the dosing
3 schedule of rifapentine or because these patients were
4 inherently noncompliant.

5 Next slide, please.

6 In summary, we have seen first that the
7 rates and times of compliance are comparable between
8 the rifampin and rifapentine arms.

9 Second, the relapse rates were
10 statistically significantly higher on rifapentine
11 relative to rifampin.

12 Third, potential confounding factors, such
13 as sputum status at the end of the intensive phase,
14 baseline chest X-ray, and compliance with other drugs
15 in the regimen, do not completely explain the higher
16 relapse rate for rifapentine.

17 I now return the presentation to Dr.
18 Korvick.

19 DR. KORVICK: Next slide.

20 I'd like to address a few comments on the
21 safety review.

22 As the applicant has already described,
23 there were few withdrawals due to adverse events in
24 the controlled study, and in general we agree with
25 them for their conclusions regarding safety, that

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1 rifapentine has a safety profile similar to rifampin,
2 except for that seen for hyperuricemia.

3 Next slide.

4 Again, these are the conclusions that we
5 just brought to you, that the conversion rates were
6 similar for rifapentine and rifampin. Relapse at any
7 time during the follow-up were increased with
8 rifapentine compared to rifampin, and that the
9 subanalysis for the relapse rates were informative.
10 However, they may not explain the entire reason for
11 the increased rifapentine relapses.

12 Next slide.

13 These are the questions that you have
14 before you.

15 Is rifapentine safe and effective for the
16 treatment of pulmonary tuberculosis?

17 If yes, for what population is its use
18 recommended?

19 What additional studies are recommended
20 given the accelerated approval regulations?

21 If no, what additional research is
22 required?

23 That's the conclusion of our presentation.
24 Are there any questions?

25 CHAIRMAN HAMMER: Thank you.

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1 Can we have the lights, please?

2 We're running a bit behind, but I would
3 ask do any of the Committee members have questions for
4 the FDA presenters?

5 Dr. D'Agostino.

6 DR. D'AGOSTINO: In Slide 5 where you have
7 the loss to follow-up as 38 and 30, are those the
8 individuals that the sponsor is saying the cultures
9 are not available?

10 DR. HAMMERSTROM: There are -- yeah.
11 Well, let me clarify that. There are for many
12 subjects individual visits at which a culture is
13 missing. Then that subject comes in later.

14 DR. D'AGOSTINO: What I'm -- what I'm --

15 DR. HAMMERSTROM: These subjects are all
16 subjects -- these 38 or -- sorry -- 68 are all
17 subjects for whom there is no culture data on day 180
18 or later.

19 DR. D'AGOSTINO: I'm trying to get at the
20 question I was asking this morning in terms of the
21 individuals who are listed as failures because culture
22 is no available.

23 DR. HAMMERSTROM: In the applicant's
24 analysis, subjects like these from whom no data is
25 available from day 180 or later, they count, in at

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1 least one of their several sensitivity analyses, they
2 do count as failures. They do another analysis in
3 which they're not in the denominator or the numerator,
4 and they do a third analysis in which they are counted
5 as having converted.

6 DR. HAMMERSTROM: Yeah, the answer is
7 probably yes on that.

8 Let me ask one other thing. It would be
9 nice if this was the only time I would have to talk
10 about equivalency trials and say that let's chalk them
11 all into the same and let's say that the two
12 treatments are equivalent. Unfortunately, I have to
13 go in other arenas and talk about equivalent trials,
14 and I'm very much bothered by the fact that the loss
15 to follow-up somehow or other can be treated the same
16 and pulling the two groups together say that the
17 conversion rates are similar. I'm really bothered by
18 the missing data being handled in a cavalier fashion
19 to pull the groups together and then call them
20 equivalent.

21 Can you comment a little bit about that?

22 What I think would have been -- let me
23 just say what I think would have been a nicer approach
24 would have been to say the two groups, the rates could
25 differ by no more than this. If we made one case all

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1 converters, another case all nonconvertors, this would
2 have been the maximum difference that you would have
3 observed between the two groups.

4 DR. FLYER: I think normally that we would
5 do something like that if the numbers were some doubt
6 what would happen. For this particular case, there's
7 so many more subjects who were lost to follow-up than
8 have actually been called failures that almost any
9 analysis that you do could push the confidence
10 intervals sort of as wide as you would like.

11 DR. D'AGOSTINO: I agree. I think that
12 would have been nice, and I think it would have been
13 nice to see it.

14 DR. FLYER: Right. I understand, but also
15 we don't have a fixed definition, sort of like, well,
16 what is the appropriate bound. What we were hoping
17 here was just by showing the numbers as they are, the
18 intervals of what, seven, eight percent, the lower
19 bound, that you could see it could be driven to ten,
20 12, 13 percent with just slight perturbations between
21 the two arms.

22 DR. D'AGOSTINO: Well, if you flipped them
23 around, one positive and one negative, they could have
24 even extended further. I think it's just a bad
25 precedent to make a presentation that you treat them

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1 in a similar fashion and say equivalent.

2 DR. FLYER: We're in agreement.

3 DR. HAMMERSTROM: I think another issue is
4 that I guess we're not exactly convinced this is an
5 equivalent trial in the sense that my analysis has
6 largely been focusing on the relapse rates where there
7 is not an equivalence.

8 DR. D'AGOSTINO: Well, I agree, but the
9 first analysis, the word "equivalence" was used a
10 number of times as even a criteria for equivalence in
11 the sponsor's material.

12 The other thing is that in terms of the
13 post hoc test looks and so forth, I think what
14 everybody should do, they should want to understand
15 the data a bit and so forth, but you get yourself in
16 sort of the epidemiologist point where you say that
17 I'm doing so many tests I can't believe statistical
18 significance anymore. I've looked at significance.
19 I don't talk about things unless there's significance,
20 but then I look at the magnitude, and the magnitude of
21 the relative risk, say, has to be like two or three
22 before I start believing it.

23 So I need statistical significance, and I
24 need very large numbers, and I think some of the
25 effects you're seeing may be real, but they may not

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1 also be real, and I think that sort of post hoc test
2 criteria would be --

3 DR. KORVICK: I think those are good
4 points, and the other issue you raised earlier about
5 how to count all of these people, if we showed this
6 kind of slide, we tried to give you some description
7 of what was going on.

8 If you do the kind of analysis where you
9 lump everybody as positive and who has missing results
10 as being positive, et cetera, there were patients who
11 came in for visits who apparently had successful
12 therapy, who didn't have any culture results because
13 they couldn't produce sputum. In one of the sponsor's
14 analyses all of those patients were counted as
15 failures, and we didn't really want to do that.

16 So we tried to tease out for the panel,
17 and this is one of the slides that we did, exactly
18 what was going on at the time that these people were
19 lost to follow-up. We agree with you that this is a
20 problem, but this is a historic problem, I think. In
21 a lot of classic tuberculosis trials that have been
22 done, there are a lot of lost follow-up.

23 DR. D'AGOSTINO: In any arena, I do a lot
24 of statistical analyses in different arenas, and
25 everybody describes their arena as the most difficult

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1 arena to deal with. So --

2 (Laughter.)

3 DR. MURPHY: I guess the question would be
4 that you were saying that in an equivalence trial it
5 would have been nice to have seen if you lumped the
6 worth case scenario, and I think what they've said is
7 that they've tried to. In a way it's a little more
8 valid, if you would, to take what you actually knew in
9 both the groups and that we did have this much
10 information on those follow-up patients and did look
11 at that as trying to define what happened in that loss
12 to follow-up group because otherwise you're having to
13 say you know nothing about that.

14 DR. D'AGOSTINO: But you made them all
15 negative. I don't think the point -- I think my
16 point --

17 DR. MURPHY: No, not here.

18 DR. D'AGOSTINO: I know here you didn't,
19 but that's not the analysis that was presented.

20 DR. KORVICK: That is the analysis. We
21 didn't include those patients in the data sets.

22 DR. D'AGOSTINO: The intent to treat -- it
23 isn't worth going. I think my point has been made.
24 Thank you.

25 CHAIRMAN HAMMER: Thank you.

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1 Other questions?

2 (No response.)

3 CHAIRMAN HAMMER: If not, the next agenda
4 item is a presentation about tuberculosis in HIV
5 infected patients. That will be by Dr. Neil Schluger
6 of NYU.

7 DR. SCHLUGER: Thanks.

8 Actually I feel like I'm here as a
9 representative of the stone age. I'm the only person
10 with 35 millimeter slides.

11 (Laughter.)

12 DR. SCHLUGER: Okay. I've been asked and
13 will take as my charge to discuss in general the
14 treatment of tuberculosis in HIV infected persons and
15 make specific reference to experience gained with the
16 treatment regimens using rifapentine in a small number
17 of HIV positive patients who are enrolled in a study
18 that's being sponsored by the CDC, and I'll try and
19 put those results in context of HIV associated TB.

20 Generally, I think it's fair to say that
21 the treatment of TB in HIV infected persons is of
22 great interest to many of us in New York City, for
23 example. Twenty-five to 30 percent of all TB patients
24 are infected with HIV, and a conservative estimate, I
25 think, by the World Health Organization indicates that

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1 there are probably at least six million people
2 globally infected with both HIV and tuberculosis. So
3 this is an area of great concern.

4 Okay. I think it's fair to say that the
5 treatment of tuberculosis in HIV infected persons is
6 guided largely by consensus or expert opinion and
7 rests in only rare instances on practice that's guided
8 by well conducted controlled clinical trials, and
9 several issues in the treatment of HIV associated
10 tuberculosis are listed on this slide.

11 Several issues in the treatment of HIV
12 associated tuberculosis are listed here, and they
13 include the optimal drug regimen and dosing schedule,
14 duration of therapy or number of doses used in
15 treatment regimens, how monitoring for response and
16 relapse should be done, the use of alternative
17 regimens for drug susceptible disease. Specifically
18 non-rifamycin containing regimens for patients on
19 protease inhibitors has become a real issue. The
20 possibility of using immunomodulating therapies, like
21 interferon, thalidomide, pentoxifyline, and then
22 issues related to the treatment of drug resistant
23 disease.

24 So these are just some of the issues in
25 HIV associated tuberculosis, and as I said before,

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1 almost none of these have been addressed by controlled
2 clinical trials. Yet we're left having to treat an
3 awful lot of patients.

4 I thought I would just review for you some
5 of the clinical trials that have been reported in the
6 treatment of HIV associated TB to give you some flavor
7 of treatment success and relapse rates in these
8 populations. So these are the studies that have been
9 published.

10 This one by Dick Chiasson, published in
11 the American Journal of Respiratory and Critical Care,
12 reported on groups of HIV positive and HIV negative
13 patients treated with what I think most of us would
14 consider standard chemotherapy, INH, rifampin,
15 pyrazinamide, and ethambutol in the induction phase,
16 followed by intermittent INH and rifampin in the
17 continuation phase. In this study the bacteriologic
18 cure rates were similar -- this is a six-month trial
19 -- similar in HIV positive and HIV negative
20 populations.

21 The relapse rate, the raw relapse rate in
22 HIV positive patients was 5.4 percent, in the HIV
23 negative patients 2.8 percent. This did not achieve
24 statistical significance.

25 A similar trial reported from Cote

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1 d'Ivoire, where again -- could someone just sharpen
2 that up a bit. I don't think I have the focus --
3 reported from Cote d'Ivoire, looking at the treatment
4 of HIV positive and HIV negative patients, again, with
5 what we would consider standard short course
6 chemotherapy, with 18 months of follow-up.

7 In these patients the relapse rate --
8 there were patients with both HIV I and HIV II
9 infection, as well as combined infection -- the
10 relapse rates ranged from three to seven percent. The
11 cure rates were essentially equivalent, and in the HIV
12 negative group the relapse rate was three percent.

13 A study from Azire by Perriens was
14 reported in the New England Journal of Medicine,
15 randomized HIV positive patients to six or 12 months
16 of chemotherapy. The six-month treatment arm
17 consisted of, again, what we would consider standard
18 short course chemotherapy, two month of INH, rifampin,
19 pyrazinamide, and ethambutol, followed by INH and
20 rifampin in the continuation phase. That was six
21 months.

22 The 12-month group just got ten months of
23 this instead of four months of this, compared to an
24 HIV seronegative group that received the standard
25 short course chemotherapy for six months.

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1 This trial was notable for a nine percent
2 relapse rate in the HIV positive patients treated with
3 standard six-month short course chemotherapy, and this
4 trial generated quite a bit of discussion.

5 So that's to give you some context about
6 the treatment success and relapse rates in trials that
7 have been reported up to date in HIV infected patients
8 with tuberculosis.

9 Now, in that context, I'm going to tell
10 you a little bit about U.S. Public Health Service
11 Study 22, which is a randomized controlled trial of
12 weekly rifapentine in the continuation phase of
13 tuberculosis treatment. This trial was primarily
14 designed as a trial of rifapentine in HIV negative
15 patients and designed to provide -- designed as an
16 equivalency trial to provide sufficient statistical
17 power to judge the efficacy of this regimen in HIV
18 negative patients only.

19 The decision was made when the trial was
20 begun to include or to allow enrollment of HIV
21 positive patients because it was felt that some useful
22 experience might be gained, but it was recognized
23 early on by the CDC and the investigators that there
24 was no expectation that the trial would really provide
25 significant statistical power to draw definitive

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1 conclusion in HIV positive patients treated with these
2 regimens.

3 Study 22 has a relatively simple design.
4 Patients with culture proven drug susceptible
5 pulmonary tuberculosis. Pulmonary and extra pulmonary
6 TB, was allowed. Extra pulmonary TB was not allowed,
7 but culture proven drug susceptible pulmonary
8 tuberculosis patients received -- all patients
9 received standard two-month induction phase
10 chemotherapy. All doses were enrolled. At the end of
11 induction phase, patients were randomized to receive
12 four months of twice week INH and rifampin by DOT or
13 four months of once week INH and rifapentine by DOT,
14 and the primary study endpoint for the trial is
15 relapse rate at two years of follow-up.

16 So early on enrollment of HIV positive
17 patients was permitted, and 71 HIV infected persons
18 were enrolled in the study of whom 60, 30 in each arm,
19 completed therapy.

20 And the study enrollment of HIV positive
21 patients in this trial was stopped roughly a year ago
22 by the Data Safety -- at the recommendation of the
23 Data Safety Monitoring Board because it seemed as
24 though the number of relapse, and as I'll mention in
25 further detail in a moment, the number of relapses due

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1 to rifampin resistant tuberculosis seemed high.

2 Again, if someone could sharpen that up.

3 Of the 30 patients in each arm, there were
4 three relapses in the rifampin arm. This was biweekly
5 INH and rifampin. There were five relapses in the
6 rifapentine arm. The raw rate then is ten percent or
7 17 percent. This is not statistically different.

8 However, the relapses, four of the five
9 relapses in the rifapentine arm occurred with isolates
10 that were now resistant to rifampin. Zero of the
11 three relapses in the rifampin arm were resistant to
12 rifampin.

13 When an analysis was done that tried to
14 identify factors that were associated both with
15 relapse and perhaps rifampin resistant relapse, the
16 following factors fell out as being significant.

17 Patients, as are shown here, patients who
18 received rifapentine who relapsed, patients who
19 received rifapentine who did not relapse, and then
20 rifampin patients who relapsed and rifampin patients
21 who did not relapse.

22 Patients who received rifapentine and
23 relapsed -- there should be an asterisk here -- were
24 younger than rifapentine patients who did not relapse,
25 had lower CD4 positive cell counts, were more likely

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1 to have extra pulmonary TB and were more likely to
2 have at some point taken azoles, usually at some point
3 during the induction phase of their chemotherapy.

4 These were all significant in the patients
5 who received rifapentine who relapsed compared to the
6 patients who received rifapentine and did not relapse.
7 There was a trend towards a lower CD4 cell count in
8 the rifampin patients who relapsed, but it did not
9 reach this level of significance.

10 So that in the rifapentine patients who
11 relapsed again, low CD4 counts, extra pulmonary TB,
12 and azole use fell out in the univariate analysis as
13 factors associated with relapse.

14 Now, I'd like to just take a few minutes
15 and discuss what we know about rifampin in
16 monoresistant tuberculosis. This was extremely
17 alarming in this trial to find these four cases, and
18 so I've gone back and reviewed the literature, which
19 is relatively small on this subject, but I think it's
20 instructive.

21 A recent study from New York City that was
22 published in Clinical Infectious Disease by the New
23 York City Department of Health identified 96 cases of
24 rifampin monoresistant tuberculosis in New York from
25 1993 to 1994. Obviously none of these patients would

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1 have received rifapentine, the drug not being used,
2 and these rifampin monoresistant cases accounted for
3 1.5 percent of the incident cases of TB in New York
4 during that time period, and I'm told that at present
5 about 0.7 percent of all cases of TB in the United
6 States demonstrated rifampin monoresistance.

7 In New York City in this study, resistance
8 was felt to be primary. That is, the patient was
9 initially infected with the rifampin monoresistant
10 strain. In about half of the cases, it was acquired.
11 That is, the patient initially was infected with the
12 drug susceptible strain which became drug resistant in
13 a third, and resistance could not be classified at 17
14 percent.

15 Interestingly enough, 79 percent of these
16 96 patients were HIV positive, and four of the 76 had,
17 in addition to their TB treatment, taken rifabutin
18 prior to the development of rifampin monoresistant TB,
19 and in other case report rifabutin has been associated
20 with the development of rifampin monoresistant
21 tuberculosis. You may have seen a case report from
22 Bill Bushei (phonetic) and Chiasson (phonetic) at
23 Hopkins describing the development of rifampin
24 monoresistant TB in a patient who had been taking
25 rifabutin prophylaxis for MAC infection.

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1 This study from New York was essentially
2 descriptive, and these are some of the characteristics
3 of the patients with rifampin monoresistant TB. They
4 were typical of the patients we see in New York
5 generally in that they were relatively young, mostly
6 male. Homelessness, drug abuse, and alcohol abuse
7 were common, but interestingly, as I mentioned before,
8 HIV infection seemed to be somewhat over represented
9 in this cohort. As I said before, 25 to 30 percent of
10 all TB patients in New York City are HIV seropositive,
11 and in this cohort 79 percent were.

12 Okay. We from NYU and Bellevue last week
13 at the ATS meeting presented a case controlled study
14 of rifampin monoresistant tuberculosis that we've
15 done, and we identified -- this is my mistake. It
16 should be 26 cases of rifampin monoresistant TB
17 diagnosed at Bellevue in the years from 1990 to 1995.
18 Twenty-one of the 26 records were available for
19 review, and we matched each case of rifampin
20 monoresistant tuberculosis with at least two controls
21 who were patients with drug susceptible tuberculosis
22 diagnosed in the same time period at our hospital.

23 And in a similar breakdown to what I
24 showed you before, eight of these patients, of the 21
25 we identified, were classified as primary resistance,

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1 nine acquired, and four had an unclassified mode of
2 resistance.

3 When we looked at the risk factors for
4 rifampin monoresistant TB in our cohort, only one by
5 univariate analysis fell out as being significant.
6 Age, male gender, race, birthplace, homelessness,
7 incarceration history, and drug use history were not
8 different between the groups, but again, compared to
9 controls cases of rifampin monoresistant TB were much
10 more likely to be HIV infected than persons with drug
11 susceptible TB.

12 When we looked at the characteristics of
13 their tuberculosis itself, cases of rifampin
14 monoresistance were more likely to have had a prior
15 history of TB, and interestingly enough, were less
16 likely to have only pulmonary TB and, conversely, more
17 likely to have extra pulmonary tuberculosis.

18 And I'd like to mention one other study
19 that was reported as an abstract last week at the
20 American Thoracic Society meeting. This is a study
21 from the CPCRA and ACTG, a prospective randomized
22 trial of six versus 12 months of therapy for drug
23 susceptible tuberculosis in patients with HIV
24 infection, and patients received in this treatment
25 what we would consider again standard short course

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1 chemotherapy either for six months or nine months of
2 four drugs in the induction phase and two drugs in the
3 continuation phase.

4 The mean CD4 cell counts in the study were
5 relatively low, and interestingly enough, the relapse
6 rates were low. The study investigators -- I am not
7 a study investigator for this study -- but the study
8 investigators initially classified two cases out of 50
9 treated for six months as failure or relapses.
10 Apparently there's some reason to think that one of
11 these two is a new infection rather than a relapse.

12 But interestingly enough, both of these
13 failure or relapses demonstrated acquired rifampin
14 monoresistance, and as I mentioned, this was a study
15 of rifampin for six or nine months, but both of these
16 developed rifampin monoresistance. In the nine-month
17 study only one patient relapsed out of 50, and that
18 patient relapsed with a drug susceptible isolate.

19 I think it's also interesting to point out
20 in this study -- I showed you several other studies
21 where the relapse rates ranged from three to ten or 17
22 percent in this trial. This trial at least in the
23 six-month arm has a study design that's identical to
24 the control arm of the CDC Study 22, and the relapse
25 rate is lower. I think the numbers in all of these

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1 trials are small, and that's why you get these numbers
2 that bounce around.

3 Okay. I wanted to comment, you know,
4 having discussed a little bit about the epidemiology
5 and clinical and demographic factors associated with
6 rifampin monoresistance, a little bit about the
7 molecular basis of this because I think it's important
8 in terms of what happened in Study 22.

9 Rifampin resistance is seen in about one
10 in ten to the eighth wild type organisms in any
11 clinical situation with TB. So it's a naturally
12 occurring event, as are resistances to all other anti-
13 microbacterial drugs.

14 And the mechanism of this is laid out on
15 this slide. Rifampin interferes with RNA synthesis by
16 binding to the beta chain of RNA polymerase. So in
17 the wild type drug susceptible MTB, the RPOB gene
18 encodes this beta subunit of RNA polymerase, and
19 rifampin binds to this subunit and blocks RNA
20 synthesis.

21 In drug resistant mutants, there's a
22 mutation in the gene for RPOB such that you have an
23 abnormal protein formed, and rifampin cannot bind.
24 RNA synthesis continues, and the organism continues to
25 grow.

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1 In the past several years, it's become
2 obvious that most of the, really all of the mutations
3 associated with rifampin resistance in tuberculosis
4 occur in a relatively small hot spot region of this
5 gene from base pairs 1,500 to 1,600 or amino acids 500
6 roughly to 530, and as I said, all rifampin resistant
7 mutations that have been previously described fell in
8 this hot spot.

9 The four cases of rifampin monoresistant
10 tuberculosis that developed in the CDC's trial have
11 been sequenced, and they're listed here. Three of
12 them were amino acid substitutions based on a base
13 pair change, and the fourth was an amino acid deletion
14 based on a sixth base pair deletion in the gene.

15 The point is that all of these mutations
16 occurred in this hot spot region and were mutations
17 that had been previously described with other
18 rifamycins.

19 So to sort of summarize what I've been
20 talking about, rifampin monoresistant tuberculosis has
21 occurred with all rifamycins in clinical and
22 investigational use. Rifampin monoresistant TB, both
23 primary and acquired, appears to be strongly
24 associated with HIV co-infection, and the risk factors
25 in these patients appear to include advanced

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1 immunosuppression, extra pulmonary TB, and perhaps co-
2 administration of azole compounds, and I think it's
3 fair to say that further studies will be required to
4 precisely define the risk of relapse of TB in HIV
5 positive patients generally and the development of
6 rifampin monoresistant TB in patients with HIV
7 infection who were treated with rifamycins in general,
8 including rifapentine.

9 So I'll stop there, and if anyone has any
10 questions, I'll be happy to try and answer them.

11 CHAIRMAN HAMMER: Thank you very much.

12 Could we have the lights, please? Thanks.

13 Are there questions for Dr. Schluger?

14 DR. POMERANTZ: One of the questions that
15 was brought up by Dr. Hammer earlier is, I think, an
16 important one, and that is whether there is going to
17 be a use at least in the United States for rifamycin
18 in the treatment of HIV infected individuals because
19 of the interaction certainly not only with crixivan,
20 but with ritonavir.

21 And being someone who feels that patients
22 who are HIV infected nowadays should be treated early
23 and very aggressively, do you think that -- this is
24 interesting data -- do you think that there is a cause
25 for backing off on rifamycins in HIV infected

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1 individuals based on the new treat -- I'm not sure how
2 important this is going to be.

3 DR. SCHLUGER: Well, the treatment of TB
4 in HIV infected patients was hard enough without
5 active antiretroviral therapy, and now it's much
6 harder. Speaking broadly, I guess there are three
7 options if you have an HIV TB patient whom you're
8 talking about, let's say, protease inhibitors.

9 One would be to treat the TB first and
10 know that you've given effective TB therapy, and I
11 think in the TB community there's a bias towards that,
12 and in the virology community there's maybe a bias
13 towards the other, but that's one option.

14 Another option is to use a non-rifampin
15 containing regimen for these patients, and really the
16 regimen that in the literature has the best chance of
17 success in a relatively short period of time would be
18 a regimen of isoniazid, streptomycin, and PZA given
19 for nine months, which in a British-NYC trial done
20 many years ago was associated with a five to six
21 percent relapse rate, although that was obviously in
22 HIV negative persons, and that regimen has never been
23 tested in HIV positive individuals.

24 The third option is to give indinavir or
25 perhaps nelfinavir in combination with rifabutin at a

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1 dose of 150 milligrams per day substituted for
2 rifampin. There are no data about the efficacy of
3 that regimen.

4 So you know, you pay your money and you
5 take your choices.

6 DR. POMERANTZ: Yeah, it's a little hard.
7 It's one thing if someone has a CD4 count, just
8 getting on that because it is an important issue, of
9 six, 700 to be let's treat the TB for a year and then
10 get back to the virus.

11 When you're dealing with the patients whom
12 you're looking at with a CD4 count of 38, that's a
13 life and death issue for many of those people for a
14 year. So it is a question.

15 DR. SCHLUGER: My personal bias is that,
16 you know, rifamycins are incredibly potent anti-TB
17 drugs, and it's certainly preferable to use regimens
18 that contain them. The strep., PZA and INH regimen,
19 which as I said has never been tried in HIV positive
20 patients, will probably be effective in people with
21 relatively preserved immunity, but that's a reasonably
22 difficult regimen to give. There are a lot of
23 patients and physicians who object to nine months of
24 injections. It's a hard regimen.

25 So I think we would like to study

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1 rifamycin containing regimens in HIV positive patients
2 and maybe identify -- it may be likely; I think it
3 probably is likely that HIV infected patients who have
4 relatively high CD4 counts with just pulmonary TB can
5 be treated with rifapentine or the other rifamycins
6 perfectly adequately.

7 DR. POMERANTZ: Thank you.

8 CHAIRMAN HAMMER: Thank you.

9 Dr. Bertino.

10 DR. BERTINO: In that first study that you
11 presented to us on HIV positive patients, did you
12 capture adverse event data in that?

13 DR. SCHLUGER: In the CDC's trial, Study
14 22?

15 DR. BERTINO: Yeah.

16 DR. SCHLUGER: Adverse events were similar
17 in the control arm to the rifapentine arm, and I
18 believe -- well, they were similar.

19 DR. BERTINO: Were they high?

20 DR. SCHLUGER: I don't think so, no.

21 CHAIRMAN HAMMER: Dr. Hopewell.

22 DR. HOPEWELL: Were gastrointestinal
23 systems and more specifically diarrhea looked at as
24 possible factors associated with developing rif.
25 monoresistance?

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1 DR. SCHLUGER: Yeah, I don't think -- the
2 answer is no. Because of these results, there's a
3 pharmacokinetic study that's been planned now in some
4 of these patients, but it's just started.

5 DR. HOPEWELL: And I might ask the same
6 thing of the applicant investigators. Did they look
7 for the presence of gastrointestinal symptoms, as to
8 whether or not that was associated with relapse?

9 DR. GORODETZKY: We have not formally done
10 such an analysis. We did, of course, look at adverse
11 experiences in all of the patients. GI upset was not
12 a particularly predominant adverse event reported in
13 our studies.

14 CHAIRMAN HAMMER: Thank you.

15 Dr. Lipsky.

16 DR. LIPSKY: Was an interpretation of the
17 development of the rifamycin resistance that the INH
18 was not working, that you were essentially giving
19 rifabutin as a single drug?

20 DR. SCHLUGER: I think that's certainly a
21 possible explanation. You know, in general, we think
22 that monoresistance to any antimicrobial comes
23 when you have a single drug exposed to a multiplying
24 population of organisms. So that may well be.

25 It may well be that if there were long

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1 acting isoniazid available that we wouldn't have seen
2 this.

3 DR. LIPSKY: And have there been other
4 trials with once weekly isoniazid, you know, for
5 people whom you're treating with pulmonary
6 tuberculosis?

7 DR. SCHLUGER: Yeah, I believe there have
8 been trials of once weekly isoniazid in the
9 continuation phase, old studies that suggested that it
10 might be adequate if essentially sterilization has
11 been achieved early on, and that may have been the
12 problem in this study. With patients who were more
13 severely immunocompromised, perhaps sterilization
14 wasn't achieved early on, and that's why once weekly
15 isoniazid was not effective.

16 But it has previously been used.

17 DR. LIPSKY: And has that been the
18 assumption?

19 DR. SCHLUGER: Un-huh.

20 DR. LIPSKY: I presume that was the
21 underlying assumption for the development of this
22 protocol.

23 DR. SCHLUGER: That's right.

24 DR. LIPSKY: And it was felt that the
25 induction phase would create, you know, sterilization?

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1 DR. SCHLUGER: Right. That's right.

2 CHAIRMAN HAMMER: Thank you.

3 Any other questions?

4 (No response.)

5 CHAIRMAN HAMMER: If not, I'd like to
6 adjourn the morning session with the announcement that
7 the session will resume at 2:00 p.m., and for the
8 Committee members, there's been a request for us to
9 pick up our lunch on the buffet line and eat here.

10 So 2:00 p.m. for the reconvening of the
11 session.

12 (Whereupon, at 12:00 noon, the meeting was
13 recessed for lunch, to reconvene at 2:00 p.m., the
14 same day.)

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AFTERNOON SESSION

(2:00 p.m.)

CHAIRMAN HAMMER: Okay. I'd like to convene the afternoon open session.

The first point on the agenda for the afternoon is the open public session for which there is just one individual signed up, Dr. Richard O'Brien from the CDC. Is he here?

Thank you.

And disclosures are important as part of the open public discussion.

DR. O'BRIEN: Thank you.

I'm Rick O'Brien, the Chief of the Research and Evaluation Branch at CDC's Division of Tuberculosis Elimination, and it's our branch that is sponsoring the study you just heard about, Study 22, so called because it's the 22nd in a series of United States Public Health Service therapy trials for tuberculosis that date back to the late 1940s and the first trial of streptomycin for tuberculosis.

Today I'm not here to speak about the merits of rifapentine. You've heard quite a bit and will be deliberating that, and I actually remain blinded to the results of our study and for the first time today heard the results of the company study.

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1 But what I wanted to present, a personal
2 perspective on tuberculosis drug development during
3 the past 15 years, during the time I've been with CDC
4 and working the area of research and TB drug
5 development and also then in that perspective tie in
6 the context of this meeting and its importance in that
7 history and really the future history of tuberculosis
8 drug development.

9 During the past decade or so, there have
10 been many calls for new tuberculosis drugs, and
11 particularly forceful from this country with the
12 increase in TB cases that you all know about and the
13 outbreaks of MDR TB.

14 There have been a number of meetings
15 sponsored by NIH, CDC, WHO on tuberculosis drug
16 development during this period and yet relatively
17 little progress.

18 As you heard earlier today, the
19 rifapentine NDA is the first to be considered in 26
20 years by FDA, and not only is it the first, but it
21 probably will be the last for some time. There are no
22 other new drugs coming soon. There's another
23 rifamycin derivative just entering Phase 2 trials, but
24 it will be some time, given the length of Phase 3
25 trials, before you might consider a new drug

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1 application for that product. And there are no new,
2 novel compounds for tuberculosis that are in the
3 current pipeline for clinical trials.

4 Despite this relatively slow progress,
5 there are some signs of hope. One of the important
6 signs, I think, is FDA itself. It certainly has
7 changed a good bit in the last 15 years. I can
8 remember in the mid-1980s when Mike Iseman and I gave
9 presentations to the Anti-infective Drug Advisory
10 Committee that was considering the design of a
11 protocol for the study of what then was called
12 ansamycin (phonetic) and we now know as rifabutin for
13 the treatment of patients with MAC pulmonary disease.

14 And we didn't get very far during that
15 meeting. We found that not only the Advisory
16 Committee itself, but FDA had very little knowledge of
17 mycobacterial disease and the design of clinical
18 trials, and if anything, there seemed to be an
19 antagonism between FDA and industry.

20 That's certainly changed with HIV/AIDS and
21 the establishment of the Antiviral Drug Advisory
22 Committee, on which I served as a member for two years
23 in the early 1990s, with the accelerated approval
24 process and the development of expertise in
25 mycobacterial disease.

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1 And now with the establishment of the
2 Division of Special pathogens and immunologic drug
3 products, I think that represents an even greater
4 advance, and particularly the division's Director,
5 Mark Goldberger, who over the past five years has
6 become internationally known as an expert in
7 tuberculosis trial design and regulatory issues.

8 CDC has also changed over this period. We
9 began Study 21, the predecessor to Study 22, in 1981,
10 and it took six years to recruit the required number
11 of patients in that trial, which was stopped -- at
12 least almost stopped -- on two occasions because of
13 lack of funding.

14 And I've made jokes or light of this and
15 suggested that Study 21 investigators had to pay us to
16 participate in the trials --

17 (Laughter.)

18 DR. O'BRIEN: -- rather than the other way
19 around, but with Study 22 we have a well functioning
20 consortium that now has been reorganized, functioning
21 along the lines of the CPCRA that I'm sure you know
22 quite well and taking on additional trials, a lot of
23 investigator initiative, and quite exciting potential
24 for future work.

25 We also have an active engagement with and

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1 partnership with industry, typified by our
2 relationship with Hoechst Marion Roussel and Study 22.

3 The last important player in this and the
4 most important has been industry, which has often been
5 criticized by those who maybe don't understand the
6 industry perspective. There are a number of reasons
7 why a company would take on a new drug development.
8 One of the most important, as was mentioned earlier,
9 is to meet medical needs, and there have been
10 arguments presented as to why rifapentine would make
11 a major advance in our ability to treat tuberculosis.

12 On the other side, there have been
13 comments suggesting otherwise, and notably last year
14 the Director General of the World Health Organization
15 proclaimed DOTs that you heard about earlier to be the
16 major health breakthrough of this decade.

17 Now, not only researchers in tuberculosis,
18 but a number of the pharmaceutical companies were
19 quite alarmed by that, thinking that it was promoting
20 exactly the wrong message, that we have everything we
21 need now and new drugs and other research aren't
22 important.

23 Another important consideration is the
24 scientific rationale, and importantly in this is our
25 lack of understanding of dormancy and why bacilli are

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1 able to persist, and consequently we don't know about
2 the important drug targets that might be a potential
3 for new drugs in the future.

4 However, with the DNA sequencing that's
5 been done now for two strains of mycobacteria for
6 tuberculosis, there's certainly great potential for
7 new drug discovery.

8 Strategic fit within an individual company
9 is important. Companies that aren't involved in
10 antimycobacterial drugs -- I'm sorry -- antimicrobials
11 are unlikely to embark on anti-TB drugs, and if
12 anything, some of the mergers that have occurred over
13 the last decade are not at all conducive to TB drug
14 development.

15 Dixie Snider and I participated in a WHO
16 sponsored meeting in London in 1986, when Merrill Dow,
17 thence to become Marion Merrill Dow and now Hoechst
18 Marion Roussel, had rifapentine in Phase 2 studies.
19 So about 12 years ago we could have been able to
20 embark on Phase 3 trials of rifapentine, but because
21 of mergers and de-emphasis on mycobacterial drugs, it
22 took another decade almost before the trials were
23 begun.

24 Development feasibility is an important
25 consideration, and I think if you didn't know before,

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1 you're now appreciating the complexity of clinical TB
2 trials, and particularly their cost in terms of length
3 and number of patients to be recruited and followed
4 over time.

5 And most important is the bottom line. A
6 few years ago I heard that on the average it took \$250
7 million to bring a new product to market. I don't
8 know what the current figure is. I suspect it might
9 be somewhat higher than that. I was also told that
10 marketing people would not recommend the development
11 of new product unless the projected annual sales were
12 over \$100 million a year.

13 At the same time, a few years ago the
14 total audited sales of all TB drugs in established
15 market economy countries was only around \$150 million.
16 so on that basis you can understand why people who
17 have to answer to stockholders don't see all that much
18 future in TB drug development.

19 Despite this, there have been a few
20 companies, notably Hoechst Marion Roussel and several
21 others who are represented here today at this meeting,
22 that have maintained an interest in TB drug
23 development.

24 But importantly, the decisions reached
25 today, I think, will have a great influence on what

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1 these companies and others might do in the future. A
2 positive outcome at this meeting would certainly
3 encourage the industry, whereas a negative outcome
4 would be a significant disincentive.

5 Now, in a sense, this is much less
6 important for the United States than for the world.
7 Last year we reported fewer than 22,000 TB patients in
8 the United States. Now we're at an all time low, and
9 hopefully the trend will continue.

10 But we've heard that over the next decade,
11 unless there are advances in our ability to diagnose
12 and treat tuberculosis patients, that more than 30
13 million people will die unnecessarily from
14 tuberculosis.

15 CDC has been working with WHO and the
16 International Union Against Tuberculosis and Lung
17 Disease, a major nongovernmental organization in
18 tuberculosis, on the design of an international,
19 multi-center, clinical trial of rifapentine to provide
20 for even more optimal use of what we consider to be a
21 very important drug.

22 And, again, your deliberations this
23 afternoon will have a great bearing on the future of
24 this and other efforts.

25 Thank you.

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1 CHAIRMAN HAMMER: Thank you very much.

2 There's no one else that's signed up to
3 speak at the open public hearing, but is there anyone
4 that wishes to come forward?

5 (No response.)

6 CHAIRMAN HAMMER: If not, before the
7 charge to the Committee, I want to give the Committee
8 members just a few more minutes if there are any
9 critical questions.

10 I do have one question for the sponsor,
11 and that is perhaps you could outline what your own
12 clinical development plans are further for
13 rifapentine. What types of additional studies,
14 monitoring, et cetera?

15 DR. WALLER: Well, first it is our intent,
16 of course, to complete Protocol 8 and to take that
17 through to its completion of two-year follow-up data,
18 and we certainly recognize the need for additional
19 work and, in fact, have already contacted CDC, and
20 hopefully we'll be able to support the trial to which
21 Rick O'Brien just referred.

22 We've had many discussions as to what the
23 possibilities are, but we come here today knowing that
24 you were asked the question as to what additional
25 studies might be recommended, and so we come here

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1 today prepared to listen to your recommendations, as
2 well.

3 CHAIRMAN HAMMER: Thank you.

4 But part of the reason I asked is it helps
5 our deliberations to know what your thinking is in
6 relation to if there are trials we haven't heard
7 about.

8 DR. WALLER: Nothing specific at this
9 time.

10 CHAIRMAN HAMMER: Thank you.

11 Are there other critical questions?
12 Please, Dr. Hamilton.

13 DR. HAMILTON: I wish you hadn't said
14 "critical questions."

15 CHAIRMAN HAMMER: It's all relative.

16 DR. HAMILTON: I understand completely why
17 the sponsor has used the sputum culture as an
18 important endpoint in the analysis of these studies
19 for the very reason that there needs to be something
20 hard that one can look at and compare, one that has
21 public health implications surely.

22 But, you know, we all don't practice
23 medicine in this great, rarified atmosphere of
24 controlled clinical trials, and I'm wondering if
25 someone from the sponsor can put into context for me

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1 what relapse means for an individual patient.

2 Because I can imagine if I were a patient
3 and the doctor told me, "Okay. We have one drug you
4 can take this frequent, and I have another drug you
5 can take that frequent, and here's the risk. You
6 know, you may have a slight chance that, you know,
7 this first one won't work."

8 And my next question would be, "Well, what
9 do you mean by not work? Am I going to die? Am I
10 going to develop a serious disease and have to do
11 something radical or, you know, is it possible we
12 could just change the treatment? I'm not really
13 feeling too bad right now. I have a little cough,
14 maybe a little fever. I know my X-ray still is not
15 normal."

16 But I think real people make decisions on
17 bases such as that, and just because we recommend a
18 strategy to a patient doesn't mean they can abide by
19 it and do it. They'll do it if they damned well want
20 to, and you'd better have a good strategy, an outline,
21 a plan as to convince them.

22 And if it's based on niceties and rare
23 events and things that patients can't relate to very
24 well, they won't pay any attention to you at all.

25 So I guess I'd like some clarification

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1 from the sponsor as to what it means to fail and to
2 relapse. Maybe Mike or somebody.

3 DR. ISEMAN: This means I'm the only one
4 who can speak through the microphone now. They put it
5 down.

6 (Laughter.)

7 DR. ISEMAN: That's a very poignant
8 question, and I think all too often we start looking
9 at numbers and trends and lose sight of the individual
10 patient.

11 I think what you're referring to in the
12 context of a study like this is essentially different
13 than it is in the real world because in a study
14 there's aggressive follow-up and pursuit, looking at
15 sputum, follow-up symptoms, because we have to report
16 the results to the FDA or somebody else.

17 The consequence of a relapse in the
18 setting of a study like this is usually rather modest
19 because it's detected early. The patient doesn't have
20 a long period of time in which they're aggressively
21 symptomatic, and lung destruction goes on.

22 In the real world when we treat patients
23 and typically discharge them back to the wilds,
24 relapses are very commonly associated with progressive
25 damage of the lung.

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1 One of the artifacts of tuberculosis
2 description is we talk of cures, and if I can extend
3 on your point, a cure is not a return to normal
4 because the damage done to the lungs or the kidneys or
5 the brain while you arrest the infection never
6 reconstitutes itself. So over the time the reserve
7 capacity of whatever organs are the target of
8 tuberculosis is damaged and not restored to normal.

9 So a relapse which advances compromises
10 the lung condition, and as you know, patients who die
11 of tuberculosis in the world largely die of
12 destruction of the lung, respiratory failure, the
13 classic death of consumption. So every one of those
14 relapses pushes him or her towards that.

15 The consequence, therefore, of the
16 reactivation is rather modest, I'm going to guess, in
17 the patients in this study because they're detected
18 early, put back on therapy, but in the real world,
19 they would be considerably greater. Therefore, you
20 have to really look at what does that three or five
21 percent greater risk of relapse mean.

22 And I think any of us who think about the
23 future of this drug or TB therapy would say that
24 rather than accepting something that's slightly less
25 good, we should try to revise the next wave of

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1 treatments to be better.

2 Having said that, I've been exposed to
3 people who talk about study design not in terms of the
4 efficacy of the drug or the regimen, but in terms of
5 the efficiency of the TB program, which is if you have
6 a very easy to administer program that's cheap and you
7 put it in a community that's under served and it's
8 very easy to do, can you actually treat more people
9 well with a simple, economical program and result in
10 a net economy of morbidity and loss of life.

11 So I think it's a complex question, and
12 I'm glad you asked it. I don't think I answered it
13 very well other than to say it has many dimensions.

14 DR. SBARBARO: I'm John Sbarbaro,
15 University of Colorado.

16 But I want to talk from the World Health
17 Organization perspective, and that is that as an
18 advisor to the World Health -- and I've been doing
19 that for about ten years -- the problem that you face
20 is how do you take people who are so overwhelmed with
21 other disadvantages, get their attention, and get them
22 to actually treat their tuberculosis? Because the
23 impact of relapse not only affects the wage earner,
24 because that's the age group that we're dealing with,
25 but the remainder of the family as well.

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1 And when we announced that DOTs was the
2 answer to the world, what we were really saying is
3 that government or a nongovernmental agency taking
4 responsibility for insuring therapy is the answer.
5 The trouble is when you have to do it twice a week or
6 daily, it consumes more governmental resources and it
7 consumes more community resources, and the goal is to
8 come up with a regimen that does allow us to do once
9 a week, better yet once a month. Obviously the best
10 is as in gonorrhoea, once, period, but anything that
11 helps to reduce that approach.

12 And so when you come up with a drug like
13 rifapentine that says, "Hello. We can do this once a
14 week," you can increase the dose. You can come up
15 with modified approaches with isoniazid, the matrix
16 isoniazid which we've had around for ten to 15 or 20
17 years and we keep trying to find it again, or you can
18 use ethambutol, 90 milligrams per kilogram as they did
19 in India, and are offset, rapid inactivation of
20 isoniazid in the liver.

21 So there's many opportunities to use the
22 drugs wisely, but the goal is to reduce relapse on a
23 community basis, and that requires the tools by which
24 government can then intervene. So this is really a
25 very important drug from the world organization

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1 approach.

2 CHAIRMAN HAMMER: Thank you.

3 I think we'll move on now to the charge to
4 the Committee if there are no other critical
5 questions, and that was a critical question, I would
6 say.

7 Dr. Dianne Murphy.

8 DR. MURPHY: Thank you.

9 You all have heard today of the need. You
10 have heard of a company that has stepped forward to
11 try to meet this need, and the charge to the Committee
12 today is: have we or has the intended need been met
13 by the data, information that you've been presented
14 today?

15 Could I have the first slide?

16 Really the first slide is nothing but the
17 questions that -- well, leave it there. Can you go
18 back, Brenda? Okay.

19 This list is the questions. Go on to the
20 next one please.

21 If your answer is yes, then we would like
22 to hear your discussion concerning how we would label
23 this for use, how this drug would be used, and I've
24 put up three different ways to think about it: the
25 way it was used in the study; if not exactly in that

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1 way, what are we talking about? We're talking about
2 what regimens you would recommend.

3 You've heard a number of regimens
4 described today. We would like to hear your
5 discussion about that.

6 And in your discussion, not just to limit
7 you to labeling, but how do you think it's really
8 going to be used? We like to hear that also.

9 Next slide, please.

10 And in, again, your discussion in trying
11 to answer your questions, this is based on accelerated
12 approval request for the first six months of data. We
13 hear what the company is proposing to present. We'd
14 like to hear what you think you'd want to hear under
15 accelerated approval as proof of efficacy and safety
16 at two years.

17 And what, if any, other studies do you
18 think should be completed either that have been
19 mentioned or that have not been mentioned?

20 In summary, as far as if yes, we need you
21 to talk about three particular things, which are
22 relapse, the regimen, and the next slide is safety or
23 efficacy. You could almost put resistance in any
24 category or both categories. Are there concerns you
25 think that we should receive particularly intense

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1 attention in the label? And are there concerns that
2 we should comment upon as far as relapses and
3 resistance?

4 Next slide. If you do not feel that the
5 data presented today should warrant recommendation,
6 approval, was there a failure in a subgroup or a
7 regimen, or was it in all aspects of the study
8 population?

9 And what evidence must be present in
10 future trials? You've heard about the difficult to
11 provide convincing data of efficacy.

12 We appreciate your thoughts and discussion
13 today. I don't think you have -- let's put it this
14 way. I think it's been a terrifically wonderful
15 scientific discussion, and we look forward to how
16 you're going to grapple with it.

17 Thank you.

18 CHAIRMAN HAMMER: Thank you.

19 May I just ask, and this is for the non-
20 veterans of the Committee, just for clarification of
21 the accelerated approval guidelines under which we're
22 deliberating, there are two issues: one, the use of
23 a, quote, surrogate as an indication of future
24 benefit, and for purposes today those are the six-
25 month data predicting two-year efficacy; and the

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1 second aspect is that the drug provides a meaningful
2 therapeutic benefit over existing therapies, and that
3 can be broadly interpreted in this context as the once
4 weekly potential, but perhaps other things about this
5 agent.

6 I just mention that for the Committee's
7 benefit for those who have not served before. I don't
8 know if there's anything further that you would like
9 to add to that, but okay.

10 DR. WALLER: Thank you.

11 CHAIRMAN HAMMER: We'll turn right now --
12 a few of our members need to leave early, and so we're
13 going to try to move to be sure that all opinions are
14 heard.

15 And the first question, which is really
16 the key question and will be the voting question, is
17 the following: is rifapentine safe and effective for
18 the treatment of pulmonary tuberculosis?

19 And what I'll do is go around the table
20 and ask for thoughts about that question from
21 everyone, and then we will have a vote, and then
22 following the vote, we'll take on the subsequent
23 questions that were outlined.

24 I'd like to begin on my left with Dr.
25 Bass.

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1 DR. BASS: Do you want a discussion or a
2 vote?

3 CHAIRMAN HAMMER: I'd like a discussion
4 first. You certainly can voice your opinion, but the
5 vote will be an official vote later after everyone has
6 had his or her points made into the record.

7 DR. BASS: Well, let me just make a couple
8 of observations: that those of us who are used to
9 dealing with tuberculosis studies for years and years
10 take for granted, but some who are less familiar may
11 not, and it's frequently impossible to separate the
12 question of the drug from the regimen.

13 We're stuck with having to use drugs in
14 regimens, and generally the regimen that's picked has
15 other implications based on the way the other drugs
16 are picked for the study.

17 I guess if we were strictly to ask
18 efficacy questions, we would have the in vitro data,
19 and we would have some other data that we think,
20 again, as surrogate, like early bactericidal activity,
21 data which we have in this case, but we would be left
22 with theoretical questions of efficacy, such as the
23 different hypothetical populations discussed by Dr.
24 Iseman, which we really don't know how not only this
25 drug, but some of the other drugs might affect those.

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1 So we're always stuck with those things in
2 tuberculosis. I would say that from the data that
3 I've seen presented today, I would say that there's no
4 question that the drug has efficacy. The question is:
5 what are the limitations?

6 Some of the limitations have been imposed
7 by the study designs that we have heard, questions
8 that we have all voiced about the study design, but
9 strictly on the basis of is the drug efficacious, I
10 think we have heard data to suggest that it is. It
11 has in vitro susceptibility to early bactericidal
12 activity. The rifamycins have theoretical advantage
13 in the hypothetical populations that we believe to be
14 important in tuberculosis, and in trials it has
15 demonstrated success.

16 Now, you can argue about the limitations
17 of some of the success, but I would say yes.

18 CHAIRMAN HAMMER: Dr. Hopewell.

19 Thank you.

20 DR. HOPEWELL: I think that if you look
21 back over the history of anti-tuberculosis treatment
22 trials and see the way they've evolved over the years
23 that it actually presents what for me is a quite
24 satisfying sequence of hypothesis testing results and
25 application that has progressively decreased the

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1 amount of effort, time, resources that need to be
2 devoted to the treatment of patients with
3 tuberculosis.

4 Early on it was 24 months of therapy in a
5 hospital, often longer periods of time in a hospital.
6 It evolved to being an out-patient treatment regimen
7 to being intermittently administered, and with the
8 USPHS and BMRC studies, the amount of time required
9 for treatment progressively shortened to the current
10 six months.

11 I think this presents a very nice, quite
12 sort of aesthetic, scientifically aesthetically -- if
13 that's not a contradiction -- evolution of our
14 understanding of how to treat patients with
15 tuberculosis.

16 I think this study is quite consistent
17 with that evolutionary approach and does represent, I
18 think, taking treatment to the next step, that is,
19 decreasing the total number of doses required.

20 My unease about this, I guess, is probably
21 the same unease that was present in nearly everybody
22 or in many persons at the time, the next steps looking
23 back over the TB history, that the time the next steps
24 were taken with regard to shortening from 18 to 12 to
25 nine to six months, and that is that you're

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1 progressively decreasing the margin of safety that's
2 built into the treatment regimen to the point where
3 the failure to take a relatively small number of
4 doses, for example, in the intensive phase may
5 compromise the overall results, the overall outcome of
6 the full six-month regimen.

7 I think this is sort of what John was
8 saying as well. The limits have to be taken into
9 account. We have or we are, I think, reaching some of
10 the limits of what therapy with current drugs -- what
11 can be done with current drugs, and we have to be very
12 cognizant that in so doing we've probably reduced the
13 margin of safety, the buffer that's built into most
14 treatment regimens, and therefore, there has to be
15 considerable attention paid to making certain that the
16 drug, the regimen under consideration or the drug
17 under consideration, is used in the context of a
18 regimen and a program that maximizes compliance so as
19 to minimize the effect of reducing the margin of
20 safety.

21 But, yes, I think the data support both
22 safety and efficacy.

23 CHAIRMAN HAMMER: Thank you.

24 Dr. Snider.

25 DR. SNIDER: Relative to other anti-

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1 tuberculosis drugs, I do think rifapentine is safe and
2 effective for the treatment of pulmonary tuberculosis.

3 As has been mentioned, there are a lot of
4 things we don't know, and we need to come back to
5 those later, I think.

6 With regard to the safety, I think the
7 hyperuricemia is interesting enough to look into a
8 little bit more, but it's not something that bothers
9 me from a clinical standpoint, but I think from a
10 mechanistic standpoint we need to understand what's
11 going on there to be sure that future problems don't
12 evolve as a result of whatever the mechanism might be;
13 that we appreciate what they are and anticipate any
14 adverse effects that might result from that.

15 The serious effects for the rifamycins, of
16 course, have not been demonstrated with rifapentine in
17 the data we've seen. It's conceivable that
18 rifapentine might be safer as it relates to
19 thrombocytopenia, the flu type syndromes, renal
20 failure, and some of the other things that have
21 occurred very rarely and mostly with higher doses of
22 rifampin given at longer intervals apart.

23 But these things do occur, and there was
24 no data provided on that.

25 As far as the effectiveness compared to

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1 rifampin, those data weren't presented because
2 rifapentine was given twice a week instead of every
3 day, and it was given once a week in the continuation
4 as compared to twice a week.

5 So as a drug, the comparability really
6 wasn't looked at. As John mentioned at the beginning,
7 what we're looking at are two different regimens, and
8 the evidence that we have suggests that the
9 rifapentine containing regimen is tending toward
10 inferiority. How significant that might be in the
11 larger context, as Dr. Sbarbaro and Dr. Iseman were
12 pointing out, we really don't know when it comes to
13 trying to take into account all of the different
14 factors that determine the therapeutic outcomes in an
15 actual operating, TB controlled program either in this
16 country or in development countries.

17 There are a lot of different factors that
18 come into play, and being able to utilize resources
19 wisely to supervise more patients by seeing them, all
20 patients, only once a week could -- it is conceivable
21 as has been implied that from a population-wide
22 standpoint there would be benefits that would accrue
23 to the population from the once a week therapy as
24 compared to the twice a week therapy.

25 Nevertheless, I think when we get down to

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1 asking what we would do for ourselves or our family
2 members if they had tuberculosis, I think that I
3 personally would feel less comfortable using a
4 rifapentine regimen on a once a week basis and tend to
5 agree with what Dr. Iseman had suggested, that one of
6 the potentials here is to use rifapentine in twice a
7 week therapy.

8 And I think if the drug were on the
9 market, depending upon other factors such as cost and
10 so forth, it's conceivable that clinicians might use
11 it as -- might prefer it for twice a week therapy in
12 a continuation phase, for example, as a way of dipping
13 their toe in the water here and expecting to derive
14 positive benefits perhaps.

15 So I think the data, to again get back to
16 the effectiveness, I think the drug is -- if you were
17 to compare them in another way, we would find that
18 rifapentine as a drug is as good as rifampin, if not
19 better, but when you throw it in the regimen, the once
20 a week regimen, there is -- and what I'm doing is I'm
21 answering two different questions because I think FDA
22 is asking more than the question that's on the paper
23 here.

24 I think they're asking the question about
25 the drug, but they're also asking questions related to

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1 the use of it, and that's why I'm perhaps going on too
2 long, but I'm trying to say that I think the drug
3 itself has great utility, and somehow we want to send
4 a signal in that direction, and yet I'm not sure we
5 have a solid handle on exactly how we're going to
6 follow through with making recommendations for its
7 use.

8 I think we can probably come up with some
9 ideas of how to -- what kind of research to do to
10 answer some outstanding questions.

11 I'll stop.

12 CHAIRMAN HAMMER: Thank you.

13 Dr. Bertino.

14 DR. BERTINO: As to rifapentine being
15 safe, I think that the data appears to show that its
16 side effect profile is in many ways similar to
17 rifampin, although there are some differences with
18 each drug.

19 I do think more analysis needs to be done
20 specifically for sex related differences and adverse
21 reactions, and I would just stop safety with that.

22 In terms of effectiveness, I was thinking
23 one way until Dr. Hamilton asked his question and Dr.
24 Iseman gave his response. In terms of relapse rates,
25 Dr. Iseman mentioned that on an individual patient

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1 basis this affects the patient, the wage earner, and
2 the family, and I also wonder about its effect on
3 society when you have someone who's relapsed, you
4 know, mingling, perhaps exposing people to their
5 disease.

6 And so I think the higher relapse rate is
7 a concern. It does appear to be effective, but it
8 does not appear to be as effective as rifampin, at
9 least in the study that was presented today when you
10 look at relapse rates.

11 CHAIRMAN HAMMER: Thank you.

12 Dr. D'Agostino.

13 DR. D'AGOSTINO: What we have before us is
14 a positive controlled trial where there's two
15 different regimens, a couple of drugs, but mixed with
16 two different regimens, and I think if you honestly
17 look at the original analyses in terms of conversion,
18 that what you have is a difference between the two,
19 but the question is: how big is that difference, and
20 how much does it matter?

21 I mean if you push the analyses and do
22 some of the things I was talking about and some of the
23 things the FDA was talking about, you might be willing
24 to say that the difference is something like seven or
25 eight percent. It's certainly not 27 percent. It

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1 isn't that we have a drug before us with its regimen
2 that clearly is way out of whack with the standard
3 treatment.

4 It's close, and the question is: how
5 close must close be for us to think of it being
6 effective?

7 And when you go to the relapse, you have
8 a five percent versus 11 percent relapse, and you have
9 to ask: is that tolerable? I mean it's not everybody
10 relapsed. It's five percent versus 11 percent. Is
11 that tolerable? It's twice. It's a relative risk of
12 two, and do we want to live with that?

13 I think that, you know, we don't have a
14 placebo controlled trial here where we're talking
15 about how does it compare against nothing. We have it
16 against a regimen that is quite standard, and I think
17 we have to ask ourselves what does it mean, the five
18 versus 11 percent, and the possible difference in
19 terms of conversion of seven percent, eight percent
20 difference.

21 I think also that I have to ask if you
22 think that the data looks like there's effectiveness
23 going on with possibly not as much effectiveness in
24 the trial, you have to ask the question, well, how is
25 it being used and the things that were just being

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WASHINGTON, D.C. 20008

1 said. How will it be used in practice?

2 I mean, there's efficacy that we're
3 dealing with before us, but there's effectiveness
4 later on. I mean if you mount this as a single dose
5 per week type of regimen or maybe a couple of times
6 versus every day, will you ultimately get more
7 compliance, not compliance in the study here, but
8 compliance later on?

9 And I think that, you know, I don't want
10 to give any impression that I think there's
11 equivalence. This is not equivalence. It's really
12 not equivalent by any standard of statistical rigor.
13 It's not equivalent, and I think there's a possibility
14 that it's not as good as the standard treatment that
15 we're looking at or the other comparative treatment,
16 but I think there is effectiveness going on, and I
17 think it's a margin of safety that really is the
18 question of whether or not we're willing to tolerate
19 it.

20 And there's also the question of how does
21 it play out in the sort of use and the effectiveness
22 arena, and I think that, you know, when we come to
23 giving our final vote, that we really have to be clear
24 on those issues.

25 CHAIRMAN HAMMER: Thank you.

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1 Dr. Self.

2 DR. SELF: Well, the data presented show
3 the overall success criteria. It's close, as was just
4 mentioned, but probably not quite as good, and there
5 are challenges in interpreting that data because of
6 the dropout rates and all, and one can do the
7 sensitivity analysis and maybe it is not even as good
8 by that outcome measure as the standard.

9 Even though generally one must approach
10 the subset analyses very carefully, and the relapse
11 rate analysis is essentially a subset, there is strong
12 reason to look critically at that, and the relative
13 risks are two.

14 And there was a display earlier of the
15 cumulative relapse rates, and those two curves were
16 significantly different, and they were still spreading
17 apart, and so there is, it does seem to me, pretty
18 clear evidence that this is not as good as the
19 standard.

20 What we're being asked to do, I think, is
21 to deal with either one of two leaps. The first is
22 based on some theoretical considerations, some
23 modeling, hypothetical populations of organisms
24 combined with information about in vitro assays that
25 would suggest some modification of dose or schedule or

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1 working with compliance could change the profile that
2 we've seen from the data as it was presented to bring
3 it into line with what the standard is.

4 The other argument is perhaps even more
5 delicate than that, is that the higher relapse rate
6 can be more than offset by the economic and logistical
7 advantages of having less frequent administration, and
8 this we've seen really no presentation of the kind of
9 supporting evidence for this argument, which is a
10 fairly delicate population modeling type of exercise
11 that's specific to the different situations where this
12 drug might be used.

13 It may be; it may not be. I don't know.
14 We haven't seen it, and based on the presentations
15 today, I think there are still questions whether
16 either of these arguments are really viable, and I
17 would suggest that either one or both of those
18 arguments can and should be addressed empirically by
19 additional studies.

20 CHAIRMAN HAMMER: Thank you.

21 Dr. Feinberg.

22 DR. FEINBERG: Well, I would say that
23 rifapentine as presented to us today certainly seems
24 to me to be safe and effective, especially for the
25 initial sputum conversion in previously untreated HIV

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1 seronegative adults who have susceptible pulmonary TB
2 and no extra pulmonary disease. That's the population
3 the study was done in.

4 And while you can certainly see the public
5 health advantages in the less frequent dosing and,
6 therefore, the decrease in the total number of doses
7 that you need to get a patient through, you know, a
8 complete course of treatment, I guess, you know, as
9 for other members of the panel, niggling in the back
10 of my mind is the sense that rifapentine in the
11 context of the regimen that was studied raises
12 questions about whether this was the most appropriate
13 dose and schedule of both rifapentine and, you know,
14 of the companion INH for the continuation phase.

15 And I think those are questions that can
16 certainly be addressed in the future, in future
17 studies.

18 This is an area with which I do not have
19 intimate familiarity. So other than the PAS era study
20 that Dr. Iseman described, I don't really know what
21 other precedents there are for the use of once a week
22 INH for the continuation phase, and you know, I'll
23 leave it to the TB experts on the panel to educate
24 myself and the rest of us.

25 Clearly, the increase in the relapse rate

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1 is a concern. The Kaplan-Meiers showed divergent
2 curves. The relative risk was clearly two, and you
3 know, how I categorize this in my own mind -- and I
4 think other people are thinking of it in these terms
5 as well -- is, you know, the issues around the
6 approval of this drug speak to the tension between the
7 broader public health benefits that you can get from
8 a drug that could be used more easily because you can
9 use it less frequently, and then the potential lesser
10 benefit to a given individual that a physician has to
11 face, you know, across the desk and write those
12 prescriptions.

13 And sometimes those things line up very
14 nicely, and sometimes there is a real tension between
15 what is the overall public health benefit and what
16 benefit accrues to an individual patient, and I'm not
17 sure that the data, although many elegant attempts
18 were made to analyze and sub-analyze the Protocol 8
19 data; I'm not sure in my own mind that it's clear to
20 me that the baseline features clearly pick out who, as
21 a physician caring for an individual patient, you
22 would really be concerned would be at risk of
23 ultimately not doing well.

24 The male versus female, that's only half
25 the population, and there was quite a lot of

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1 discussion, which I won't go into, about whether the
2 chest X-rays were really terribly much worse in one
3 group than the other, and I'm not really left with a
4 whole lot in this.

5 I think the FDA presenters made clear to
6 us compliance with the drug regimen isn't the baseline
7 characteristic and may well be influenced by the
8 regimen you're receiving. So that doesn't help you a
9 priori as the prescriber to know how to sort out this
10 tension in favor of the public, the common good and
11 the individual patient.

12 I think clearly on the basis of the common
13 good this could potentially be a very, very useful
14 drug. Whether for an individual patient it will prove
15 to be the best drug or the best drug and regimen as
16 studied, questions remain in my mind.

17 CHAIRMAN HAMMER: Thank you.

18 Dr. Hamilton.

19 DR. HAMILTON: Is rifapentine safe? Yes,
20 relatively. Is it effective? Yes, relatively.

21 It's the same we would say for virtually
22 every drug in existence. One makes choices, and on
23 balance, I would guess the FDA is asking us to engage
24 in a dialogue that comes to grips with the paradoxes
25 that may be apparent.

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1 On the one hand, I'm not convinced that
2 rifapentine, the rifapentine regimen, I should say, is
3 comparable to the standard regimen that exists today.
4 I don't believe we've been shown that.

5 On the other hand, there are data that are
6 emerging from a variety of ongoing studies that may
7 shed some light on that question and will be very
8 useful. Unfortunately we don't have that information
9 available at hand today.

10 With those comments in mind, why would
11 any, on the one hand, rational person accept something
12 that's less good than something that already exists?
13 Well, there are answers to that I suspect that we can
14 talk ourselves into, and they revolve around those
15 other incentives, which include the putative benefits
16 that would accrue to the public health organizations
17 in terms of resources required and so on.

18 But, you know, soon or later if we keep
19 doing this, we're going to (a) talk ourselves out of
20 a job, but secondly and more importantly, we're going
21 to talk ourselves out of the resources that we need to
22 do the job.

23 So I could envision taking the resources
24 that we would save by administering the drug once a
25 week and potentially apply those resources to the

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1 follow-up of the relapses even if they do occur with
2 another regimen. Get the drug out into the field.
3 Put our money where our mouth is and see if, in fact,
4 this does result in improved compliance and better
5 access to health care, with the full recognition that
6 we may be doing some harm in the form of relapses
7 which we then must take responsibility for and
8 resolve.

9 In addition, I think it's critical that
10 some of these unclarified points that were raised in
11 the course of the morning be addressed very
12 specifically. I'm talking now about the extrapolation
13 from populations that may not be representative of
14 where we're going to put this drug at least in the
15 immediate future.

16 The gender issue, I think, is not at all
17 irrelevant and should be and can be addressed. The no
18 compromised host, whether HIV infected or otherwise,
19 would seem to be pretty clear-cut to me.

20 So I'm going to come down, I'm sure, on
21 balance here concluding that this drug is effective
22 and safe for use currently in this country.

23 CHAIRMAN HAMMER: Thank you.

24 Dr. Pomerantz.

25 DR. POMERANTZ: Yeah, my answer to the

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1 question is yes, and that is all as a molecular
2 virologist, I really have to add.

3 (Laughter.)

4 DR. POMERANTZ: But then I do have to put
5 on my other hat, which is clinical as the chief of the
6 Academic ID Division and say just a few things, that
7 I liked what Dr. Snider said at the end of the day,
8 and that is -- and I wrote it down -- that it is
9 tending towards inferiority, and I think at the end of
10 all of the statistics, that's probably the best
11 statement that I've heard so far.

12 So as a clinician, I don't know who I
13 would recommend this for in our practice, knowing that
14 myself and our division practices in center city
15 Philadelphia. That does not mean that the whole world
16 is center city Philadelphia. So I could extrapolate
17 where this might be used, albeit I don't see it in the
18 area that we practice because of this tendency at this
19 point towards inferiority.

20 So its use will have to be found somewhere
21 out there, and I do worry about one thing that has
22 been brought up and that I mentioned before, and
23 that's its use in HIV infected individuals. Clearly,
24 that was not what was put forward here today. The
25 group took great pains to try to remove those people,

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1 but I would not recommend in what I've heard today its
2 use in HIV infected individuals either with or without
3 protease inhibitors until more data is back because of
4 this tendency towards inferiority.

5 That being said, I think it does have some
6 uses. I won't reiterate them, and I would say yes to
7 the question.

8 CHAIRMAN HAMMER: Thank you.

9 Dr. Lipsky.

10 DR. LIPSKY: Thank you.

11 To, I guess, be symmetrical, I'd like to
12 reiterate some of the comments that Dr. Bass made
13 initially, which I think are very important, and that
14 is to separate the drug from the regimen, and it's
15 very difficult to do particularly -- and it may be
16 purely a psychological phenomenon -- but both the
17 sponsor and the FDA presented slide after slide which
18 had in one column rifapentine and in the other one
19 rifampin, and you get thinking, you know, in your
20 mind, this is this drug; this is that drug, when in
21 actuality it's the regimen.

22 And it may well be what's going on with
23 that regimen, you know, the INH component was the
24 crucial difference between the two components, but yet
25 psychologically we get stuck on talking about a drug

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1 and we're talking about approving a drug. We've seen
2 the drug's name up against another drug, but in no way
3 were those studies designed as a head-to-head
4 comparison, but almost psychologically it's getting
5 drummed in over and over again, and I'm glad to see
6 that I think the Committee overcame that, but I would
7 find myself, you know, occasionally slipping into
8 that. Probably members of the audience would think
9 the same thing.

10 I was interested in some of the background
11 material, and I checked over lunchtime about, you
12 know, INH. There are ancient reports that claimed
13 that the once weekly regimens did not do as well as
14 the twice. So maybe that's well known and not to be,
15 you know, unexpected of what happened.

16 The other thing, of course, we don't know
17 is if you gave rifampin, you know, once a week. How
18 would it do in a regimen? Perhaps the more expert
19 people here, you know, know of specific studies.

20 Now, there is also a suggestion with INH
21 that if you have a rapid acetylator status, you do a
22 bit more poorly in the previous studies. It's
23 interesting. If you're looking at something that is,
24 you know, given once or twice a week that you're
25 comparing a half-life between one, two, three hours,

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1 you know, in one way, yes, that's three times as much.
2 In another way over a period of time that could be
3 relatively trivial.

4 I mean, so those are some things that can
5 go into the overall, you know, thought process, but
6 what do you come down to? Does the drug itself -- is
7 it a safe drug? I think we've talked about that
8 certainly.

9 Is it an effective drug? I think
10 certainly it is. Has it been stacked up in the best
11 possible regimen? Well, I don't think we know.

12 Can we give advice on how best to use it
13 without data? No, I don't think that we can. I think
14 that would be out of keeping with what certainly
15 historically the FDA has done.

16 Do we know conclusively that, you know, in
17 the broad picture of things that a once weekly regimen
18 in practical use, even if there is a slight increase
19 in relapse late in the clinical trial; will the
20 practicality of a once weekly regimen far outweigh
21 that throughout the world? We don't know the answer
22 to that, but that may not be an unreasonable
23 assumption.

24 CHAIRMAN HAMMER: Thank you.

25 I'll keep my own comments relatively brief

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1 since the issues have been eloquently stated by other
2 members of the panel.

3 First though to go through things, I
4 personally have no safety concerns beyond what we know
5 about this class of agents.

6 When we talk about efficacy, certainly the
7 overall efficacy in the trial was okay, but more
8 specifically this part of an initial regimen of
9 rifapentine appeared to work quite well, and as has
10 been stated, it's the continuation phase and the
11 follow-up phase where there were issues as far as the
12 relapse, particularly in the follow-up phase.

13 And thing to remember there, although we
14 need more data, is that at least those relapses were
15 not associated with resistance, but there are still
16 transmission and other issues that Dr. Iseman
17 mentioned that I think are important.

18 I think we should also as a Committee
19 realize that there were differences between the FDA
20 analyses and the sponsor analyses with respect to the
21 predictors of relapse, and that creates even more
22 problems for us as far as the kinds of guidance that
23 clinicians need to predict relapse, as Dr. Feinberg
24 was saying, and I think it's gnawing at all us, this
25 issue of the relapse rate, and if this drug is

1 ultimately approved, this is one of those situations
2 in which the available data probably have to be
3 somewhat used in an inferential fashion to come up
4 with regimens that try to minimize, in fact, the
5 relapse rate.

6 The third part of my comments, I think,
7 refers to the experience of this Committee with
8 accelerated approval and trying to put this
9 application in that context, and as I mentioned
10 earlier, there are two issues here. One is the
11 surrogate issue, and we're being asked, first, if the
12 six-months data that we're being provided, follow-up
13 data, is indicative of the future two-year rates and
14 whether we're comfortable with that.

15 And I personally am and actually have
16 heard no differing opinions voiced by other members of
17 the Committee.

18 The other issue which is more difficult
19 for us to wrestle with is the second aspect of
20 accelerated approval, and is there a meaningful
21 therapeutic benefit over existing therapies, and given
22 the concern about the relapse rate, if it were used
23 exactly as used in this trial, one would have
24 difficulty saying that, but, again, that's where the
25 experience of this Committee is helpful, because at

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1 least in dealing with antiretroviral agents in the
2 past, it's more than just the data that we deal with.
3 It's the expertise, as well as looking a little bit
4 into the future with as much help as we can garner,
5 and that inferences from the data and inferences with
6 clinical experience and future clinical research can
7 be helpful in trying to assuage some of the concerns
8 one might have with a limited database.

9 You have to realize we're being asked to
10 make a decision today based on a drug that has a good
11 in vitro profile, a good PK profile, but a single
12 clinical trial.

13 The other experience about this Committee
14 is the issue of signals that this Committee sends and
15 the agency sends to sponsors and the incentives for
16 drug development in certain areas, and those are very
17 important, particularly when there is a sponsor or
18 sponsors with dedication to a particular field.

19 So I just mention that in general because
20 I think the Committee as it comes to its vote should
21 recognize some of those issues that are wrapped up in
22 accelerated approval, which also comes with it the
23 issue of what additional responsibilities the sponsor
24 has during the time between accelerated approval and
25 traditional approval.

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1 So my conclusion is, yes, that it's safe
2 and has demonstrated efficacy, but how specifically
3 this drug will be used is what the rest of our
4 discussion will entail.

5 Dr. Snider.

6 DR. SNIDER: When we have a vote, I would
7 appreciate a clarification of the question we're going
8 to vote on because to me, I mean, this is vitally
9 important.

10 If we're talking about the question of the
11 drug, rifapentine, being safe and efficacious, I have
12 a very clear answer there. If we're talking about the
13 rifapentine regimen that has been shown to us, then
14 the safety I still think I have a pretty clear answer,
15 but the efficacy, well, I think it's becoming pretty
16 clear in terms of the lower efficacy.

17 But then when we use the term "effective,"
18 which is included in this question, at least at CDC we
19 use the term "effective" as relating to the use in the
20 general population under usual conditions, in which
21 case the other issues that I don't go over again that
22 people have raised come into play.

23 So the wording of this question makes a
24 big difference in terms of how I at least would
25 answer.

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1 CHAIRMAN HAMMER: I'll ask Dr. Murphy to
2 comment in a moment, but the specific indication that
3 has come forward to us is specifically this drug for
4 the treatment of pulmonary tuberculosis obviously in
5 combination. I think we're being asked specifically
6 about this drug's safety and efficacy.

7 You can't dissociate it completely from
8 the regimen, but we're not being asked to approve or
9 certify a specific regimen. In part, that's where our
10 inference has to come to play, but I think Dr. Murphy
11 should probably give us, and Dr. Goldberger,
12 additional guidance here.

13 DR. MURPHY: Give him first shot.

14 DR. GOLDBERGER: I think that when I made
15 my introductory comments this morning, you know, I
16 spoke at the end that we obviously need to be able to
17 provide some advice in labeling to provide a guide for
18 how the drug should be used.

19 We have seen data today on a particular
20 regimen done in the 08 trial. As was just said, we do
21 not necessarily have to give advice to use exactly
22 that same regimen in, for instance, all patients with
23 tuberculosis. We can make some extrapolations from
24 what we've seen today and to some degree what we know
25 about tuberculosis in doing this.

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1 To give an example of something we did a
2 few years ago, it's almost lost now in the fog of
3 history, that perhaps actually the first accelerated
4 approval, I believe, formally after the regulations
5 went through was clarithromycin for the treatment of
6 mycobacterium avium bacteremia.

7 The company put forth three clinical
8 trials, all of which used clarithromycin as
9 monotherapy for the treatment of M. avian bacteremia.
10 In the label, however, for the product, we made the
11 clear statement that it ought to be used with a second
12 drug at least, and we listed three possibilities.

13 The citation for that information was a
14 USDHS task force, but in fact, there was no clinical
15 trial data in that application for any of those drugs,
16 nor was there really any substantial data submitted on
17 them. Rather, it was based on the deliberations of
18 some experts that had occurred in the preceding year,
19 and I think was reasonable given what we know about
20 mycobacterial disease, even though by the standard of
21 what we would be asked to do today, we were making a
22 rather broad leap from primarily tuberculosis to an
23 entirely different mycobacteria.

24 So there is some flexibility. We do need
25 to ultimately feel that we can provide some advice how

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1 this product ought to be used, even if it is not
2 identical to how it was used in the clinical trial.

3 DR. MURPHY: I think your concern is that
4 normally we would approve a product for the population
5 in which it was studied, and that is what we would do
6 here, but what we're saying is that we do have data
7 that's been presented to us that maybe this was not
8 the best regimen, and there is other data, and that's
9 why we have the experts here to help us advise on what
10 might be the best way to recommend to use this drug.

11 CHAIRMAN HAMMER: Thank you.

12 So with that, I think now we have to
13 commit ourselves. There are 11 members permitted to
14 vote today. They are Drs. Feinberg, Lipsky, Hamilton,
15 Pomerantz, D'Agostino, Self, Bertino, Hopewell, Bass,
16 Snider, and me.

17 And so I'll read the question, and we have
18 to vote on the question that's put before us. Is
19 rifapentine safe and effective for the treatment of
20 pulmonary tuberculosis?

21 And if you say yes to this question,
22 please raise your hand of the voting members.

23 (Show of hands.)

24 CHAIRMAN HAMMER: And Dr. Pomerantz's vote
25 is yes.

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1 Are there any no votes?

2 (Show of hands.)

3 CHAIRMAN WINTERS: Okay. Now we're going
4 to go on to consider the corollary question, and what
5 we'd like to do is really ask the Committee members to
6 comment about these in a group for efficiency sake and
7 also because a couple of members need to leave a bit
8 early.

9 So if the answer to Question 1 is yes, as
10 the majority has, are there certain patient groups for
11 whom the drug should be recommended?

12 And I think also given Dr. Murphy's
13 introduction, issues of the patient groups, but also
14 how any suggestions for the label indications and what
15 might be included in the label.

16 Part B is: as part of the accelerated
17 approval, what other studies should be performed? And
18 I think we were also asked about advice about
19 particular regimens that might be studied. I think
20 that also might go for clinical practice.

21 So I think I'll start again on my left.
22 Dr. Bass.

23 DR. BASS: Boy.

24 CHAIRMAN HAMMER: Although you can defer.

25 DR. BASS: This is a lot harder than the

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1 other.

2 (Laughter.)

3 DR. BASS: Based on what I've heard, I
4 would have reservations about using it in HIV positive
5 patients. Based on what I've hear if I were going to
6 use the drug in the continuation phase, I would pay
7 particular attention to the strength of the induction
8 phase, and I don't know how best to elaborate on that,
9 but --

10 CHAIRMAN HAMMER: Are there issues of
11 maybe intensity or length of the introduction phase?

12 DR. BASS: The data, yeah, I could talk
13 for hours about it.

14 (Laughter.)

15 DR. BASS: But I don't know that you're
16 going to be able to put it in the package insert very
17 easily. I think the more drugs or good quality that
18 you've used during the initial eight weeks of therapy
19 and the more consistently that they have been taken in
20 the appropriate doses increases the likelihood that
21 your overall regimen would be successful.

22 I don't know what sort of comments to make
23 about the induction phase, although it seemed to be
24 used -- as used, it seemed to be successful. I would
25 still have some questions. I would not have designed

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WASHINGTON, D.C. 20008

1 the study exactly as it was designed.

2 I even have questions about whether giving
3 a drug twice a week during an observed therapy might
4 actually decrease the interest in the population for
5 coming back those other days; that somehow the way the
6 study was designed may have decreased the compliance
7 with the other medications. It seemed to perhaps
8 influence the relapse rate.

9 So I don't know what to say about the drug
10 during the induction phase personally.

11 DR. MURPHY: Could I ask you to comment on
12 what you would -- if you had the ideal situation, how
13 would you like to see the drug used during the
14 induction phase or would you not use it during the
15 induction phase since we're here to hear --

16 DR. BASS: You mean me?

17 DR. MURPHY: We have an opportunity to
18 pick your brain today, and we are.

19 DR. BASS: Me personally today?

20 DR. MURPHY: Yes, sir.

21 DR. BASS: I probably would not use it
22 because I have alternate regimens that I know to be
23 effective, and I don't know exactly how to use this
24 drug during the induction phase.

25 I would have questions. For example, it

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WASHINGTON, D.C. 20008

1 might be a useful addition to intermittent therapy
2 during the induction phase, which again might offer
3 the same sorts of advantage to directly observed and
4 personnel and use of resources and stuff like that.

5 You might get the same advantage during
6 the induction phase that you got during the
7 continuation phase. If you could do that, that would
8 be a tremendous boon worldwide, the application of
9 therapy, but I don't know the answer. I think that's
10 a study. I wouldn't know what to recommend.

11 DR. GOLDBERGER: This question, Dr. Bass,
12 is for you and also for our other two consultants in
13 terms of thinking about the use of the drug, for
14 instance, in the continuation phase at some point. Is
15 knowing whether the sputum culture has converted to
16 negative helpful in making the decision? That's the
17 kind of information that's so easy to put in the
18 label.

19 DR. BASS: Based on the information I have
20 today, I would say yes, that all indicators that you
21 have of the success of the induction phase, which
22 would include whatever access you have to knowing how
23 many doses they took, the assurance that they really
24 did, the speed with which the sputum converted,
25 perhaps the extent of disease. I would right now

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1 utilize all of that information.

2 CHAIRMAN HAMMER: Dr. Hopewell.

3 DR. HOPEWELL: I guess I would jump to the
4 maybe unjustified conclusion that rifapentine is at
5 least the equivalent of rifampin and that, therefore,
6 at a minimum it could be used in the way that rifampin
7 is used.

8 So I think the question kind of boils down
9 to the dosing interval that you can recommend and more
10 specifically in what situations could you recommend a
11 less than twice weekly dosing interval in the
12 continuation phase.

13 Unless one is using thrice weekly therapy
14 in the induction phase, there's probably no advantage
15 to rifapentine in the induction phase, but where it is
16 advantageous is the potential for using it once weekly
17 in the continuation phase.

18 I think that's the question that we really
19 ought to be addressing, and are there ways that we
20 could label the drug that would indicate when it
21 should be used once weekly in the continuation phase?

22 Again, my assumption would be perhaps not
23 justified by the data that it is the equivalent of
24 rifampin. Therefore, it can be used with equal
25 efficacy twice weekly in the continuation phase. So

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1 again the question boils down to: how can we decide
2 whether or not or how can we develop guidelines that
3 indicate in what situations can be used once weekly in
4 the continuation phase?

5 I think the compliance with the induction
6 phase therapy and whether or not the person has
7 converted by month two have been shown to be useful
8 indicators of whether or not the once weekly
9 administration is going to work. So I think I would
10 try to work those two in.

11 And I agree with John that I wouldn't use
12 it once weekly in persons with HIV infection or other
13 severe forms of immunocompromise.

14 CHAIRMAN HAMMER: Thank you.

15 Dr. Snider.

16 DR. SNIDER: I think I agree with a lot of
17 what Phil and John have said. I guess I see this drug
18 as potentially being very useful in the real world
19 situation of intermittent dosing for directly observed
20 therapy. Whether that might be having an induction
21 phase that is intermittent three times a week, which
22 you know is possible already, but to my knowledge, we
23 don't have a regimen which you switch from three times
24 a week to twice a week. You have to go three times a
25 week throughout really to get the level of efficacy

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1 we're talking about.

2 So I think one possibility would be three
3 times a week induction and then twice a week
4 continuation that rifapentine would replace rifampin.
5 There is the potential for an advantage also in terms
6 of dropping back on the number of drugs throughout the
7 continuation would just be two, whereas it would be
8 four during the induction.

9 So I see some regimens, some like those,
10 in which rifapentine might reduce the number of visits
11 that are necessary or interactions, and I think that's
12 terribly important in the real world because in the
13 real world people on directly observed therapies do
14 miss some of their doses, and I think rifapentine
15 might give you a margin of benefit.

16 I think even today with, you know, let's
17 say three and a half to five percent relapse rate that
18 in those doses in which the induction period is daily
19 and then the continuation is twice weekly, that
20 although I don't know the cost of doing this, that for
21 those who can afford it, whether they are people or
22 programs or countries, there's the potential that
23 rifapentine might reduce the relapse rate down even
24 further below what it is now and offer a more
25 certainty of cure than an individual has now, which

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1 is, you know, 19 out of 20 is your chances of cure.
2 Perhaps rifapentine could change those odds
3 considerably.

4 In terms of groups that are not
5 considered, of course, some of those are obvious, the
6 HIV group, the drug resistant group. Extra pulmonary
7 TB is also problematic here in terms of groups to
8 leave out. Although for years we've had to
9 extrapolate from pulmonary disease to extra pulmonary
10 disease because we don't have enough extra pulmonary
11 disease in this country, and in many countries they
12 don't have enough of a specific site of extra
13 pulmonary disease to be able to say whether a regimen
14 is equivalent or not.

15 We do have some concerns in that regard or
16 at least concerns have been raised about the adequacy
17 of some of our standard therapies for pulmonary
18 disease. Are they adequate for certain forms of extra
19 pulmonary disease?

20 And so although I wouldn't exclude extra
21 pulmonary disease, I certainly would say that it would
22 be used with caution with extra pulmonary disease in
23 the absence of data at the present time.

24 With regard to the once a week, I think,
25 the data are somewhat suggestive of about populations

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1 that you might be able to use it once a week in the
2 continuation phase. I think we still have to
3 recognize that if we're going to do that, we ought to
4 have some good post marketing surveillance to see what
5 actually happens because given the statistical
6 analyses that were done, I'm a little confused about
7 how good those markers for relapse and failure really
8 are.

9 It sounds as if you have a good record of
10 taking your drugs in the induction phase and you
11 respond, namely, you convert, that you might be in
12 pretty good shape for once a week therapy, but if it
13 started being used for that, I would want to confirm
14 in some post marketing studies that, indeed, that was
15 the case.

16 CHAIRMAN HAMMER: One of the issues, and
17 I'll press our three consultants, that can occur or
18 that does occur with accelerated approval is that
19 discussion with the agency and the sponsor about
20 additional data to be accrued. That's really
21 important to the use of this drug in a broader fashion
22 and for ultimate traditional approval.

23 So if there are specific suggestions for
24 the kinds of information that you'd like to see that
25 may not be necessarily forthcoming from the other

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1 trial that's in place, this is the time to put that
2 forward for the agency's consideration and to be on
3 the record.

4 I don't know if that's --

5 DR. SNIDER: I think most of the things
6 I've said would have to be data that are gathered
7 later on, whether we're talking about the intermittent
8 regimens I was talking about, use in extra pulmonary
9 disease and so forth.

10 We really don't have the data. I think
11 I'm extrapolating, as we often have done in
12 tuberculosis, based on what I know about this drug and
13 its pharmacokinetics and so forth, but I think it
14 would be important to look at it in a real world
15 situation to see what is actually happening.

16 I think some of the potential benefits
17 that we've talked about that might accrue from the use
18 of the drug on a once a week basis in terms of savings
19 to health departments and larger numbers of patients
20 being supervised in completing therapy and so forth,
21 there are lots of issues that can't be very easily
22 studied in clinical trials and we're going to have to
23 gather that information once the drug, if it gets on
24 the market -- you're going to have to gather it after
25 it's on the market. I don't see that it's possible

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1 for the sponsor to gather all of that kind of
2 information prior to licensure.

3 CHAIRMAN HAMMER: Thank you.

4 Are there any other --

5 DR. GOLDBERGER: Scott, could I just ask?

6 CHAIRMAN HAMMER: Yes, please.

7 DR. GOLDBERGER: Just before we leave the
8 three of you, just two other issues, one of which I
9 think John, I know, already commented on a little.

10 Do you believe that baseline severity of
11 disease would play any role in selecting who might or
12 might not get the disease? Drug. Sorry. Thank you,
13 Joyce.

14 And in addition, would the suggestions
15 about substituting it for rifampin in those
16 circumstances -- do you feel that that would still be
17 precluded in patients who are HIV positive or do you
18 want to make any comment at all about that latter
19 point?

20 I think you've made it clear that as
21 studied, that you did not support its use in HIV
22 positive.

23 DR. SNIDER: Yeah, I think your point's
24 well taken, Mark. I mean, clearly, using it once a
25 week, I think, again, we're getting caught up in are

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1 we talking about a regimen or are we talking about the
2 drug. I don't see any contraindications for the use
3 of rifapentine in HIV infected individuals.

4 The issue is the particular dosing of the
5 drug, I think, in HIV infected individuals, and what
6 we've seen is that once a week dosing appears at least
7 to have adverse consequences beyond just a relapse,
8 but a drug resistant type relapse, and consequently,
9 I think, if we wanted to use it, if I were going to
10 use it in an HIV positive individual, I wouldn't use
11 that dosing.

12 As far as the severity of the disease, you
13 know, that's one of the reasons I am interested in the
14 way the data are analyzed. The severity of disease,
15 response to therapy, if you do a multivariate
16 analysis, how much are they tied up with one another
17 and confounded?

18 I guess my pragmatic mind says that I'm
19 more interested in seeing the response than I'm
20 worried about the extent of the disease at the
21 beginning of therapy, but that's just a clinical
22 impression, not necessarily one that's driven by data
23 because some of the data did, indeed, suggest that the
24 more extensive disease, the more likely it was that a
25 person would relapse, particularly on the once a week

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1 regimen.

2 But you know, is that also associated with
3 being male and being macho and putting off visiting a
4 physician and also not taking your drugs for similar
5 or other reasons? I don't know how much these things
6 are related to one another, and their individual
7 predictive value we've been shown, but I don't know
8 when you put it into a model which ones fall out as
9 being the most important.

10 Maybe it's because I'm having trouble
11 assimilating all of the different variables and their
12 impact.

13 DR. HOPEWELL: I think trying to vary the
14 indication based on the severity of disease would be
15 fraught with problems, and it would be very difficult
16 to do. It's often a pretty subjective assessment,
17 other than by looking at the number of bacilli in a
18 smear, and, yes, you can get an idea from the chest
19 radiograph, but it's a very rough idea at best unless
20 you go to the fairly difficult approach that was used
21 in this study that I don't think can be used under
22 anything other than study conditions.

23 So I wouldn't advocate using severity of
24 disease as an indicator.

25 I still do think though, however, the

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1 question boils down to not whether or not you can use
2 this drug or not, but when it can be used once a week,
3 and other than that, I would be willing to say, you
4 know, as I said, that it's equivalent to rifampin and
5 could be used in all of the ways rifampin is used, and
6 so we need to define when it can be used in ways other
7 than in the way in which rifampin is used, i.e., once
8 a week rather than twice a week at a minimum.

9 I think the question of extra pulmonary
10 disease is important, as well, in that you don't want
11 to force people to have to exclude extra pulmonary
12 disease in every person with pulmonary disease in
13 order to use the drug. That would be fairly laborious
14 and not something that's routinely done. So you'd
15 like to know that it's effective for extra pulmonary
16 disease, as well.

17 CHAIRMAN HAMMER: Okay. Dr. Bertino.

18 DR. BERTINO: Well, I'd say I'm kind of a
19 data guy, and so based on the data today, I think that
20 the label should say that this is for non-HIV infected
21 patients with pulmonary tuberculosis in the regimen
22 that was studied.

23 I do think a lot of additional research is
24 needed. It concerns me, for example, that we don't
25 know if patients took this in a fed or fasted state

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1 because, according to the sponsor, the AUC data showed
2 that when given with a high fed meal AUC increased
3 about 43 percent.

4 It would be interesting to know if you
5 just gave this drug with food, if you could just give
6 one and a half times the dose once a week or something
7 like that.

8 The other concern I have about its use in
9 HIV infected patients is, once again, the issue of
10 protease inhibitors, and in the document, briefing
11 document, we have, there's a discussion about
12 indinavir and suggesting that, you know, an
13 indinavir/rifapentine combination -- that even with
14 that combination the trough of indinavir remained
15 close to the IC-95. These findings may support the
16 use of rifapentine and indinavir combination.

17 I would say that that's not true until you
18 look at viral loads and effect on HIV with this
19 combination. I also think we probably need data on
20 not only the proteases, but the NNRTIs, and also the
21 other drugs that these patients take, like
22 clarithromycin, ezithromycin, SSRIs because they're
23 depressed, which certainly can affect the SIP system.

24 So I would say that those were the
25 studies, some of the studies at least from my point of

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1 view, that are needed. I guess I would just advocate
2 being very specific in the labeling, you know, that
3 this study only looked at non-HIV infected patients,
4 only using this regimen.

5 CHAIRMAN HAMMER: Thank you.

6 Dr. D'Agostino.

7 DR. D'AGOSTINO: In the interest of
8 accelerated approval, I'll give an accelerated answer.
9 For 2(a), I think the HIV positive group is clearly
10 not recommended. I think worrying about the induction
11 phase and how quickly there is a response there, I
12 think, should certainly be brought into consideration
13 in terms of the populations that this is appropriate
14 for.

15 As far as 2(b), I think that follow-up of
16 existing study, the continued follow-up, is essential.
17 Are those trends that we're seeing in terms of the
18 relapse real, or are they going to settle down? And
19 if they are real, how much bigger is it?

20 And, again, I don't think that a drug has
21 to beat out an existing drug to be approved. I mean
22 a drug can be not as good as an existing drug, but
23 still be very useful, and I think that there is a
24 margin where you can tolerate it not being as good and
25 have higher relapse rates as long as there are other

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1 compensations for it.

2 I think the further analysis of this data,
3 as was alluded to earlier in terms of the
4 multivariate, I'm concerned that we don't really have
5 a good sense of what might be indicators of poor
6 response or relapse because we're looking at things
7 one at a time and not seeing how they really compete
8 against each other.

9 I think we need some post marketing data,
10 and I think this question about the regimens -- I
11 mean, I don't know how the studies are going to be put
12 together and so forth, but clearly we keep coming back
13 to that, and it isn't going to be resolved by talking
14 about it. It's going to be resolved by some studies.

15 That's it. Thank you.

16 CHAIRMAN HAMMER: Dr. Self.

17 DR. SELF: Because of my vote, I get to
18 answer a little bit different question, what
19 additional research is required.

20 (Laughter.)

21 DR. SELF: And the main thing, I think, is
22 some additional clinical trial data, mature trial
23 data, that directly evaluates some of the regimens
24 that are a little closer to the ones that might
25 actually be used in practice. Most of the discussion

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1 so far has been focused on how to modify the regimen
2 in the induction phase, and you know, that's obviously
3 the place to look.

4 I think some of that data is not too far
5 in the future from becoming mature, and that is
6 something that should be considered.

7 I'd also, in order to meet this second
8 criterion for the accelerated approval of meaningful
9 therapeutic benefit, would suggest at least some
10 rudimentary modeling of effectiveness since it's just
11 anticipating that there's not going to be a large
12 clinical benefit in terms of an improvement in relapse
13 rates. We're still back to talking about roughly
14 equivalent or not too inferior in terms of relapse
15 rates.

16 And so then the question is, okay, in
17 terms of effectiveness, economics, logistics, and so
18 on, do those benefits outstrip the clinical profile,
19 and so a little modeling of that, I think, would be
20 useful.

21 And then finally, these studies may
22 already have been done. I don't know because I don't
23 work in this area, but there were some theoretical
24 models about what happens during the very early
25 portion of the induction phase in terms of clearance

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1 of the organism, and maybe some more detailed
2 biological studies of the kinetics of that particular
3 phase of treatment would be also useful.

4 CHAIRMAN HAMMER: Thank you.

5 Dr. Feinberg.

6 DR. FEINBERG: Oh, let's see. Well, I
7 agree with other speakers that as used in this regimen
8 in this study, at the moment this does not seem to be
9 the best possible approach to treating tuberculosis in
10 HIV infected people.

11 I'm intrigued by the thought though that
12 because of the half-life, that actually if you gave
13 the drug more frequently, say, twice a week, in the
14 continuation phase you might make up for some
15 noncompliance and patients might actually ultimately
16 do better, HIV positive patients included.

17 So I think it's germane, especially since
18 there are so many co-infected people, to actually
19 study the seropositive population, and I think as a
20 corollary to that, I share Dr. Bertino's disquiet
21 about the wording of the interaction study. I
22 actually found that wording a little disingenuous. I
23 think a 70 percent decrease in the area under the
24 curve is something that ought to make you stop and
25 take notice, and I wasn't relieved by the fact that,

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1 you know, the trough was still above the IC-50 or IC-
2 90, however it was described.

3 And there's more than indinavir out there
4 in the therapeutic world of HIV. So as I think Dr.
5 Bertino indicated, there are other drugs, non-
6 nucleocides and other protease inhibitors that would
7 need ultimately to be looked at because even if you
8 could convince a patient that in the immediate
9 induction phase they needed to focus on managing their
10 TB more than they needed to focus on managing their
11 HIV, you know, ultimately you would clearly want to
12 manage their HIV disease. It might, of course, have
13 an impact on how they do with their TB, and you might
14 imagine that lots of clinicians would want to give
15 protease inhibitors, you know, during the continuation
16 phase, the more chronic phase of dosing.

17 So I think it's worthwhile to look at
18 those interactions.

19 You know, I think you ought to look at
20 this drug in children since clearly there are a lot of
21 children with tuberculosis in this world.

22 You know, the population pharmacokinetic
23 data that we got shown in the question and answer
24 period I thought showed what appeared to me, as well
25 as to another member of the panel, striking

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1 differences between men and women. So I think gender
2 differences ought to be, you know, more fully explored
3 because maybe you would want to dose this drug somehow
4 differently in men and women if that difference holds
5 up.

6 What else?

7 And I guess, of course, that it goes
8 without saying that you would want to monitor failures
9 of therapy and relapses for the development of
10 resistance. I think that was that *sine qua non*.

11 Let me hand it to Dr. Hamilton.

12 DR. HAMILTON: Well, I would defer to the
13 expert colleagues, consultants who have been present
14 throughout the day providing knowledgeable guidance to
15 the rest of us in the selection of the appropriate
16 patient populations to be included in the package
17 insert, with one addition that perhaps won't be too
18 arguable, and that is extending the definition of
19 AIDS/HIV to those who are immunocompromised on other
20 bases as well.

21 I think it's cutting it a little fine to
22 include one and not the other.

23 Fortunately, I agree with almost
24 everything everyone has said, whether they answered
25 the question yes or no.

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1 (Laughter.)

2 DR. HAMILTON: And heartily endorse the
3 prospective maturing of clinical trials that will help
4 us make decisions about the potential of stiffening
5 induction phase therapy, which given my own druthers,
6 I would choose to do.

7 I think there are some patient populations
8 issues that remain unresolved, and I would like to see
9 some concrete data that addressed that from a
10 pharmacodynamic point of view, and that would seem
11 reasonably easily achievable, if it's not available
12 already.

13 I think I have nothing else. Thank you.

14 CHAIRMAN HAMMER: Thank you.

15 Dr. Lipsky.

16 DR. LIPSKY: Thank you.

17 Most, I think, of the comments have been
18 made. I would just reiterate that caution should
19 always be taken in pontification about data and
20 medicine. I hardly need to tell the FDA that, and I
21 think our three consultants also would agree to that,
22 too.

23 It would be nice to come up with this is
24 exactly how to use that, but here we have a disease
25 which is difficult to treat, and if we're treating it

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1 now currently with a four-drug regimen, that means I
2 don't think we're going to get simple answers to
3 exactly how best, you know, to use this, although
4 certainly with accelerated approval, having sat on
5 this Committee for a little while, I think we've
6 certainly seen, you know, situations where a lot, lot
7 less data with efficacy has allowed for accelerated
8 approval.

9 In this Committee by the former Director
10 of Antivirals said that perhaps sometimes we are a bit
11 too conservative with accelerated approval. The whole
12 idea of accelerated approval is to be a bit more
13 liberal in the approval process.

14 Just a couple of points of clarification,
15 that we should separate the regimen from the drug in
16 the use of people who are infected with HIV in that
17 we're concerned about the regimen, but the drug
18 certainly perhaps in a better regimen could certainly
19 be used in that situation.

20 Also, you know, the use of protease
21 inhibitors. It isn't that we're looking at a drug
22 interaction which, you know, causes Toursade du Quint
23 (phonetic) and sudden death. We're looking at one
24 that decreases the levels of another drug, and a way
25 around that is the more widely availability of

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1 therapeutic modeling so that you can increase the dose
2 and do that, you know, appropriately.

3 So particularly when we're talking about
4 someone who may be infected with two life threatening
5 illnesses, I mean, it's something to think about.

6 Finally, what further studies to be done.
7 There was one specific hypothesis recommended by Dr.
8 Iseman which was intriguing. He thought one of the
9 reasons for the increased relapse was the use of
10 ethambutol instead of streptomycin as the fourth drug
11 in the induction regimen, and it seems like that would
12 make a nice study to do, and perhaps an
13 immunoglycocide with a nice gamma phase of elimination
14 could be useful in the treatment of tuberculosis, and
15 also since streptomycin was first used by Dr. Hinshaw
16 at the Mayo Clinic and coming from there, I have no
17 problem, I guess, in recommending a study of that
18 nature.

19 With that, thank you.

20 CHAIRMAN HAMMER: Thank you.

21 I just have a couple of brief comments.
22 I don't have much to add to what's been said.

23 With respect to Question 2(a), the patient
24 groups, I think we're clearly left with the HIV
25 negative group with pulmonary tuberculosis. One has

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1 to be cautious about the HIV positive group for all of
2 the reasons that have been stated, and particularly at
3 least in the developed world, the interaction with
4 protease inhibitors.

5 That being said, the drug because of its
6 activity may well be used in extra pulmonary
7 tuberculosis, and clinicians will make that choice.

8 As far as regimens within the clinical use
9 of the drug, I think it hard for a Committee to really
10 come up with specific regimens, aside from learning
11 from the clinical trial experience that's been
12 presented, and there are more clinical trials that
13 will be coming.

14 But it certainly seems reasonable to
15 consider it as part of initial four-drug regimens, and
16 as far as the continuation phase, which is what is
17 troubling individuals, and the fact that there were
18 differences in the analyses presented with regard to
19 predictors of relapse, irrespective of the treatment
20 arm, the sputum conversion at the end of the induction
21 phase was predictive, and as Dr. Goldberger indicated
22 earlier, these at least raised a question.

23 One practical thing to take away from the
24 data we had is that, I think, great caution should be
25 used before going to once weekly therapy with

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1 rifapentine, should the drug be approved. In the
2 absence of documented sputum conversion, I think one
3 will increase the likelihood of long term success
4 until we have more data if one at least puts that
5 somewhere in the label, and that would be helpful to
6 clinicians.

7 With respect to additional studies, I
8 would agree with what's been said before, but maybe
9 emphasizing the other side of the coin with this drug.
10 We've emphasized the relapse rate, but remember that
11 in the trial presented today, it was twice weekly
12 during the initiation phase and once weekly during the
13 continuation phase.

14 And unless there's something very strange
15 about this drug, the PK profile is favorable and its
16 in vitro activity is even greater than rifampin. So
17 one can think about actually building on the activity
18 of this drug to improve regimens and even shorten
19 courses further, as came up a little bit during the
20 discussion today.

21 So as far as additional studies, and maybe
22 this can come up in the discussions about the
23 international trial that sounds like it's in the
24 planning phase about intensive initial -- improving
25 the intensity of initial phases or at least thinking

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1 about flexibility, and when one moves to the
2 continuation phase, to some extent, based on what
3 we've learned from this trial, and one may shorten
4 course even further, and the use of rifapentine as a
5 twice weekly regimen may even diminish relapse rates
6 lower than what we see with rifampin.

7 So I think there's an opportunity to use
8 this drug like rifampin, but in a way that actually
9 improves our outcomes over the future.

10 There's also potentially some room, I
11 guess, to look at, as Dr. Iseman, I think, mentioned,
12 the dose as far as also increasing activity.

13 I would also recommend that in these
14 studies that are being planned or future studies, that
15 we look at adherence perhaps in a bit more
16 sophisticated fashion than just calculating numbers of
17 doses, although that's one way one does that, but
18 particularly in once weekly regimens, a missed dose
19 may be more important than just a single missed dose
20 versus a twice weekly regimen.

21 We need to gather the data on extra
22 pulmonary disease, which will come from culling it
23 from the clinical experience or cross-trials, and I
24 would echo what Dr. Feinberg mentioned about
25 resistance monitoring.

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1 Lastly, the clinicians are going to need
2 guidance and education about this drug so that it's
3 used properly, and I think that will come from the
4 clinical trial information and post marketing sorts of
5 issues, but I think we have to be careful that we make
6 sure that the potential of this drug is well known,
7 but the caveats we have at the moment, until more data
8 are available, are well out there.

9 It's through the experience, I think, that
10 -- and tuberculosis treatment is one of those classic
11 infectious diseases -- that we have certain
12 information from trials, but we develop a lot of this
13 as we go on in the clinical experience, and we
14 shouldn't forget the importance of that.

15 So I don't have more to say. I would ask
16 Drs. Murphy and Goldberger whether there are other
17 points that we should consider before --

18 DR. GOLDBERGER: Yes. I wanted to just
19 make one more brief use of our consultants.

20 CHAIRMAN HAMMER: Please.

21 DR. GOLDBERGER: In terms of designing a
22 new treatment trial, I think Dr. Hammer just raised
23 the issue of certainly potentially exploring another
24 dose. How would you feel, for instance, about a trial
25 modeled on the Denver regimen with some sort of

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1 induction for a couple of weeks followed by twice
2 weekly therapy of everything and then going to once
3 weekly rifapentine and INH?

4 Would you, for instance, be relatively
5 comfortable with a model like that or are there other
6 designs along that line?

7 DR. BASS: I would be comfortable with
8 that. I think that's relatively conservative. I'd be
9 interested to see what you could do with a brief
10 period of twice weekly therapy followed by once weekly
11 therapy, and I don't know how to define those periods
12 of time.

13 I might even be interested to see if you
14 could treat people with once weekly therapy from the
15 beginning.

16 DR. GOLDBERGER: Dr. Hopewell?

17 DR. HOPEWELL: Yeah, I think I could go
18 along with that. I do think that, as I said earlier,
19 we're beginning to bump up against the sort of lower
20 limit of what we can do with current agents, including
21 rifapentine, but I think we do need to explore and
22 sort of probe in that direction to see if we can
23 further reduce the number of doses and, therefore, the
24 supervision required.

25 DR. BASS: I didn't mean to be suggesting

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1 specific regimens right now. It's just off the top of
2 my head, but I mean looking at ways to minimize the
3 induction phase.

4 I mean, I think we already have some
5 anecdotal evidence that you can probably treat people
6 twice weekly with the drugs we've got right now, or
7 you know, you could think of a lot of things. A week
8 of daily therapy followed by whatever, you know.

9 I think ways to reduce the burden of the
10 induction period would be extremely valuable if they
11 could be shown to be successful, and I think there's
12 a reasonably likelihood they could.

13 DR. GOLDBERGER: Dr. Snider?

14 DR. SNIDER: I'm very much in favor of
15 doing conceptually what is being proposed. I guess I
16 have some concerns about trying to step out too far
17 too fast with this drug because it seems to me, as I
18 tried to say before, that this drug, I think, has some
19 potential advantages, and unfortunately this
20 particular trial design didn't, as much as everybody
21 intended that and hoped that it would, didn't show
22 forth those advantages.

23 But I think, as you know, there's some
24 tremendous advantage in terms of directly observed
25 therapy, you know, for curing TB patients. I think

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1 that's been very adequately demonstrated, and in our
2 country that's tremendously resource consuming.

3 So the extent to which we can reduce the
4 number of encounters with the patient and still
5 maintain efficacy is terribly important. So I think
6 we should take sort of a medium step forward, not a
7 tiny step, but not try to do a giant step either
8 because what I'm afraid of is, again, showing lesser
9 efficacy in trying to do something which doesn't do
10 anything -- well, it doesn't help the company, and it
11 certainly doesn't help TB programs move forward.

12 So I think something along the lines you
13 talked about of a relatively short first phase and
14 then a twice or three times a week, depending on how
15 you set this whole thing up, twice or three times a
16 week second phase, and then once a week third phase is
17 a reasonable approach to getting at regimens that are
18 more feasible to supervise, that don't require so many
19 encounters, while at the same time have a high enough
20 probability of success that they wouldn't set us up
21 again for another trial in which we might see
22 inferiority of a rifapentine regimen.

23 DR. MURPHY: I just wanted to thank the
24 Committee and everyone. We did seem to hammer you a
25 bit on the studies because under accelerated approval,

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1 we have one study here, and we are saying what
2 information do you think we have to have to say that
3 this drug is safe and effective as it's going to be
4 used, and so that's why we've been continuing to pick
5 your brains and ask for that guidance today.

6 Because we have -- you have voted that we
7 should approve. Your advice would be that we do
8 approve it under the accelerated approval program,
9 which means we must have data to verify that decision
10 in the future.

11 And so that's why we keep picking on you
12 today. So I thank the Committee for a very thorough
13 discussion of what's obviously, as someone said, a
14 multifactorial, complicated issue here.

15 CHAIRMAN HAMMER: Thank you.

16 I personally would like to thank the
17 Committee members, guests and consultants, the agency,
18 and most specifically the sponsor for today, Hoechst
19 Marion Roussel.

20 Thank you. This meeting is adjourned.

21 (Whereupon, at 3:54 p.m., the Advisory
22 Committee meeting was concluded.)

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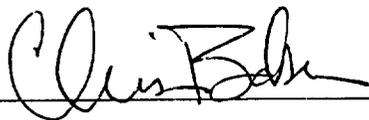
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This is to certify that the foregoing transcript in
the matter of: Meeting of the
 Antiviral Drugs Advisory Committee

Before: DHHS/FDA/CDER
Date: May 5, 1998
Place: Gaithersburg, MD

represents the full and complete proceedings of the
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 OF PAGE

 - \$ -

\$100 [1] 171:12
 \$150 [1] 171:15
 \$250 [1] 171:6

 - 1 -

10:29 [1] 113:25
 0:45 [1] 113:23
 0:52 [1] 114:1
 12-month [8] 17:12; 23:5;
 35:8; 39:6; 110:4, 5; 129:24;
 147:23
 12:00 [1] 164:13
 12A30 [1] 6:18
 15-minute [1] 113:22
 1940s [1] 165:19
 1990s [1] 167:23

 - 2 -

22nd [1] 165:17
 24-month [1] 24:8
 26-week [1] 60:23
 270/279 [1] 120:8
 2:00 [4] 164:8, 11, 14; 165:2

 - 3 -

3:54 [1] 244:21

 - 5 -

50-50 [1] 95:17
 55-day [1] 39:16

 - 6 -

62-day [1] 39:12

 - 8 -

3:04 [1] 4:2
 8th [2] 23:1; 35:6

 - 9 -

90-10 [1] 95:19
 90-plus [1] 30:19
 96-day [1] 39:10

 - A -

a.m. [3] 4:2; 113:25; 114:1
 abbreviated [2] 25:2, 3
 abbreviation [1] 22:14
 abide [1] 175:18
 ability [6] 10:23, 24; 12:16;
 53:19; 169:11; 172:11
 able [10] 12:16; 114:3; 170:1,
 19; 173:20; 189:18; 210:16;
 214:16; 220:13; 221:1
 abnormal [2] 72:14; 156:24
 abnormalities [1] 49:20
 absence [4] 93:20; 98:1;
 220:23; 238:2
 absolute [4] 29:11; 30:15;
 113:5; 127:4
 absorption [4] 20:20; 21:15,
 16; 79:7
 abstract [1] 154:20
 abuse [4] 24:1; 153:7
 Academic [1] 202:6
 accelerated [32] 4:11; 9:24;
 11:10; 17:3, 13; 53:4; 63:21;
 109:25; 115:17; 116:5, 14;
 137:21; 167:23; 181:11, 15;
 182:21; 207:8, 20; 208:22, 24;
 211:3; 213:16; 221:18; 228:8;
 230:8; 235:4, 7, 11, 12;
 243:25; 244:8
 accept [1] 200:11
 accepting [1] 177:24
 access [2] 201:5; 216:22
 accessible [1] 62:5
 accompany [2] 58:22; 60:8
 According [1] 35:10
 according [1] 227:1
 account [6] 76:18; 124:14, 20;
 126:21; 187:9; 189:13
 accounted [1] 152:3
 accounting [2] 77:17; 119:8
 accrue [3] 189:22; 200:16;
 222:17
 accrued [1] 221:20
 accrues [1] 198:16
 accumulated [1] 35:6
 acetylation [2] 94:25; 109:5
 Acetylator [1] 95:15
 acetylator [1] 204:21
 acetylators [2] 95:7; 109:12
 achievable [1] 234:11
 achieve [4] 28:5; 59:19;
 75:22; 146:24
 achieved [4] 54:22; 127:11;
 163:12, 15
 achieving [1] 27:18
 acid [3] 48:1; 157:13, 14
 acidic [1] 55:25
 acids [1] 157:6
 acknowledge [1] 16:23
 Acquired [1] 53:3
 acquired [5] 51:22; 152:11;
 154:2; 155:14; 157:24
 ACTG [1] 154:22
 acting [3] 64:2; 78:11; 163:2

action [1] 20:1
 active [16] 15:4; 22:17, 22,
 23; 23:2; 27:19; 28:6, 8, 19;
 55:17; 56:4; 79:22; 104:11;
 127:1; 159:6; 168:25
 activity [23] 54:9, 18; 55:18;
 56:17; 57:1, 11, 15, 23; 60:10;
 61:7; 78:11; 93:21; 104:2;
 105:24; 107:24; 108:5; 109:4;
 184:20; 185:12; 237:6; 238:16,
 17; 239:12
 actual [5] 37:21; 40:23; 67:16;
 83:6; 189:15
 actuality [1] 203:21
 add [5] 132:12; 133:22; 183:9;
 202:2; 236:22
 added [1] 42:3
 adding [1] 91:12
 addition [23] 6:20; 13:12;
 16:13; 17:16; 20:19; 21:14;
 23:12; 28:16; 39:5; 48:2; 50:4,
 13; 51:5; 58:19; 59:16; 63:24;
 68:15; 116:8; 152:18; 201:9;
 216:1; 223:14; 233:17
 Additional [1] 115:14
 additional [26] 17:12, 14;
 30:3, 11; 68:6; 98:3; 100:3;
 110:6; 116:13, 16; 119:18;
 137:20, 22; 168:22; 173:13,
 18, 24; 196:19; 208:23;
 210:12; 221:20; 226:23;
 229:19, 22; 238:7, 21
 address [3] 7:10; 83:17;
 136:21
 addressed [8] 60:25; 95:2;
 146:2; 196:18; 197:16; 201:11,
 17; 234:9
 addresses [1] 6:1
 addressing [1] 217:19
 adds [3] 43:18; 125:17;
 128:17
 adequacy [3] 109:15; 117:13;
 220:16
 adequate [6] 45:25; 51:17;
 63:10; 79:2; 163:11; 220:18
 adequately [2] 161:7; 243:1
 adhere [1] 11:2
 Adherence [1] 14:22
 adherence [2] 14:20; 239:15
 adherent [1] 61:25
 adjourn [1] 164:7
 adjourned [1] 244:20
 adjusted [3] 24:15; 25:6, 14
 administer [4] 10:23; 15:17;
 53:19; 178:6
 administered [10] 11:1;
 24:12, 14; 25:4; 36:17; 37:14;
 38:11; 46:14; 48:10; 186:7
 administering [1] 200:24
 administration [8] 15:10;
 20:25; 36:3; 106:4; 109:16;
 117:1; 196:7; 218:9
 Administrative [1] 7:1
 admitted [1] 91:1
 adult [1] 46:15
 adults [1] 197:1
 advance [4] 15:13; 61:16;
 168:4; 169:11
 advanced [1] 158:1
 advances [2] 172:11; 177:9
 advantage [6] 185:12; 216:3,

5; 217:14; 219:5; 242:24
 advantageous [2] 61:20;
 217:16
 advantages [6] 53:11, 24;
 196:7; 197:5; 242:19, 22
 Adverse [2] 48:11; 161:17
 adverse [28] 29:2; 46:10;
 47:13, 16, 19; 48:21, 24; 49:3,
 8, 9, 15, 19, 24; 50:2, 19;
 51:20; 61:5; 80:11, 12, 17, 19;
 136:24; 161:13; 162:11, 13;
 188:14; 191:20; 224:7
 advice [6] 205:12; 210:17, 21;
 211:25; 213:18; 244:7
 advise [1] 212:9
 advisor [2] 65:7; 178:18
 Advisory [6] 12:20; 18:11;
 167:9, 15, 21; 244:21
 advocate [2] 225:23; 228:1
 advocated [2] 52:10; 59:22
 AEs [1] 80:13
 aesthetic [1] 186:12
 aesthetically [1] 186:12
 Affairs [1] 13:7
 affect [4] 22:2; 52:14; 184:25;
 227:23
 affected [1] 113:13
 affects [2] 178:23; 192:1
 afford [1] 219:21
 aforementioned [1] 60:15
 afraid [1] 243:8
 Africa [13] 16:9; 22:19; 27:24;
 72:21; 91:22; 92:7, 17, 20, 23;
 98:19, 25; 99:10; 108:6
 African [4] 26:24; 92:9, 14;
 93:1
 Africans [1] 95:21
 afternoon [5] 65:16; 86:18;
 165:4, 6; 172:23
 Age [1] 154:7
 age [3] 26:21; 144:10; 178:24
 agency [8] 6:18; 16:6; 17:15;
 179:3; 208:15; 221:19; 222:2;
 244:17
 agenda [6] 6:5; 7:4; 18:9;
 114:5; 144:4; 165:5
 agent [4] 51:15; 56:16; 60:19;
 183:5
 agents [4] 62:5; 206:5; 208:1;
 241:20
 ages [1] 23:7
 aggressive [1] 176:14
 aggressively [2] 158:24;
 176:20
 agree [11] 136:25; 140:12;
 141:9; 142:20; 190:5; 218:11,
 16; 231:7; 233:23; 234:21;
 238:8
 agreed [4] 11:12; 17:7; 22:25;
 35:5
 agreement [2] 116:4; 141:3
 AIDS [3] 13:23; 167:20;
 233:19
 aimed [1] 74:2
 Alabama [1] 4:17
 alarmed [1] 169:19
 alarming [1] 151:18
 albeit [2] 98:17; 202:17
 alcohol [2] 27:13; 153:7
 Ali [1] 64:14
 allow [4] 10:6; 60:22; 148:21;

- 179:8
allowed [6] 23:6; 35:25;
 71:13; 149:7; 235:7
allows [2] 15:4, 15
alluded [1] 229:3
ALT [2] 23:14; 48:17
alternate [1] 215:22
alternative [2] 11:17; 145:17
amendment [1] 17:11
America [6] 16:9; 27:25;
 92:16, 18, 22
American [8] 13:7; 18:10;
 52:7; 64:11; 92:9, 25; 146:12;
 154:21
amino [3] 157:6, 13, 14
amount [8] 8:2; 9:18; 11:18;
 72:14; 82:17; 122:2; 186:1, 8
amplify [1] 102:16
analog [1] 19:23
Analyses [1] 32:16
analyses [33] 25:24; 26:16;
 30:12, 17; 32:17, 19; 33:6;
 34:25; 35:5; 37:20; 40:22;
 52:3; 62:24; 68:5; 70:5, 7;
 83:7, 17; 84:17; 86:20, 21, 22;
 130:4; 139:2; 142:15, 25;
 192:17, 21; 195:10; 206:20;
 221:6; 237:18
analysis [61] 17:9; 25:23;
 26:2, 15; 27:15; 29:4, 12, 13;
 30:2, 4, 6, 20; 31:3; 36:16;
 40:14; 41:1; 58:20; 66:2, 8, 12;
 71:13; 76:17, 24; 80:11, 17,
 21; 83:9, 22; 84:19; 95:11;
 101:23; 108:21; 112:2, 18;
 119:14, 17, 21; 120:2, 4;
 127:19; 129:16;
 138:25; 139:3, 5; 140:10;
 141:6, 10; 142:9; 143:20, 21;
 150:14; 151:13; 154:6; 162:11;
 174:18; 191:19; 195:7, 11;
 224:16; 229:2
analyze [1] 198:18
analyzed [5] 27:25; 30:14;
 37:13; 112:16; 224:14
analyzes [1] 44:19
anatomic [1] 55:8
ancient [1] 204:12
anecdotal [1] 242:5
Animal [1] 60:17
animal [3] 53:21; 57:6; 61:6
announced [1] 179:1
announcement [2] 5:25;
 164:7
annual [1] 171:11
anorexia [1] 27:7
ansamycin [1] 167:12
answer [26] 19:1, 6; 63:23;
 69:22; 82:13; 98:21; 107:19;
 139:7; 158:11; 162:3; 171:17;
 179:2, 4; 180:21; 181:11;
 191:10; 201:25; 205:21;
 209:12, 14, 25; 213:9; 216:9;
 228:8; 229:18; 232:23
answered [2] 178:12; 233:24
answering [1] 190:21
answers [2] 200:13; 235:2
antagonism [1] 167:19
Anther [1] 108:3
anti [2] 48:25; 187:25
Anti-infective [1] 167:9
anti-microbacterial [1]
 156:13
anti-TB [2] 160:17; 170:11
anti-tuberculosis [6] 51:17;
 61:7; 62:7; 115:12, 24; 185:21
anti-tuberculous [9] 13:16;
 19:14, 17; 30:18; 34:24; 45:20;
 46:11; 48:11; 94:22
antibiotic [1] 45:20
antibiotics [3] 20:2; 49:1;
 51:7
antibody [1] 24:2
anticipate [2] 61:20; 188:13
anticipating [1] 230:11
antimicrobacterial [1] 162:23
antimicrobials [1] 170:10
antimycobacterial [1] 170:10
antiretroviral [2] 159:6; 208:1
Antiviral [1] 167:21
Antivirals [1] 235:10
anymore [1] 141:19
apart [3] 76:15; 188:22;
 195:17
apologies [1] 101:20
apologize [1] 103:19
apparent [2] 54:19; 199:25
Apparently [1] 155:11
apparently [3] 10:17; 47:21;
 142:12
appear [4] 40:8; 158:1; 192:7,
 8
appearance [1] 6:3
appeared [2] 206:9; 232:24
appears [11] 10:5; 34:22;
 38:19; 53:5; 56:2; 103:22;
 105:4; 135:21; 157:24; 191:15;
 224:6
applicability [4] 9:20; 10:19;
 94:17; 102:2
applicant [18] 9:9; 115:9, 20;
 116:5; 117:4, 18, 24; 119:9,
 13; 123:17; 124:5; 129:14;
 130:4; 133:20; 134:22; 136:23;
 138:24; 162:7
application [12] 4:10; 7:24;
 8:7, 17; 9:6; 17:17; 114:17;
 167:1; 185:25; 207:9; 211:15;
 216:8
applied [2] 117:19; 118:9
apply [3] 18:7; 35:18; 200:25
appreciate [3] 182:12;
 188:13; 209:7
appreciating [1] 171:1
approach [14] 10:10; 11:23;
 14:16; 52:9; 76:25; 77:10;
 139:24; 179:11; 180:1; 186:17;
 195:9; 225:20; 231:9; 243:17
approaches [3] 76:13; 84:19;
 179:15
appropriate [8] 55:2; 63:8;
 87:6; 140:17; 197:12; 214:20;
 228:13; 233:15
appropriately [1] 236:2
approval [40] 4:11; 9:16, 24,
 25; 11:10; 17:3, 4, 13; 61:18;
 63:21; 109:25; 115:17, 21;
 116:5, 14; 137:21; 167:23;
 181:12, 15; 182:6, 21; 198:6;
 207:8, 20; 208:22, 24, 25;
 211:4; 213:17; 221:18, 22;
 228:8; 230:8; 235:4, 8, 11, 12,
 13; 243:25;
 244:8
approve [4] 210:8; 212:4;
 244:7, 8
approved [6] 8:11, 22; 61:23;
 207:1; 228:21; 238:1
approves [1] 82:8
approving [1] 204:1
approximately [9] 22:4, 7;
 37:25; 38:7; 53:1; 82:1; 134:1,
 2, 9
Area [1] 81:22
area [12] 7:25; 34:9; 81:20;
 98:23; 100:21, 25; 145:4;
 166:4; 197:18; 202:18; 230:23;
 231:23
areas [2] 102:5; 208:16
aren't [2] 169:21; 170:9
arena [6] 55:20; 56:6; 142:24;
 143:1, 2; 194:22
arenas [2] 139:14; 142:25
arguable [1] 233:18
argue [2] 78:1; 185:16
argument [3] 76:8; 196:4, 9
arguments [3] 169:10;
 196:16, 18
arises [1] 78:2
arising [1] 70:4
arms [25] 27:14; 29:15; 34:19;
 36:12, 18; 37:10; 38:22; 41:15;
 44:12; 47:23; 49:5; 54:12;
 70:19; 71:4, 10; 117:1; 119:10;
 125:21; 126:21; 127:15, 17;
 128:11, 12; 136:9; 140:22
arrest [1] 177:5
arthralgia [1] 48:3
arthritis [1] 48:4
artifacts [1] 177:1
artificial [1] 69:16
Asian [1] 95:16
Asians [2] 95:18, 20
aside [2] 9:1; 237:10
asking [8] 12:10, 12; 138:21;
 190:1, 22, 24, 25; 199:23
aspect [2] 183:1; 207:19
aspects [1] 182:7
assay [1] 20:7
assays [1] 195:24
assess [1] 102:3
assessment [2] 73:22; 225:16
assign [2] 83:10, 11
assimilating [1] 225:11
Associate [2] 4:20; 6:24
associate [1] 64:14
associated [20] 32:8; 59:8;
 133:9; 144:20; 145:10, 13;
 146:1, 7; 150:15; 151:14;
 152:20; 156:6; 157:4, 25;
 159:21; 161:25; 162:9; 176:24;
 206:15; 225:2
assuage [1] 208:7
assume [1] 57:9
assumption [4] 163:19, 22;
 205:23; 217:22
assurance [1] 216:23
asterisk [1] 150:24
asymptomatic [1] 20:17
Atkins [1] 114:18
atmosphere [1] 174:23
ATS [3] 45:17; 59:22; 153:14
attempting [1] 8:4
attempts [2] 8:14; 198:17
attention [7] 16:2; 51:2;
 175:24; 178:21; 182:1; 187:15;
 214:7
attenuate [1] 79:18
attenuating [1] 79:21
attractive [1] 10:17
attributes [2] 52:20; 58:12
AUC [2] 227:1, 2
audience [3] 7:21; 94:19;
 204:8
audited [1] 171:14
availability [3] 92:3, 5; 235:25
Available [1] 120:25
available [23] 8:2; 12:9;
 26:19; 28:25; 34:6; 63:18;
 83:21; 96:16; 119:6; 120:1, 13,
 23; 123:15, 22; 138:10, 23;
 139:1; 153:19; 163:2; 200:9;
 207:2; 234:11; 240:8
average [1] 171:6
avian [3] 46:22; 49:23; 211:9
avium [2] 101:24; 211:6
avoid [3] 14:24; 46:2; 51:4
aware [2] 7:6; 123:11
awful [1] 146:4
Azire [1] 147:14
azole [2] 151:13; 158:3
azoles [1] 151:3

- B -

- bacilli** [9] 55:7, 12, 23; 56:9,
 14; 57:2; 108:16; 169:25;
 225:17
back-up [1] 107:22
background [7] 10:2; 19:13,
 22; 103:23; 104:1; 115:19;
 204:10
backing [1] 159:1
bacteremia [2] 211:6, 9
bacterial [3] 34:14; 74:22;
 105:12
bactericidal [14] 54:8, 18;
 55:18; 56:17; 57:15, 23; 60:10;
 93:21; 104:1; 105:24; 107:24;
 108:5; 184:20; 185:11
bacteriologic [1] 146:18
bacteriology [3] 74:10, 18, 25
balance [4] 75:2; 84:11;
 199:23; 201:21
balanced [13] 26:8; 27:14;
 29:5; 31:14; 48:23; 49:10, 20;
 72:17; 73:14; 74:20; 84:15;
 92:24; 126:3
Baltimore [1] 53:10
bars [9] 41:14, 21, 22; 42:4,
 17, 19; 43:1; 67:1; 77:20
base [3] 157:6, 13, 15
Based [6] 6:5; 53:21; 63:18;
 214:3, 5; 216:19
based [36] 11:15; 17:6; 27:22;
 28:12; 37:20; 40:23; 41:18;
 50:20; 53:10, 11; 57:5; 67:16;
 70:1; 73:10; 85:15; 86:25;
 103:24; 116:5; 119:15; 131:4;
 133:19; 134:22; 157:13, 15;
 159:2; 175:22; 181:11; 184:15;
 195:22; 196:14; 208:10;
 211:17; 222:12;
 225:14; 226:19; 239:2

Baseline [1] 27:5
 baseline [29] 23:10; 26:5, 6, 20; 33:2, 3, 9, 16, 22, 25; 34:5, 17; 72:11; 73:18; 76:11; 90:18; 104:18; 119:24; 123:18; 124:7; 130:6; 133:15, 21; 136:1, 15; 198:20; 199:6; 223:10
 bases [2] 175:17; 233:20
 basically [4] 10:11; 89:24; 95:16; 110:23
 basis [13] 9:15; 24:15; 48:13; 50:18; 135:25; 156:8; 171:16; 179:23; 185:9; 190:4; 192:1; 199:12; 222:18
 BASS [25] 4:16; 65:18; 66:1, 11, 15, 21; 67:1, 22; 69:5; 70:13; 71:19; 98:1; 184:1, 7; 213:23, 25; 214:3, 12, 15; 215:16, 19, 21; 216:19; 241:7, 25
 Bass [11] 4:15, 16; 65:17, 22; 70:1; 71:18; 183:25; 203:12; 212:15; 213:22; 216:11
 Bassett [1] 4:23
 bearing [1] 172:23
 beat [1] 228:21
 beating [1] 87:5
 becoming [3] 126:22; 209:15; 230:5
 begun [2] 148:21; 170:23
 behind [3] 113:21; 114:3; 138:3
 believe [22] 9:9; 12:7; 34:16; 54:3; 60:14; 66:4, 8; 72:4; 74:1, 20, 24; 77:1; 92:2; 106:4; 109:19; 141:18; 161:19; 163:8; 185:13; 200:4; 211:4; 223:10
 believed [6] 55:8, 22; 56:1, 5, 9, 10
 believing [2] 96:25; 141:23
 Bellevue [2] 153:13, 18
 benefit [10] 182:24; 183:2, 7; 198:10, 15, 16; 207:21; 219:15; 230:9, 12
 benefit-risk [1] 62:23
 benefits [6] 189:22; 190:14; 198:7; 200:15; 222:16; 230:18
 BERTINO [20] 4:22; 80:5, 9, 20, 23; 81:19, 23; 82:4, 7, 23; 111:8, 14; 112:9, 15, 21; 161:11, 16, 20; 191:14; 226:18
 Bertino [9] 4:22; 80:4; 111:7; 161:10; 191:13; 212:15; 226:17; 231:20; 232:5
 beta [2] 156:17, 19
 Beth [1] 5:9
 bias [4] 85:15; 159:12, 13; 160:16
 bigger [2] 87:8; 228:19
 bilateral [8] 34:8; 100:23; 102:24; 103:3, 10; 133:18; 134:4, 10
 bilirubin [1] 23:14
 Bill [1] 152:23
 bind [1] 156:24
 binding [2] 61:3; 156:17
 binds [1] 156:20
 bioavailability [2] 18:2; 111:24
 Biodynamics [1] 64:3

bioequivalent [1] 18:1
 biological [1] 231:2
 Biometrics [1] 64:11
 biopharmaceutics [1] 114:19
 biostatistics [1] 114:17
 birthplace [1] 154:7
 bit [24] 88:14; 106:17; 112:7; 115:2; 138:3; 139:22; 141:16; 147:3; 148:5, 11; 156:5, 7; 165:22; 167:7; 188:8; 204:22; 208:3; 213:7; 229:18; 235:10, 12; 238:19; 239:15; 243:25
 biweekly [1] 150:5
 black [1] 26:23
 blank [1] 114:22
 blinded [4] 27:25; 34:4; 102:12; 165:24
 blocks [1] 156:20
 blood [1] 75:23
 Blot [1] 99:8
 BMRC [1] 186:8
 Board [2] 34:1; 149:24
 body [5] 23:23; 24:16; 25:6, 14; 33:2
 boils [3] 217:8; 218:1; 226:1
 book [10] 70:17; 71:22; 74:16; 80:10; 91:13; 100:17; 104:1, 8, 23; 108:1
 boon [1] 216:8
 borders [1] 129:15
 Boston [2] 4:25; 5:10
 bothered [2] 139:15, 18
 bothers [1] 188:8
 bounce [1] 156:3
 bound [4] 127:2, 5; 140:17, 20
 Boy [1] 213:23
 brain [2] 177:5; 215:18
 brains [1] 244:5
 Branch [1] 165:14
 branch [1] 165:15
 break [2] 113:22, 23
 break-up [1] 67:6
 breakdown [1] 153:24
 breaking [1] 77:17
 breakpoints [1] 123:10
 breaks [1] 68:6
 breakthrough [1] 169:16
 Brenda [3] 114:12, 18; 180:18
 Breslav-Day [2] 131:17; 132:15
 brief [9] 19:1, 13; 48:14; 109:23; 114:24; 205:25; 236:21; 240:19; 241:9
 briefing [8] 40:15; 70:17; 71:22; 74:16; 80:10; 91:12; 108:1; 227:10
 Briefly [1] 93:15
 briefly [1] 96:3
 British-NYC [1] 159:20
 broad [2] 205:17; 211:22
 broader [3] 113:9; 198:7; 221:21
 broadly [3] 56:17; 159:7; 183:3
 broke [1] 89:18
 broken [2] 68:14; 88:24
 buffer [1] 187:13
 buffet [1] 164:10
 Building [1] 6:19
 building [1] 238:17
 built [3] 63:8; 187:2, 13

bump [1] 241:19
 burden [2] 59:5; 242:9
 Bushei [1] 152:23

- C -

calculated [1] 28:22
 calculating [1] 239:16
 calculation [1] 29:11
 California [1] 4:19
 call [5] 4:3; 76:21; 89:17; 90:21; 139:20
 calls [1] 166:10
 Canada [2] 22:20; 92:12
 Cancer [1] 5:2
 capacity [1] 177:7
 capture [1] 161:13
 Care [2] 4:23; 146:12
 care [2] 63:9; 201:5
 careful [2] 71:22; 240:5
 carefully [3] 88:20; 103:6; 195:10
 caring [1] 198:21
 carried [5] 20:22; 22:12; 30:2, 12; 32:16
 case [24] 8:3; 9:11; 10:19, 24; 29:10; 30:4; 75:7; 76:3; 90:10; 99:16; 109:12; 116:6; 133:6; 140:1, 2, 7; 143:7; 152:20, 22; 153:14, 20; 184:21; 209:21; 221:15
 caseous [1] 55:16
 cases [19] 9:5; 14:1, 2, 8, 11; 89:11; 93:3; 151:18, 24; 152:3, 4, 6, 11; 153:17; 154:10, 14; 155:9; 157:10; 166:12
 catch [1] 114:3
 categorical [1] 118:7
 categories [6] 37:18; 67:15; 88:24; 91:7; 125:9; 181:24
 categorize [1] 198:3
 category [3] 88:25; 90:3; 181:24
 Caucasians [1] 95:21
 caught [1] 223:25
 causal [1] 79:25
 causality [1] 135:24
 caution [5] 82:19; 83:2; 220:22; 234:18; 237:24
 cautious [1] 237:1
 cavalier [1] 139:19
 caveats [2] 119:23; 240:7
 cavitation [15] 34:7, 9; 73:19; 100:20, 24; 101:6; 102:1; 103:8, 12; 133:17, 18; 134:4, 11, 12
 cavities [5] 74:23; 100:16, 23; 101:1; 133:17
 cavity [3] 55:16; 56:3; 103:11
 CD4 [7] 151:1, 8, 12; 155:5; 160:8, 13; 161:5
 CDC [21] 4:21; 7:1; 9:4; 16:16, 24; 45:17; 59:22; 92:5; 144:19; 148:24; 155:25; 157:11; 161:14; 165:8, 14; 166:3, 15; 168:8; 172:15; 173:19; 209:18
 cell [3] 151:1, 8; 155:5
 censored [1] 128:1
 Center [10] 4:23; 5:3, 9; 6:8; 18:20; 64:16, 19, 21; 65:1, 6

center [2] 202:14, 16
 Centers [3] 6:25; 16:15; 52:7
 centers [2] 91:23; 113:7
 central [1] 27:24
 century [1] 8:20
 certainty [1] 219:25
 certified [1] 34:1
 certify [1] 210:9
 cessation [1] 58:1
 cetera [2] 142:11; 173:14
 chain [1] 156:17
 chalk [1] 139:11
 challenges [2] 88:15; 195:5
 chance [4] 65:10, 14; 159:17; 175:6
 chances [1] 220:1
 change [8] 8:11; 79:17; 98:13; 117:23; 157:14; 175:12; 196:1; 220:2
 changed [4] 48:19; 167:7, 20; 168:8
 changes [3] 14:6; 33:2; 125:22
 changing [1] 96:16
 characteristic [4] 15:1; 33:1; 136:1; 199:7
 characteristics [3] 124:6; 153:3; 154:13
 characterized [2] 20:12; 55:14
 charge [4] 144:14; 173:7; 180:3, 11
 Charles [1] 18:9
 cheap [1] 178:6
 checked [4] 72:7, 8; 204:11
 chemistries [1] 74:4
 chemistry [1] 114:20
 chemoprevention [1] 62:7
 chemotherapy [13] 51:17; 58:17; 62:7; 94:5; 146:15; 147:7, 17, 19; 148:1, 4; 149:11; 151:4; 155:2
 chest [10] 33:25; 34:2, 5; 124:7; 130:6; 133:15, 21; 136:15; 199:2; 225:18
 Chiasson [2] 146:11; 152:23
 Chief [2] 18:18; 165:13
 chief [1] 202:5
 children [3] 14:4; 232:20, 21
 China [1] 17:22
 Chinese [1] 17:25
 Choice [1] 90:4
 choice [3] 54:10; 90:1; 237:7
 choices [2] 160:6; 199:22
 choose [1] 234:6
 choosing [1] 31:16
 chose [2] 90:11; 120:3
 chronic [1] 232:16
 Cincinnati [1] 5:5
 circumstances [1] 223:16
 citation [1] 211:13
 City [5] 144:23; 151:22, 24; 152:8; 153:11
 city [2] 202:14, 16
 claim [1] 106:24
 claimed [1] 204:12
 claiming [1] 106:25
 claims [1] 96:20
 clarification [6] 70:15; 102:17; 175:25; 182:20; 209:7; 235:14

- clarify [3] 80:5; 103:19; 138:12
 clarifying [1] 107:17
 clarithromycin [3] 211:5, 8; 227:22
 clarity [1] 19:4
 class [2] 20:2; 206:5
 classic [4] 109:22; 142:22; 177:13; 240:10
 classification [2] 117:20; 134:22
 classifications [2] 117:22; 121:19
 classified [4] 127:19; 152:14; 154:1; 155:9
 clear [12] 96:4; 98:15; 101:3; 194:23; 195:18; 198:19; 199:5; 209:12, 14, 16; 211:11; 223:20
 clear-cut [1] 201:19
 clearance [5] 111:4, 22; 113:1, 5; 230:25
 Clinic [3] 5:16; 53:10; 236:16
 Clinical [6] 4:22; 5:15; 18:18; 64:4, 23; 151:23
 clinical [67] 9:14; 10:13; 12:6, 20; 16:7, 17, 22; 17:6, 14; 18:4; 19:12, 19; 20:5; 47:2, 4, 8; 49:22; 50:8, 21; 51:14; 61:9; 62:12, 17; 63:12, 18; 74:3; 98:2; 102:2; 103:25; 104:11; 114:16, 24; 127:8; 145:9; 146:3, 6; 156:6, 12; 157:22; 167:3, 17; 171:1; 172:19; 173:12; 174:24; 188:9; 202:5; 205:19; 208:6, 12; 211:7, 14; 212:2; 213:20; 222:22; 224:21; 229:22; 230:12, 18; 234:3; 237:8, 11, 12; 239:23; 240:4, 13
 clinically [2] 23:23; 80:1
 clinician [1] 202:12
 clinicians [7] 59:22; 190:10; 206:23; 232:14; 237:7; 238:6; 240:1
 closer [2] 95:21; 229:24
 closing [1] 62:4
 Cmax [4] 22:9; 81:10, 13, 19
 co-administration [6] 22:1, 2, 5, 8; 79:9; 158:2
 co-infected [1] 231:18
 co-infection [1] 157:25
 cobwebs [2] 94:24; 109:19
 cognizant [1] 187:12
 coherent [1] 94:2
 cohort [3] 153:10, 12; 154:5
 coin [1] 238:9
 coincidental [1] 102:19
 Coincidentally [1] 33:13
 collaborative [1] 15:21
 colleagues [4] 13:9; 76:22; 80:15; 233:13
 Colorado [4] 18:24; 64:21; 65:6; 178:15
 colored [1] 84:25
 column [1] 203:18
 columns [2] 131:24; 132:20
 combination [12] 24:23; 45:19, 22; 70:25; 81:2; 106:21; 160:1; 210:5; 227:13, 14, 16, 19
 combine [1] 51:23
 combined [4] 37:13; 82:19; 147:10; 195:24
 comfort [1] 102:12
 comfortable [5] 87:12; 190:3; 207:14; 241:5, 7
 coming [6] 111:18; 166:22; 215:5; 229:12; 236:16; 237:13
 comment [11] 7:12; 91:10, 11; 94:3; 139:22; 156:4; 182:2; 210:2; 213:6; 215:11; 223:18
 commented [1] 223:9
 comments [12] 7:16; 9:19; 136:21; 169:13; 200:10; 203:12; 205:25; 207:6; 210:15; 214:22; 234:17; 236:21
 commit [1] 212:13
 commitment [2] 13:19; 17:14
 Committee [35] 4:13; 7:19; 9:6; 12:20; 65:10, 11; 114:10; 115:7; 138:4; 164:9; 167:10, 16, 22; 173:7; 180:4, 11; 182:20; 183:6; 204:6; 206:18; 207:7, 17, 25; 208:13, 14, 20; 213:5; 235:5, 9; 237:9; 243:24; 244:12, 17, 22
 committee [2] 4:5; 101:2
 common [8] 31:15; 45:24; 47:19; 51:1; 62:20; 153:8; 199:10, 12
 commonly [2] 46:11; 176:24
 community [8] 53:7, 10; 65:3; 159:12, 13; 178:7; 179:7, 23
 Companies [1] 170:9
 companies [7] 9:12, 24; 10:18; 13:17; 169:18; 171:20; 172:1
 companion [5] 78:7; 117:2, 6; 130:7; 197:14
 company [15] 7:20, 22; 12:10; 13:18; 22:11; 40:15; 64:24; 116:16; 165:25; 169:7; 170:8; 180:10; 181:13; 211:7; 243:10
 comparability [1] 189:5
 comparable [7] 54:21; 58:24; 108:17; 125:7, 21; 136:8; 200:3
 comparative [6] 20:24; 47:1; 49:3; 50:21; 104:12; 194:15
 compare [3] 174:20; 190:17; 193:15
 compared [23] 15:8; 16:19; 19:18; 21:6; 32:3, 7; 43:16; 44:1; 49:25; 55:1; 59:14; 69:3; 81:13; 111:5; 117:11; 129:11; 137:9; 147:24; 151:6; 154:9; 188:25; 189:4, 24
 compares [2] 68:22; 111:21
 comparing [3] 18:13; 126:25; 204:25
 comparison [4] 22:5; 89:2; 108:8; 204:4
 comparisons [1] 92:8
 compelled [1] 14:8
 compensations [1] 229:1
 compete [1] 229:7
 complete [6] 65:15; 77:1; 83:11; 129:23; 173:16; 197:8
 completed [6] 17:10; 19:5; 22:23; 23:2; 149:20; 181:18
 completely [3] 136:16; 174:16; 210:7
 completing [1] 222:20
 completion [7] 11:15, 20; 12:1; 24:10; 28:3; 54:22; 173:17
 complex [3] 46:22; 49:23; 178:11
 complexity [1] 171:1
 compliance [37] 14:12, 18, 23; 15:18; 34:19; 37:19; 40:18; 62:25; 67:19; 70:2, 12, 17; 77:7, 16; 87:4; 88:2; 115:25; 117:5, 12; 124:8; 130:7; 134:15, 16; 135:23, 25; 136:8, 15; 187:18; 194:7, 8; 196:1; 199:6; 201:4; 215:6; 218:5
 compliant [3] 35:21; 36:9, 22
 complicated [1] 244:14
 compliers [9] 134:21, 24; 135:2, 4, 9, 16, 17
 component [4] 11:3; 66:19; 110:22; 203:23
 components [1] 203:24
 composed [1] 26:10
 compounds [2] 158:3; 167:2
 comprise [1] 55:12
 comprised [1] 41:4
 compromise [1] 187:5
 compromised [1] 201:18
 compromises [1] 177:9
 computer [1] 133:21
 conceivable [4] 79:8; 188:17; 189:20; 190:10
 conceivably [1] 78:15
 concentration [6] 20:25; 21:3, 10, 12; 22:4, 7
 concentrations [1] 61:8
 concept [1] 16:22
 conceptually [2] 11:8; 242:15
 concern [11] 11:24; 12:3; 86:4, 6; 97:23; 145:4; 192:7; 198:1; 207:22; 212:3; 227:8
 concerned [6] 83:16; 91:11, 16; 198:22; 229:4; 235:17
 concerning [5] 6:16, 22; 94:16; 96:2; 180:22
 concerns [8] 181:24; 182:1; 206:4; 208:7; 220:15, 16; 226:24; 242:16
 conclude [1] 50:22
 concluded [1] 244:22
 concluding [1] 201:21
 conclusion [7] 19:1; 45:18; 50:10; 137:24; 149:2; 209:1; 217:4
 conclusions [5] 26:16; 30:15; 117:23; 137:1, 5
 conclusively [1] 205:16
 concordant [1] 57:13
 concrete [1] 234:9
 concurred [1] 16:6
 concurrence [1] 17:8
 concurrent [1] 82:10
 condition [1] 177:10
 conditions [7] 27:25; 55:25; 72:21; 75:25; 76:1; 209:20; 225:22
 conducive [1] 170:13
 conduct [1] 94:7
 conducted [7] 9:15; 16:8; 18:4; 22:18; 34:3; 60:17; 145:9
 conducting [1] 16:17
 confidence [15] 29:25; 30:22, 24; 31:25; 84:4, 21; 85:2; 126:7, 11; 127:2; 128:17, 20, 24; 129:1; 140:10
 confines [1] 40:18
 confirm [4] 10:10; 11:21; 89:16; 221:13
 confirmation [1] 101:10
 confirmed [2] 89:8, 19
 conflict [3] 5:24; 6:1, 12
 confounded [1] 224:17
 confounding [4] 87:24; 99:25; 135:22; 136:13
 confuse [1] 119:20
 confused [1] 221:6
 confusion [1] 103:20
 conjunction [1] 115:11
 consecutive [3] 28:18; 118:10, 14
 consensus [1] 145:7
 consequence [2] 176:17; 177:15
 consequences [3] 24:1; 50:19; 224:7
 consequently [2] 170:1; 224:8
 conservative [3] 144:25; 235:11; 241:8
 consider [18] 4:9; 9:14; 52:16; 54:16; 55:2; 116:17, 18; 120:22; 124:6; 146:15; 147:6, 18; 155:1; 166:25; 172:20; 213:4; 237:15; 240:17
 considerable [1] 187:15
 considerably [2] 177:19; 220:3
 consideration [6] 169:23; 170:25; 187:16, 17; 222:2; 228:12
 considerations [1] 195:22
 considered [15] 10:17; 29:6; 30:5, 10; 35:14; 49:5, 11; 89:21; 115:21; 118:23; 127:25; 130:19; 166:19; 220:5; 230:6
 Considering [1] 122:6
 considering [1] 167:10
 consisted [1] 147:18
 consistency [2] 97:25; 120:3
 consistent [8] 45:16; 46:10; 61:8; 67:12; 68:25; 84:24; 92:21; 186:16
 consistently [1] 214:19
 consisting [1] 58:8
 consists [1] 125:13
 consolidation [2] 102:6; 117:10
 consortium [1] 168:20
 constitute [1] 127:10
 consultants [10] 7:20; 64:12; 94:19; 97:23; 216:12; 221:17; 233:13; 234:21; 240:19; 244:17
 consultation [1] 22:12
 consulted [1] 16:6
 Consulting [1] 64:22
 consumes [2] 179:6, 7
 consuming [1] 243:2

consumption [1] 177:13
 contact [1] 23:19
 contacted [1] 173:19
 contain [1] 160:19
 containing [15] 16:19; 19:17, 18; 20:7; 50:25; 58:18, 24; 61:14; 62:19; 116:24; 145:19; 159:16; 161:2; 189:9
 contains [5] 17:22; 134:20, 23; 135:1, 3
 context [12] 18:17; 144:20; 148:6, 10; 166:6; 174:25; 176:12; 183:3; 187:17; 189:11; 197:11; 207:9
 continuation [58] 15:8, 11; 16:20; 24:8; 25:7; 28:15, 21; 29:17; 35:3, 21; 36:12; 37:7; 45:5, 13; 57:12; 59:15, 24; 60:1, 21; 77:24; 78:17; 88:1; 93:16; 95:7; 105:25; 111:1; 113:14; 116:3; 117:12; 118:13; 122:21; 146:18; 147:21; 148:13; 155:4; 163:10; 189:3; 190:12; 197:14, 22; 206:10; 214:6; 216:7, 14; 217:12, 17, 21, 25; 218:4; 219:4, 7, 19; 221:2; 231:14; 232:15; 237:16; 238:13; 239:2
 continue [4] 45:14; 88:14; 128:7; 172:9
 continued [2] 120:16; 228:16
 continues [3] 16:24; 156:25
 continuing [1] 244:4
 contracted [1] 7:1
 contradiction [1] 186:13
 contradistinction [1] 53:20
 contraindications [1] 224:2
 contrast [4] 44:2; 57:1; 78:12, 19
 contrasted [1] 54:21
 contribution [2] 57:3; 77:25
 contributions [2] 52:18; 62:6
 Control [3] 6:25; 16:15; 52:8
 control [11] 22:17; 51:19; 52:5, 13; 60:5; 61:16; 104:11; 108:12; 127:1; 155:25; 161:18
 controlled [9] 136:25; 145:9; 146:2; 148:12; 153:14; 174:24; 189:15; 192:14; 193:14
 controls [2] 153:21; 154:10
 convene [1] 165:4
 convenient [1] 50:24
 Conversion [2] 28:17; 118:13
 conversion [46] 28:16; 34:21; 38:25; 39:2, 10, 13, 14, 17; 40:9, 13; 41:18; 42:11; 45:11; 54:20; 56:19; 59:19; 63:2; 77:2, 6; 93:12, 20; 117:24; 118:16, 24; 124:8, 13; 125:13, 24, 25; 126:2, 5, 10, 12, 17; 127:14, 16; 131:4; 133:8; 137:6; 139:18; 192:17; 193:19; 196:25; 237:20; 238:2
 conversions [1] 57:17
 convert [10] 43:10; 44:21, 25; 120:16; 121:15; 123:23, 24; 125:19; 128:4; 221:11
 converted [18] 39:21, 24; 93:16; 120:18; 122:6, 21; 125:5, 20; 128:13; 129:3;

130:12, 16; 131:7; 139:6; 216:15, 24; 218:7
 converters [5] 121:13, 21; 122:19; 123:13; 140:2
 converting [1] 130:19
 convertor [2] 68:19, 20
 convertors [25] 41:17, 21, 22, 24; 42:6, 12, 16; 43:8, 16, 17, 19; 44:1, 8, 13, 17; 59:25; 68:15, 16, 17, 18, 24, 25; 131:12, 16
 convince [2] 175:21; 232:8
 convinced [3] 98:12; 141:5; 200:1
 convincing [2] 101:6; 182:11
 cooperative [1] 8:4
 cooperatively [2] 16:13, 15
 Cooperstown [1] 4:24
 copy [3] 6:16; 10:1; 115:17
 corniforming [1] 108:15
 corollary [2] 213:4; 231:20
 correctly [4] 70:20; 71:3; 83:23; 110:1
 correspond [1] 133:16
 corresponding [1] 43:18
 corticosteroid [1] 23:24
 cost [5] 52:5; 53:9; 171:2; 190:9; 219:20
 costs [1] 51:25
 Cote [2] 147:1, 4
 cough [2] 27:6; 175:13
 count [7] 96:5; 139:1, 3; 142:6; 151:8; 160:8, 13
 counted [8] 70:8; 118:16; 119:1, 5, 6; 125:3; 139:5; 142:15
 counterbalance [1] 105:17
 counting [2] 118:6, 18
 countries [4] 171:15; 189:16; 219:22; 220:11
 country [7] 9:2, 5; 166:11; 189:16; 201:22; 220:11; 243:2
 Counts [1] 129:13
 counts [5] 74:19; 151:1, 12; 155:5; 161:5
 couple [11] 8:8; 9:13; 83:6; 118:20; 184:7; 192:15; 194:5; 213:7; 235:14; 236:21; 241:1
 course [26] 12:12; 52:9, 25; 58:15, 17, 21; 74:10; 90:25; 91:25; 93:5; 94:13; 147:6, 19; 148:1, 4; 155:1; 162:11; 173:16; 188:16; 197:8; 201:11; 204:16; 220:5; 232:12; 233:7; 239:4
 courses [2] 51:24; 238:19
 CPCRA [2] 154:22; 168:21
 create [2] 78:15; 164:1
 created [1] 8:13
 creates [1] 206:21
 creatinine [1] 23:12
 criteria [16] 23:6, 16, 25; 26:2, 14; 29:22; 30:23; 66:7, 23; 71:4, 6; 100:6; 119:16; 141:11; 142:3; 195:3
 criterion [2] 131:21; 230:8
 Critical [1] 146:12
 critical [11] 14:22; 53:14; 63:1, 5; 78:10; 173:9; 174:11, 14; 180:4, 5; 201:9
 critically [1] 195:12

criticized [1] 169:5
 crixivan [1] 158:20
 cross-hatched [1] 42:19
 cross-resistance [1] 123:11
 cross-trials [1] 239:23
 crucial [2] 61:17; 203:24
 culling [1] 239:22
 culturally [1] 89:18
 culture [52] 23:9, 10; 26:5; 27:19; 28:5, 8, 9, 24; 29:6; 32:11; 39:2; 54:22; 56:19; 57:20; 60:2; 83:14, 18, 21, 24; 88:24; 89:9, 15, 20; 90:18, 24; 93:12; 96:8, 10; 97:17, 19; 117:16; 119:2, 3; 127:21, 24, 25; 130:17; 132:18, 21, 25; 133:1, 3, 4; 138:13, 18, 22; 142:13; 149:5, 8; 174:17; 216:15
 cultures [34] 26:5; 27:22, 23; 28:13, 18; 33:4; 39:20, 23; 40:3; 78:18; 93:18; 97:11, 15, 20; 98:4; 118:7, 11, 14, 20, 21, 23; 119:4, 5; 120:13, 17; 121:2, 8; 123:22; 125:6; 128:2; 130:13; 132:12, 13; 138:9
 cumulative [3] 91:16; 122:8; 195:15
 cure [5] 146:19; 147:12; 177:3; 219:25; 220:1
 cured [1] 52:23
 cures [1] 177:2
 curing [1] 242:25
 current [17] 7:11; 10:6, 21; 18:17; 45:17; 52:18; 53:17, 21; 59:12, 22; 82:21; 167:3; 171:8; 186:9; 187:10, 11; 241:20
 currently [4] 16:17; 62:5; 201:22; 235:1
 curve [3] 81:20, 22; 231:24
 curves [8] 127:16, 18; 128:6; 129:20, 21, 24; 195:15; 198:2
 cutoff [3] 22:25; 31:8; 35:6
 cutting [2] 15:16; 233:21
 Cynamon [1] 60:18

 - D -

D'AGOSTINO [25] 4:25; 83:5; 84:6; 85:3, 17, 22, 25; 86:10, 14, 19; 87:1, 17; 88:12; 138:7, 15, 20; 140:12, 23; 141:9; 142:24; 143:15, 19, 23; 192:13; 228:7
 D'Agostino [6] 4:25; 83:4; 138:6; 192:12; 212:15; 228:6
 d'Ivoire [2] 147:2, 4
 daily [15] 15:10; 24:15; 25:5; 35:12, 18; 37:15; 48:13; 50:18; 53:20; 71:8; 117:1, 3; 179:6; 219:18; 242:8
 damage [2] 176:25; 177:4
 damaged [1] 177:8
 damned [1] 175:19
 dashed [1] 21:8
 Data [3] 64:11; 149:23, 24
 database [2] 39:5; 208:8
 date [8] 8:19; 22:25; 31:8; 35:6; 63:19; 120:19; 148:8; 165:19
 David [1] 34:1
 day [55] 18:18; 46:23; 79:16; 104:13; 108:7, 9, 17, 18; 114:4; 118:11, 15, 17, 18, 20, 22; 127:22; 130:6, 10, 12, 14, 15, 16, 18, 19, 22, 23, 25; 131:3, 4, 5, 7, 12, 22, 25; 132:5, 6, 13, 14, 18, 21; 133:1, 2; 138:18; 139:1; 160:2; 164:15; 189:3; 194:6; 202:7; 233:14
 days [15] 35:25; 39:2; 96:25; 104:14, 15; 109:8; 110:24; 113:15; 116:22; 117:1; 118:8; 120:9; 121:4, 15; 215:5
 de-emphasis [1] 170:21
 Deaconess [1] 5:9
 deal [5] 82:18; 83:1; 143:2; 195:21; 208:2
 dealing [7] 109:24, 25; 160:12; 178:24; 184:9; 194:3; 208:1
 death [5] 13:25; 87:5; 160:14; 177:13; 235:23
 Deaths [1] 49:4
 decade [6] 13:23; 166:9; 169:16; 170:13, 22; 172:10
 December [1] 17:2
 decide [3] 67:23; 69:7; 218:1
 decision [5] 29:3; 148:20; 208:10; 216:16; 244:9
 decisions [3] 171:24; 175:16; 234:4
 declare [1] 14:9
 decrease [6] 22:6; 42:23; 108:15; 197:6; 215:4; 231:23
 decreased [8] 22:3; 39:7; 41:25; 67:13; 104:18; 108:19; 185:25; 215:6
 decreases [5] 21:16; 22:9; 38:21; 43:5; 235:24
 decreasing [3] 42:6; 186:19; 187:1
 dedication [1] 208:18
 deems [1] 57:4
 deep [1] 94:24
 defer [2] 213:24; 233:12
 deficient [1] 45:3
 define [6] 32:22; 67:20; 143:12; 158:5; 226:6; 241:11
 defined [22] 25:25; 26:2; 27:18; 28:1, 4, 7, 17; 35:4; 36:2, 6; 37:19; 40:18; 67:17, 19; 70:12, 17; 88:25; 89:1, 5, 9, 21; 130:10
 definitely [1] 87:23
 definition [18] 49:8; 67:3, 11, 19, 25; 68:3; 69:9; 70:2, 10; 83:16; 118:5, 7, 9; 121:16; 127:8; 131:3; 140:16; 233:18
 definitions [4] 117:18; 118:6; 127:10; 134:16
 definitive [1] 149:1
 degree [2] 34:7; 210:24
 delayed [1] 57:17
 deletion [2] 157:14, 15
 deliberating [2] 165:23; 182:22
 deliberations [3] 172:22; 174:5; 211:17
 delicate [2] 196:5, 10
 deliver [1] 54:6

- demographic [4] 26:21; 33:1; 95:13; 156:6
 demographics [1] 96:17
 Demonstrated [1] 61:13
 demonstrated [1] 18:1; 50:11; 59:6; 60:13; 62:18; 152:7; 155:14; 185:15; 188:16; 209:2; 243:1
 denominator [1] 139:4
 Denver [2] 53:10; 240:25
 Department [2] 64:20; 151:24
 departments [1] 222:19
 Depending [1] 56:21
 depending [5] 29:9; 55:6; 134:2; 190:9; 243:14
 depicted [1] 77:8
 depressed [1] 227:23
 derivative [1] 166:23
 derive [2] 84:1; 190:13
 derived [3] 22:10; 26:17; 58:17
 descending [2] 56:24, 25
 describe [3] 12:22; 89:4; 124:16
 described [10] 88:18; 90:16; 94:5; 115:20; 136:23; 157:8, 18; 181:4; 197:20; 232:2
 describes [2] 115:15; 143:1
 describing [2] 88:22; 152:24
 description [3] 77:10; 142:7; 177:2
 descriptive [2] 88:11; 153:3
 descriptively [2] 76:25; 77:3
 design [15] 24:5; 65:19; 110:21; 114:25; 116:7, 22; 149:4; 155:24; 167:10, 17; 168:7; 172:18; 178:3; 185:8; 242:20
 designation [1] 17:18
 designed [7] 148:15, 16; 204:3; 214:25; 215:1, 6
 designing [1] 240:21
 designs [2] 185:7; 241:6
 desk [1] 198:11
 Despite [2] 167:4; 171:19
 destroyed [1] 34:12
 destruction [2] 176:21; 177:12
 detail [6] 35:1; 42:14; 52:17; 54:5; 82:12; 150:1
 detailed [1] 231:1
 details [2] 26:18; 31:18
 detected [2] 176:19; 177:17
 determinations [1] 135:24
 determine [1] 189:14
 determined [7] 6:7; 23:17; 24:18; 37:16; 65:20, 23, 25
 determining [1] 63:1
 develop [6] 16:5; 104:20; 123:25; 175:10; 218:2; 240:12
 developed [9] 14:16; 17:21; 48:16, 17; 75:7; 101:25; 155:17; 157:11; 237:3
 developing [3] 10:12; 103:23; 161:25
 Development [1] 170:24
 development [37] 7:24; 8:25; 9:12; 10:16; 11:4; 13:16; 15:20, 24; 16:7, 12, 16, 24; 32:9; 62:12; 123:8, 20; 124:1; 152:19, 21, 24; 158:6; 162:18; 163:22; 166:2, 5, 8, 16; 167:24; 169:7; 170:14; 171:10, 18, 23; 173:12; 189:16; 208:16; 233:9
 devoted [1] 186:2
 diagnose [1] 172:11
 diagnosed [3] 50:13; 153:18, 23
 dialogue [1] 199:24
 Dianne [2] 5:21; 180:7
 diarrhea [1] 161:24
 Dick [1] 146:11
 die [4] 172:13; 175:9; 177:10, 11
 differ [3] 129:13; 133:23; 140:1
 difference [57] 24:25; 29:23; 31:25; 32:15; 34:18; 39:25; 44:2; 49:16; 67:23; 68:2, 3; 69:7; 76:8; 84:24; 85:7, 14; 88:7, 11; 93:11; 98:8; 101:7; 102:23, 25; 103:9, 11, 14; 108:23; 111:10; 112:10, 12, 23; 117:7; 125:13, 14, 15; 126:2, 3, 8, 12, 21; 127:3, 14, 17; 128:11, 18, 22; 131:19; 140:3; 192:18, 19, 24; 193:18, 20; 203:24; 209:24; 233:4
 Differences [1] 44:11
 differences [27] 9:21; 11:21; 31:1; 32:18, 25; 37:8; 38:1; 43:25; 73:10, 17, 24; 77:13; 80:18; 88:5; 93:2; 94:21; 102:8; 112:22; 118:12; 129:14; 132:16; 191:17, 20; 206:19; 233:1, 2; 237:18
 differential [1] 76:2
 differently [1] 233:4
 differing [1] 207:16
 difficult [14] 11:5; 50:6; 75:5; 94:7; 100:18; 101:3; 143:1; 160:23; 182:10; 203:15; 207:18; 225:15, 20; 234:25
 difficulty [1] 207:24
 dilemma [1] 52:2
 diligently [1] 16:11
 dimensions [2] 53:24; 178:13
 diminish [2] 85:7; 239:5
 Diminished [2] 52:24; 54:18
 diminished [3] 54:8, 11; 57:15
 dipping [1] 190:12
 direction [2] 191:4; 241:22
 Director [9] 4:21; 6:24; 64:4, 17, 23, 25; 168:4; 169:14; 235:9
 disadvantages [1] 178:21
 disappearance [1] 56:23
 disappeared [1] 47:22
 disappears [1] 126:22
 discharge [1] 176:23
 discharged [1] 109:9
 disclose [1] 6:23
 disclosed [1] 6:20
 disclosures [1] 165:10
 discoloration [1] 47:16
 Discontinuations [1] 49:19
 discontinue [3] 31:16; 90:1, 4
 discontinued [8] 24:17, 22; 29:1, 7; 69:15, 18; 91:14; 96:15
 discordant [1] 57:11
 discovery [2] 13:15; 170:7
 discuss [12] 12:13; 15:24; 54:5, 15; 82:12; 123:8; 124:15; 126:10, 19; 130:5; 144:14; 151:16
 discussed [10] 12:19; 33:21; 49:9, 17; 61:21; 115:2; 121:15; 126:24; 156:5; 184:23
 discussing [3] 17:25; 110:17; 119:20
 discussion [21] 19:16; 72:23; 105:5; 117:5; 148:5; 165:11; 180:22; 181:5, 6, 10; 182:12, 15; 184:1, 3; 199:1; 209:4; 221:19; 227:11; 229:25; 238:20; 244:13
 discussions [7] 6:22; 7:3; 11:13, 16; 32:13; 173:22; 238:22
 Disease [8] 5:7, 13; 6:25; 16:15; 52:8; 64:5; 151:23; 172:17
 disease [60] 10:5; 14:7, 23; 16:3; 23:23; 33:9, 16, 24; 34:12, 17; 53:8; 54:14; 59:6; 71:24; 72:1, 9; 73:9, 25; 76:12; 90:12; 92:22; 96:11, 17; 99:24; 101:24; 102:3; 145:18, 24; 167:13, 17, 25; 175:10; 192:5; 197:2; 211:20; 216:25; 220:9, 10, 11, 13, 18, 19, 21, 22; 222:9; 223:11, 12; 224:12, 14, 20, 24; 225:14, 24; 226:10, 12, 16; 232:12; 234:24; 239:22
 Diseases [3] 18:20, 23; 64:7
 diseases [1] 240:11
 disentanglement [2] 87:7, 9
 disincentive [1] 172:4
 disingenuous [1] 231:22
 disparate [1] 101:20
 display [2] 129:21; 195:14
 disproportionate [2] 54:13; 59:5
 disquiet [1] 231:20
 dissecting [1] 76:14
 dissociate [1] 210:7
 distinct [1] 77:13
 distinguished [2] 90:1, 9
 distinguishes [1] 62:15
 distinguishing [2] 14:25; 87:15
 distributed [1] 122:2
 distribution [9] 27:2; 34:8; 37:20; 79:17; 102:23; 103:14; 113:7; 115:1; 119:9
 divergent [1] 198:1
 diverging [1] 129:22
 diverse [1] 57:10
 divided [2] 19:13; 24:6
 Division [5] 15:22; 18:19; 165:14; 168:2; 202:6
 division [2] 168:4; 202:14
 Divisions [1] 18:22
 divisions [1] 86:23
 Dixie [3] 4:20; 6:24; 170:15
 DNA [1] 170:4
 doctor [1] 175:3
 document [3] 40:15; 227:10, 11
 documented [8] 23:10; 32:11; 116:9; 119:4, 22; 121:17; 123:24; 238:2
 doesn't [7] 87:18; 175:18; 176:19; 199:8; 243:9, 10, 11
 dormancy [1] 169:25
 dose [29] 21:17, 18; 25:5, 13, 22; 45:18; 60:6; 61:2, 14, 15; 108:6, 7, 8, 16; 110:15; 119:11, 12; 160:2; 179:14; 194:4; 195:25; 197:13; 227:6; 233:3; 236:1; 239:12, 18, 19; 240:24
 dosed [3] 75:12, 13, 16
 DOT [21] 14:15, 18, 20; 15:17; 35:13, 16, 19, 22, 23; 40:19; 52:4, 5, 17, 19, 20, 25; 53:11, 13; 71:1; 149:13, 14
 DOTs [1] 52:8
 DOTs [2] 169:15; 179:1
 dots [1] 84:25
 dotted [1] 21:8
 doubt [1] 140:6
 Dow [3] 13:17; 170:16, 17
 draft [1] 115:14
 dramatic [3] 14:6; 88:6, 7
 dramatically [1] 14:1
 draw [1] 149:1
 driven [2] 140:20; 224:22
 dropout [4] 91:16, 18; 94:4; 195:6
 dropped [6] 14:1; 23:1; 36:4; 90:21; 91:2; 119:13
 dropping [1] 219:6
 Drs [3] 63:24; 212:14; 240:16
 Drug [7] 6:8; 13:7; 15:23; 35:2; 167:9, 21; 223:12
 Drugs [1] 55:17
 drugs [70] 10:12; 13:16; 17:4; 23:18; 24:12, 19, 21, 23; 25:22; 30:18; 35:15; 36:16, 17; 37:5, 14; 45:20; 46:12; 48:11; 49:6; 52:14; 53:19; 54:6; 56:4; 57:4; 63:6; 75:11, 13; 76:10; 79:6, 10; 82:16; 87:11, 19; 94:22; 106:5; 111:18; 115:24; 117:2; 130:7; 134:15; 135:4; 136:15; 155:3; 156:14; 160:18; 166:10, 22; 169:21; 170:3, 10, 11, 21; 171:14; 179:22; 184:13, 15, 25; 187:10, 11; 188:1; 192:15; 211:15; 214:17; 219:6; 221:10; 225:4; 227:21; 232:5; 242:6
 drummed [1] 204:5
 druthers [1] 234:5
 du [1] 235:22
 Due [1] 16:3
 due [14] 37:3; 47:24; 49:16, 19; 51:17; 57:22; 58:11; 69:8; 76:11; 90:18; 108:9; 117:20; 136:24; 150:1
 Duke [1] 5:7
 duration [6] 10:13; 14:19; 15:19; 53:15; 60:22; 145:15

- E -

E-162 [1] 84:4
 Early [1] 186:4
 early [51] 12:7; 40:12; 41:17,

- 21; 42:12, 15; 43:17; 44:1, 7, 16; 55:18; 57:11; 58:3; 65:16; 68:15, 17, 19, 24; 74:10; 75:14; 78:1, 20; 86:18; 93:16; 95:23; 103:25; 104:1; 105:23; 107:20, 23; 108:5; 118:18; 120:1, 24; 122:17; 131:16; 133:8; 148:24; 149:17; 158:23; 163:12, 15; 167:23; 176:19; 177:18; 183:12; 184:20; 185:11; 213:8; 230:24
- earner** [2] 178:23; 192:1
- easier** [1] 11:9
- easily** [5] 99:19; 198:8; 214:17; 222:21; 234:11
- easy** [3] 178:6, 8; 216:17
- eat** [2] 75:18; 164:10
- eaten** [1] 75:18
- EBA** [1] 74:15
- echo** [1] 239:24
- economic** [3] 53:12, 13; 196:6
- economical** [1] 178:9
- economics** [1] 230:17
- economy** [3] 60:4; 171:15; 178:10
- educate** [2] 63:9; 197:23
- education** [1] 240:2
- effect** [13] 20:19; 38:23; 53:6; 56:16; 57:5; 76:2; 78:14; 79:22; 98:18; 187:19; 191:16; 192:2; 227:18
- effective** [24] 45:20; 50:23; 52:5; 61:12; 78:21; 137:16; 159:11; 160:21; 163:16; 83:17; 188:2; 192:7, 8; 193:6; 196:24; 199:20; 201:21; 205:9; 209:17, 19; 212:19; 215:23; 226:15; 244:3
- effectiveness** [11] 53:9; 188:25; 190:16; 191:22; 193:22, 23; 194:3, 16, 21; 230:10, 17
- effects** [5] 51:20; 56:15; 142:1; 188:14, 15
- efficacious** [2] 185:9; 209:11
- efficacy** [50] 12:14; 16:18; 19:16; 22:10; 25:24; 26:15; 27:15, 17, 21; 28:11; 29:2, 12, 18; 30:2; 50:25; 54:12; 55:19; 62:19; 66:7; 78:16; 79:13; 92:25; 95:1; 96:3, 19, 20; 112:22; 148:18; 160:3; 178:4; 181:15, 23; 182:11, 25; 184:18, 22; 185:4; 187:22; 194:2; 206:6, 7; 209:2, 15, 16; 210:6; 217:25; 218:25; 235:7; 243:5, 9
- efficiency** [3] 60:4; 178:5; 213:6
- efficient** [1] 52:4
- effort** [6] 7:23; 8:24; 15:21; 102:3, 7; 186:1
- efforts** [3] 8:1; 52:13; 172:24
- Eight** [1] 25:15
- eight** [14] 29:25; 32:3; 43:21; 68:23; 77:19; 89:8; 122:19; 127:6; 129:9; 140:19; 153:25; 192:25; 193:19; 214:18
- eighth** [1] 156:11
- El-Sadr** [1] 6:21
- elaborate** [1] 214:8
- Elaine** [3] 13:2, 6; 62:10
- elderly** [1] 20:14
- elegant** [1] 198:17
- element** [1] 54:2
- elements** [3] 52:17; 53:14; 59:9
- elevated** [3] 47:25; 48:17; 135:21
- eligible** [2] 121:12, 14
- eliminate** [1] 93:24
- Elimination** [1] 165:15
- elimination** [7] 15:2; 21:5; 56:13; 62:16; 79:23; 236:13
- ELISA** [3] 99:6, 9, 12
- ELISAs** [2] 99:1, 17
- ELLER** [12] 82:1; 95:10, 20, 24; 110:19; 111:12, 15, 20; 112:12, 17, 24; 113:17
- Eller** [2] 64:2; 95:24
- eloquently** [1] 206:1
- EMB** [15] 24:15, 17; 37:12, 24; 38:5, 12, 16; 40:25; 41:6, 8, 10, 12; 45:11; 47:24; 105:20
- embark** [2] 170:11, 20
- embraced** [2] 52:6; 94:9
- emerged** [1] 33:7
- emergency** [1] 14:10
- emerging** [1] 200:6
- emphasized** [1] 238:10
- emphasizing** [1] 238:9
- empirically** [1] 196:18
- employed** [1] 59:23
- encodes** [1] 156:19
- encompasses** [1] 14:18
- encountered** [2] 26:24; 49:25
- encounters** [2] 243:4, 19
- encourage** [2] 9:11; 172:3
- encouraged** [1] 16:4
- encouraging** [2] 9:14; 59:13
- end** [42] 12:22; 27:16; 28:8, 13, 14, 20, 22; 29:16, 17, 19; 34:21; 39:21, 22, 24; 41:19; 44:25; 45:12; 47:23; 57:20; 78:24; 110:17; 117:25; 118:5; 120:4, 9, 12, 14; 124:23, 25; 125:2, 6, 12; 126:17; 129:3, 22; 136:14; 149:11; 202:7, 9; 210:16; 237:20
- endorse** [1] 234:2
- endpoint** [9] 23:4, 5; 30:9; 31:4, 8, 20; 35:8; 149:15; 174:18
- endpoints** [2] 11:17; 39:7
- engage** [1] 199:23
- engagement** [1] 168:25
- England** [1] 147:15
- enhance** [2] 52:13; 61:4
- enhanced** [1] 61:7
- enrolled** [10] 25:18; 26:25; 34:11; 90:15; 91:22, 24; 92:6; 144:18; 149:11, 19
- enrolling** [1] 96:7
- enrollment** [7] 10:15; 23:7; 24:4; 25:16; 148:21; 149:17, 21
- entail** [2] 51:23; 209:4
- entered** [2] 23:3; 40:17
- entering** [1] 166:23
- entry** [2] 34:13; 92:6
- environments** [1] 55:24
- envision** [1] 200:23
- enzyme** [1] 81:12
- epidemiologist** [1] 141:17
- epidemiology** [1] 156:5
- equal** [15] 23:13, 15; 25:19; 38:5, 11, 15, 16; 41:8, 9, 11, 12; 49:4; 57:19; 129:8; 217:24
- equivalence** [14] 29:23; 30:23; 45:22; 76:19; 88:16, 19; 127:8, 11; 141:8, 10, 11; 143:5; 194:11
- equivalency** [7] 59:13; 61:14; 83:9, 22; 85:8; 139:11; 148:17
- equivalent** [17] 50:25; 62:19; 83:8; 93:3; 139:13, 14, 21; 141:2, 6; 147:12; 194:12, 13; 217:5, 23; 220:14; 226:4; 230:14
- era** [1] 197:19
- eradication** [2] 105:13; 106:19
- ere** [2] 37:13; 128:2
- erudite** [1] 98:11
- essential** [2] 14:24; 228:16
- essentially** [13] 70:23; 73:13; 81:2; 92:10; 93:3; 97:20; 124:13; 147:12; 153:2; 162:19; 163:11; 176:12; 195:11
- established** [2] 123:10; 171:14
- establishment** [2] 167:21; 168:1
- Estimate** [1] 84:24
- estimate** [1] 144:25
- estimated** [1] 128:25
- estimation** [1] 73:9
- et** [2] 142:11; 173:14
- ethambutol** [26] 24:14; 33:11; 54:10; 55:21; 57:16; 58:4, 14, 22; 60:7; 66:24; 67:2, 24; 69:9, 13; 71:9, 10; 88:9; 134:21, 25; 135:2, 10, 17; 146:16; 147:20; 179:18; 236:10
- ethanol** [1] 23:25
- ethnicity** [1] 94:23
- evaluate** [1] 10:14
- evaluated** [1] 74:13
- evaluates** [1] 229:23
- evaluating** [2] 16:18; 101:13
- Evaluation** [2] 6:9; 165:14
- evaluation** [5] 26:20; 34:4, 6; 73:18; 120:13
- event** [9] 7:3; 24:20; 47:16, 19; 49:8; 80:17; 156:13; 161:13; 162:13
- events** [19] 29:2; 46:10; 47:13; 48:11, 17, 21, 24; 49:3, 9, 15, 19, 25; 50:3; 80:11, 12, 19; 136:24; 161:17; 175:23
- eventually** [1] 82:8
- everybody** [6] 141:15; 142:10; 143:1; 186:21; 193:9; 242:20
- evidence** [6] 79:15; 182:9; 189:8; 195:18; 196:9; 242:5
- evolution** [2] 8:15; 186:13
- evolutionary** [1] 186:17
- evolvé** [1] 188:12
- evolved** [3] 101:21; 185:22; 186:6
- exactly** [16] 57:13; 85:5; 87:14; 133:8, 12; 141:5; 142:18; 169:20; 180:25; 191:5; 207:23; 210:21; 215:1, 23; 234:24; 235:3
- exam** [1] 74:5
- examined** [6] 26:15; 28:11, 17; 35:3; 36:3, 16
- Examining** [1] 54:19
- example** [9] 28:25; 77:15; 83:13; 144:24; 187:4; 190:12; 211:1; 215:25; 226:24
- examples** [1] 118:5
- excellent** [2] 51:5; 58:2
- Except** [3] 31:12; 48:22; 49:7
- exception** [2] 19:4; 137:3
- exception [2]** 43:10, 20
- exceptions** [1] 6:13
- excess** [1] 48:10
- excessive** [1] 51:25
- exciting** [1] 168:23
- exclude** [5] 7:6; 71:23; 72:2; 220:20; 226:11
- excluded** [7] 6:21; 23:22; 24:4; 66:2; 73:2; 119:14, 17
- excluding** [1] 36:4
- exclusion** [8] 7:7; 23:16, 25; 26:3, 7; 65:19; 100:6; 119:16
- excuse** [1] 6:10
- Executive** [1] 64:25
- exemplary** [1] 62:1
- exercise** [1] 196:10
- exhibited** [1] 21:20
- exist** [1] 77:16
- existence** [2] 75:8; 199:22
- existing** [7] 55:23; 60:23; 183:2; 207:21; 228:16, 21, 22
- exists** [2] 200:3, 12
- expect** [2] 79:7; 88:3
- expectation** [1] 148:25
- expected** [1] 47:17
- expecting** [2] 96:9; 190:13
- expectoration** [1] 27:6
- experience** [14] 34:2; 50:2; 53:22; 61:9; 144:16; 148:23; 207:7, 25; 208:6, 13; 237:11; 239:23; 240:9, 13
- experienced** [1] 48:12
- experiences** [1] 162:12
- experimental** [1] 126:25
- expert** [6] 63:11, 19; 145:7; 168:6; 204:18; 233:13
- expertise** [2] 167:24; 208:3
- experts** [3] 197:23; 211:18; 212:9
- explain** [5] 34:18; 63:4; 111:11; 136:16; 137:11
- explained** [1] 93:11
- explanation** [3] 89:16; 112:21; 162:22
- explanations** [1] 32:14
- explicable** [1] 135:22
- explicitly** [1] 60:13
- exploratory** [7] 32:19; 33:6; 44:19; 62:24; 70:4, 7; 76:23
- explore** [4] 36:13; 37:11; 52:17; 241:21
- explored** [4] 33:25; 40:13; 42:13; 233:2
- exploring** [1] 240:23

exposed [2] 162:24; 178:2
 exposing [2] 96:10; 192:4
 exposure [2] 33:4; 46:25
 expressed [1] 128:13
 expressing [1] 69:6
 extend [3] 59:23; 76:11; 177:2
 extended [3] 51:24; 54:13; 140:25
 Extending [1] 60:1
 extending [1] 233:18
 extensive [2] 34:2; 224:24
 extent [8] 33:24; 59:9; 102:1, 3; 216:25; 224:20; 239:2; 243:3
 Extra [2] 149:7; 220:6
 extra [24] 71:24, 25; 72:3, 4, 9; 73:2; 149:6; 151:2, 12; 154:18; 158:2; 197:2; 220:9, 10, 12, 18, 20, 22; 222:8; 226:9, 11, 15; 237:6; 239:21
 extraordinary [1] 102:10
 extrapolate [2] 202:16; 220:9
 extrapolated [1] 18:7
 extrapolating [1] 222:11
 extrapolation [2] 60:15; 201:12
 extrapolations [1] 210:23
 extremely [3] 53:3; 151:17; 242:10
 ezithromycin [1] 227:22

- F -

F-5 [1] 114:22
 face [2] 178:19; 198:11
 facilitate [1] 115:25
 fact [26] 11:13, 24; 12:1, 7, 9; 44:17; 56:1; 60:3; 61:4; 67:20; 68:10; 71:12; 75:6; 78:6; 100:9; 101:11; 102:11; 107:22; 113:2; 139:15; 173:19; 201:3; 207:4; 211:14; 231:25; 237:17
 factor [1] 113:12
 factors [23] 27:11; 33:3, 13; 51:23; 54:4; 55:11, 15; 56:2; 92:24; 124:20; 130:3, 5; 136:13; 150:15, 17; 151:14; 154:4; 156:6; 157:25; 161:25; 189:14, 17; 190:9
 fail [1] 176:1
 failed [4] 25:17; 123:23, 24; 125:12
 Failure [1] 59:19
 failure [26] 11:2; 28:4; 31:22, 25; 32:10; 44:21; 51:21; 54:6; 88:4, 23, 24, 25; 89:1, 5, 14; 90:3; 125:14; 127:23; 155:10, 14; 177:12; 182:6; 187:3; 188:20; 221:7
 failures [15] 28:2; 29:8; 31:12, 13, 19; 32:2, 12; 52:21; 111:11; 125:4; 138:22; 139:3; 140:9; 142:16; 233:8
 fair [4] 11:18; 144:21; 145:5; 158:4
 fairly [5] 80:24; 112:5; 196:10; 225:20; 226:13
 fairness [1] 7:10
 fall [1] 225:8
 falls [1] 81:9
 familiar [3] 17:20; 132:19;

184:10
 familiarity [1] 197:19
 family [3] 178:25; 190:1; 192:2
 Faruqi [1] 64:4
 fashion [6] 85:10; 139:19; 141:2; 207:3; 221:21; 239:16
 fast [1] 242:17
 fasted [1] 226:25
 fasting [4] 21:2; 75:12, 21, 24
 favor [2] 199:10; 242:14
 favorable [4] 54:1; 62:1, 23; 238:15
 favors [1] 126:17
 FDA [47] 4:7; 5:11, 17, 18, 19, 20, 21; 7:5, 15; 8:11, 22; 10:2; 15:22; 16:4, 10, 14; 17:8; 22:12; 32:14; 35:5; 49:8; 82:8; 114:5; 115:18; 116:16; 117:17, 22; 118:4, 24; 120:4; 121:18; 124:6; 133:20; 138:5; 166:20; 167:6, 16, 19; 176:16; 190:21; 192:23; 199:5, 23; 203:17; 205:15; 206:19; 234:20
 feasibility [1] 170:24
 feasible [2] 53:13; 243:18
 features [4] 58:11; 59:8; 95:13; 198:20
 fed [2] 226:25; 227:2
 feel [9] 72:18; 87:12; 91:25; 144:9; 182:4; 190:3; 211:25; 223:16; 240:24
 feeling [2] 122:1; 175:13
 feels [1] 158:22
 FEINBERG [8] 5:4; 70:16; 71:11; 91:10; 93:4, 9; 196:22; 231:6
 Feinberg [10] 5:4; 70:14; 91:9; 94:16; 107:16; 196:21; 206:23; 212:14; 231:5; 239:24
 fell [6] 21:11; 109:13; 150:17; 151:13; 154:6; 157:8
 felt [9] 75:21; 89:12; 90:5, 6; 93:11; 105:21; 148:22; 152:9; 163:25
 female [1] 198:24
 females [6] 23:7; 24:3; 80:12; 92:16; 111:2; 112:3
 fever [2] 27:6; 175:14
 fewer [3] 115:23; 132:13; 172:7
 fewest [1] 44:16
 field [2] 201:2; 208:18
 Fifty-six [1] 113:19
 figure [1] 171:8
 file [1] 133:21
 filled [1] 115:23
 film-coated [1] 19:25
 films [1] 101:10
 final [4] 127:21, 24; 128:2; 194:23
 financial [2] 6:6; 7:5
 find [10] 63:20; 95:12; 104:4, 24; 108:22; 124:1; 151:18; 179:17; 190:17; 204:7
 finding [1] 63:5
 findings [5] 34:10; 46:9; 59:13; 97:25; 227:15
 fine [1] 233:21
 firm [2] 7:11; 8:3
 firms [2] 6:8; 7:4

First [11] 19:22; 46:9; 54:6; 98:6; 124:12, 24; 126:10; 130:12; 131:23; 132:19; 206:3
 first [49] 8:9, 10, 13; 9:4, 13; 13:12; 15:24; 28:17; 35:3; 54:7; 65:18; 68:25; 85:18; 100:18; 102:22; 106:20; 109:20; 114:12; 116:10, 22; 117:1; 118:17; 121:10; 122:9; 124:7; 131:5; 134:20; 136:7; 141:10; 159:10; 161:11; 165:5, 20, 24; 166:19, 20; 173:15; 175:7; 180:15, 16; 181:12; 183:15; 184:4; 195:21; 207:11; 210:13; 211:3; 236:15; 243:13
 fit [1] 170:8
 Five [1] 89:8
 five [28] 10:16; 21:3; 22:19; 23:18; 32:11; 38:7; 43:12; 47:12; 48:20; 55:1; 58:25; 71:9; 125:13, 22; 128:14; 129:9, 10; 131:7, 13; 150:6, 9; 159:21; 168:5; 177:20; 193:8, 10, 17; 219:17
 fixed [1] 140:16
 flavor [1] 146:7
 flexibility [2] 211:24; 239:1
 flipped [1] 140:23
 flu [1] 188:19
 FLYER [4] 5:17; 140:5, 15; 141:3
 Flyer [1] 5:17
 focus [7] 114:25; 115:1; 124:12; 127:1; 147:3; 232:9, 10
 focused [4] 16:3; 111:25; 117:5; 230:1
 Focusing [1] 118:4
 focusing [2] 116:17; 141:7
 fog [1] 211:2
 follow [6] 18:8; 22:10; 94:15; 99:7; 109:9; 191:6
 follow-up [78] 10:15; 12:9, 11; 17:10, 12; 22:24; 23:3, 4, 5; 24:9, 27:17, 20; 28:9, 22; 29:18, 20; 30:9; 31:4, 8, 19; 35:8; 39:6; 40:17; 45:2; 79:4; 97:12, 16, 21; 109:24; 110:4; 116:6, 11, 13; 118:1, 3; 119:5; 120:10, 22, 23; 121:3, 20, 23, 24; 122:2, 7, 13, 22, 23; 124:14, 25; 125:11, 15, 18; 126:20; 127:20; 128:6, 8; 129:22, 23; 137:8; 138:8; 139:16; 140:8; 142:20, 23; 143:11, 13; 147:7; 149:16; 173:17; 176:14, 15; 201:1; 206:11, 12; 207:12; 228:15, 16
 followed [19] 26:5; 45:5; 54:24; 55:20; 56:6, 13; 86:20; 108:19; 110:2; 119:3; 121:22, 25; 130:14; 146:17; 147:20; 171:3; 241:1, 10; 242:8
 Following [2] 18:9, 15
 following [12] 5:25; 6:13; 57:25; 59:18; 63:25; 64:12; 115:9; 123:5; 130:5; 150:17; 183:17, 22
 follows [1] 127:21
 food [7] 20:19; 21:14; 75:12,

16, 25; 76:1; 227:5
 force [2] 211:14; 226:11
 forceful [1] 166:11
 foregoing [1] 113:24
 forget [1] 240:14
 forgotten [1] 13:22
 form [4] 17:21; 90:10; 129:19; 201:6
 formal [4] 76:24; 80:16; 96:4; 127:7
 formally [2] 162:10; 211:4
 format [2] 42:4; 43:8
 formed [1] 156:24
 former [2] 64:23; 235:9
 forms [2] 218:13; 220:18
 forth [10] 79:14; 141:14, 16; 190:10; 211:7; 222:9, 13, 20; 229:12; 242:22
 forthcoming [1] 221:25
 Fortunately [1] 233:23
 forward [10] 7:24; 104:21; 173:4; 180:10; 182:15; 202:24; 210:3; 222:2; 243:6, 11
 found [18] 21:18; 22:1; 27:13; 32:24; 34:9; 62:22; 73:17; 90:24, 25; 100:3, 5, 20, 21; 102:4; 127:2; 167:15; 202:20; 231:22
 four [29] 11:16; 19:13; 24:8, 12; 38:13; 40:1; 55:6; 57:19; 66:4, 9; 84:18; 105:25; 120:15; 122:17; 125:4; 129:2, 8; 132:22; 133:2; 147:24; 149:13, 14; 150:9; 151:18; 152:17; 154:2; 155:3; 157:10; 219:8
 four-drug [2] 235:1; 237:15
 fourth [5] 54:11; 58:18, 23; 157:14; 236:10
 Fourthly [1] 61:2
 fourthly [1] 53:9
 fraction [1] 45:7
 Francisco [1] 4:19
 fraught [1] 225:15
 Freedom [1] 6:18
 frequency [8] 14:19; 15:19; 27:9; 33:23; 34:8; 48:4; 73:15; 113:4
 frequent [11] 15:5; 32:2, 6; 36:7; 47:12; 62:18; 95:6; 175:4, 5; 196:7; 197:5
 frequently [6] 47:20; 48:8, 21; 184:11; 198:9; 231:13
 front [2] 78:24; 104:8
 frustrating [1] 94:6
 fulfilling [1] 26:14
 full [6] 22:14; 74:4; 91:4; 105:12; 187:6; 201:5
 fully [2] 53:2; 233:2
 function [2] 20:15; 112:19
 functioning [2] 168:19, 20
 fundamental [1] 135:23
 Fundamentally [1] 10:3
 funding [1] 168:13
 future [21] 34:23; 166:7; 168:24; 170:3; 171:18; 172:1, 23; 177:23; 182:10, 23; 188:11; 197:16; 201:15; 207:13; 208:4, 6; 230:5; 239:9, 14; 244:10

- G -

gained [2] 144:16; 148:23
 gamma [1] 236:13
 garner [1] 208:4
 gastrointestinal [2] 161:23;
 32:8
 gather [4] 222:23, 24; 223:1;
 239:21
 gathered [1] 222:6
 gave [8] 70:17; 87:21; 102:12;
 167:8; 191:24; 204:17; 227:5;
 231:12
 Gender [1] 27:2
 gender [7] 33:1, 8; 34:17;
 76:12; 154:7; 201:16; 233:1
 gene [4] 156:18, 23; 157:6, 15
 generality [1] 106:19
 generalizable [1] 92:1
 generalized [1] 94:18
 generate [1] 80:17
 generated [1] 148:5
 generation [3] 61:1; 99:1, 17
 genetic [1] 109:21
 gentlemen [3] 13:4; 19:10;
 51:11
 germane [1] 231:17
 Gerry [1] 64:22
 gets [1] 222:23
 GI [1] 162:12
 giant [1] 243:7
 Give [1] 210:13
 give [24] 7:15; 18:25; 65:10,
 14; 86:16; 90:20; 97:1;
 114:24; 124:9; 142:7; 146:7;
 148:6; 159:25; 160:23; 173:7;
 194:10; 205:12; 210:11, 21;
 211:1; 219:15; 227:5; 228:8;
 232:14
 Given [1] 61:3
 given [32] 10:10; 57:18; 79:6,
 16; 82:17; 84:24; 98:11;
 105:15; 106:11; 108:7, 8, 17;
 116:23; 117:10; 118:6; 119:15;
 121:18; 137:21; 159:11, 19;
 166:24; 188:22; 189:2, 3;
 198:10; 204:24; 207:21;
 211:19; 213:12; 221:5; 227:2;
 234:5
 gives [4] 119:8; 122:1; 126:7;
 127:15
 giving [6] 78:10; 106:5, 13;
 162:19; 194:23; 215:2
 glad [2] 178:12; 204:5
 Global [1] 64:2
 global [4] 9:8; 14:9, 17; 52:10
 Globally [3] 13:22; 14:7;
 51:16
 globally [1] 145:3
 gnawing [1] 206:24
 goal [2] 179:7, 22
 goes [5] 126:13; 131:7, 8;
 176:21; 233:7
 GOLDBERGER [10] 5:20;
 7:17; 210:14; 216:11; 223:5, 7;
 240:18, 21; 241:16; 242:13
 Goldberger [6] 5:20; 7:15;
 68:5; 210:11; 237:21; 240:16
 gonorrhea [1] 179:10
 GORODETZKY [6] 19:9;
 65:22; 66:3, 14, 20, 25; 67:5;

68:2; 69:17; 71:5, 12; 72:2, 10,
 16, 20; 73:4, 12; 74:1, 7, 18;
 75:2, 6, 13; 76:21; 80:7, 14;
 81:5, 22, 24; 82:3, 6, 11, 25;
 89:6; 90:4, 20; 92:2; 93:6;
 96:14; 97:14; 98:21; 100:2, 12;
 102:16,
 22; 103:13, 18; 105:8; 106:7,
 10, 15, 18; 107:3, 9, 13, 15,
 21; 108:1; 110:5, 13; 162:10
 Gorodetzky [11] 18:10, 15;
 19:8; 58:5; 59:6, 17; 63:24;
 77:14; 84:20; 86:25; 96:2
 Gosey [1] 114:18
 gosh [1] 98:7
 government [3] 14:12; 179:3,
 24
 governmental [1] 179:6
 granted [3] 6:14; 17:18;
 184:10
 graphical [1] 129:19
 grapple [1] 182:16
 gratifying [1] 8:3
 great [11] 82:18; 83:1; 144:23;
 145:4; 170:6; 171:25; 172:23;
 174:23; 191:3; 202:25; 237:24
 greater [34] 14:3; 33:16; 34:7,
 14; 35:1; 36:14; 37:1, 2, 22,
 23; 38:5, 10; 40:6; 41:5, 6, 7,
 9; 42:13; 43:16; 45:10, 11;
 66:18; 67:12; 74:22; 78:20;
 80:12; 97:24; 126:15; 129:1, 8;
 168:3; 177:19, 21; 238:16
 greatest [1] 62:6
 green [1] 84:25
 grew [1] 23:11
 grips [1] 199:24
 group [80] 27:4, 10; 31:7, 11;
 32:25; 33:15, 20, 24; 34:10,
 13; 37:22, 24; 38:3, 4, 10, 14,
 23; 39:4; 41:4, 7, 10; 42:1, 8,
 9; 43:11, 14, 20, 23; 44:3, 5,
 13, 17, 23; 49:25; 59:11; 66:9;
 68:13, 14, 19, 21, 23; 69:3;
 70:25; 73:16; 77:21; 79:20;
 84:9; 87:8; 88:8; 90:17; 91:5;
 98:24; 103:1; 105:18, 21, 22;
 108:11; 121:16, 25; 123:1, 2,
 14; 135:15, 16; 143:13;
 147:13, 23, 25; 178:24; 199:3;
 202:25; 213:6; 220:6; 228:9;
 236:25; 237:1
 grouped [1] 40:22
 groups [75] 26:9, 22; 27:3, 8;
 29:5; 30:21, 24; 31:15, 16;
 38:1, 8, 12; 41:3, 23; 42:21;
 43:6, 15; 48:5, 7, 24; 49:10,
 21; 58:7; 67:6, 8, 11, 18, 20;
 68:13, 17; 72:17; 73:11, 14,
 25; 74:12, 14, 21; 75:3, 20;
 77:5, 7, 12, 14, 16; 83:12, 15,
 19; 84:15, 18; 85:11, 23; 86:1,
 23; 89:19; 98:17; 100:1;
 104:11; 108:21; 111:5; 119:13;
 121:9; 124:2; 139:17, 20, 25;
 140:4; 143:10; 146:13; 154:9;
 213:10, 13; 220:4, 7; 236:24
 grow [1] 157:1
 growth [2] 55:15, 24
 guess [22] 67:22; 91:11, 16,
 22; 141:5; 143:4; 159:7;

175:25; 177:16; 184:17;
 186:20; 197:8; 199:23; 203:11;
 217:3; 218:17; 224:18; 228:1;
 233:7; 236:17; 239:11; 242:15
 guest [1] 4:6
 guests [1] 244:17
 guidance [5] 206:22; 210:12;
 233:14; 240:2; 244:5
 guide [1] 210:17
 guided [2] 145:7, 8
 guidelines [5] 4:12; 45:17;
 59:22; 182:21; 218:2
 guy [1] 226:19

- H -

hadn't [1] 174:13
 half [8] 31:24; 116:3; 134:2, 6;
 152:11; 198:24; 219:17; 227:6
 half-life [13] 15:2, 14; 21:5;
 62:16; 103:24; 106:14, 25;
 107:5; 108:9; 109:15; 204:25;
 231:12
 halting [1] 53:7
 Hamedani [1] 64:6
 HAMILTON [11] 5:6; 94:15;
 96:1, 24; 97:10, 22; 174:13,
 16; 199:19; 233:12; 234:2
 Hamilton [8] 5:6; 6:14; 94:14;
 174:12; 191:23; 199:18;
 212:14; 233:11
 Hammer [5] 5:8; 7:18; 114:8;
 158:16; 240:22
 hammer [1] 243:24
 HAMMERSTROM [7] 5:18;
 124:11; 138:11, 16, 24; 139:7;
 141:4
 Hammerstrom [5] 5:18;
 114:17; 115:4; 122:3; 124:9
 hand [6] 200:1, 5, 9, 11;
 212:22; 233:11
 handle [4] 84:16; 85:6, 9;
 191:5
 handled [1] 139:19
 handling [4] 30:3, 13; 79:23;
 84:20
 hands [2] 212:23; 213:2
 hangs [1] 84:11
 happening [1] 222:15
 happens [5] 87:25; 107:11;
 131:22; 221:5; 230:24
 happy [2] 19:6; 158:11
 hard [7] 101:11; 105:12;
 159:5; 160:7, 25; 174:20;
 237:9
 harder [2] 159:7; 213:25
 hardly [1] 234:20
 harm [1] 201:6
 Harvard [1] 5:9
 hat [1] 202:5
 hatched [3] 41:22; 42:4; 43:1
 haven't [2] 174:6; 196:14
 head [3] 64:2; 113:18; 242:2
 head-to-head [1] 204:3
 Health [14] 4:23; 14:9; 52:10;
 64:21; 65:6, 7; 94:8; 145:1;
 148:11; 151:24; 165:18;
 169:14; 178:16, 18
 health [15] 14:13, 21; 15:16;
 46:14; 51:15; 63:9; 65:3;
 169:16; 174:21; 197:5; 198:7,
 15; 200:16; 201:5; 222:19
 healthy [6] 20:14; 111:5, 23,
 24; 112:6, 14
 hear [8] 180:22; 181:4, 8, 13,
 14; 214:5; 215:15
 heard [23] 51:16; 53:22;
 62:11; 98:10; 165:16, 22, 25;
 166:18; 169:15; 171:6; 172:10;
 174:6; 180:9, 10; 181:3;
 182:10; 183:14; 185:7, 10;
 202:11; 203:1; 207:16; 214:3
 hearing [1] 173:3
 heartily [1] 234:2
 Heifets [1] 64:17
 height [1] 26:21
 Hello [1] 179:13
 help [8] 32:21; 52:14; 199:8;
 208:4; 212:9; 234:3; 243:10,
 11
 helpful [6] 12:10; 76:14;
 207:25; 208:7; 216:16; 238:5
 helps [2] 174:4; 179:11
 hematuria [2] 48:6; 72:15
 hemoptysis [1] 27:7
 hepatic [2] 20:15; 46:15
 hereafter [2] 25:3; 41:2
 hereinafter [1] 25:2
 heterogeneity [1] 131:18
 High [1] 37:18
 high [25] 37:22; 41:2, 4, 22,
 25; 42:8, 20; 43:5, 10, 20;
 44:17; 54:3; 58:7; 60:6; 61:3;
 67:7; 68:12; 77:15; 105:18;
 134:18; 150:2; 161:5, 20;
 227:2; 243:19
 higher [43] 27:4, 9; 33:15, 17,
 19, 23; 38:17; 49:15, 17, 24;
 51:21; 54:25; 57:24; 58:10, 23;
 61:4, 7; 77:18; 79:19; 88:5;
 92:16; 93:22; 124:15, 19;
 126:23; 129:2; 131:6, 11, 24;
 132:4, 11, 21, 24; 133:10;
 134:4; 135:6; 136:11, 16;
 171:9;
 188:21; 192:6; 196:5; 228:25
 highest [1] 135:9
 highlights [1] 59:16
 Hinshaw [1] 236:15
 histogram [2] 113:3, 4
 historic [1] 142:21
 historically [2] 59:8; 205:15
 history [9] 23:22; 154:8, 16;
 166:7; 185:21; 186:23; 211:3
 hit [1] 105:11
 HMR [1] 21:24
 hoc [4] 32:19; 66:12; 141:14;
 142:2
 Hoechst [25] 4:7; 11:13; 13:7,
 18; 15:21; 16:5, 14, 21; 17:1,
 23; 18:11; 19:20; 46:5; 51:13;
 63:25; 64:24; 69:24; 95:24;
 97:5; 99:5; 108:3; 169:2;
 170:17; 171:20; 244:18
 hold [1] 19:3
 holds [1] 233:4
 Homelessness [1] 153:7
 homelessness [2] 27:12;
 154:7
 honestly [1] 192:16
 hope [1] 167:5
 hoped [1] 242:21

- hopefully** [2] 172:9; 173:20
HOPEWELL [20] 4:18; 71:21; 72:6, 12, 19, 24; 73:8, 20; 74:6, 9; 75:1, 4, 10; 76:4; 161:23; 162:6; 185:20; 217:3; 225:13; 241:17
Hopewell [7] 4:18; 71:20; 161:22; 185:18; 212:15; 217:2; 241:16
hoping [1] 140:17
Hopkins [1] 152:24
horizontal [1] 21:8
hospital [4] 109:7; 153:23; 186:5
host [3] 73:24; 74:3; 201:18
hot [3] 157:5, 9, 17
hour [3] 75:18; 111:4, 22
hours [13] 21:3, 4, 6, 11, 13; 75:19, 23; 78:12; 106:14; 107:1; 204:25; 214:13
human [2] 53:22; 57:6
hundred [2] 25:15; 120:18
hundreds [1] 102:11
Hutchinson [1] 5:2
hyperuricemia [9] 47:20, 22; 48:3, 22; 79:14, 18, 19; 137:3; 188:7
hypothesis [3] 93:11; 185:24; 236:7
hypothetical [4] 55:4; 184:23; 185:13; 195:23
-
- | -
- I'd** [27] 4:3, 5, 12; 5:23; 7:14, 18, 22; 13:1; 65:9; 83:5; 88:14; 94:15; 96:13; 97:22; 103:16; 136:21; 151:15; 154:19; 164:6; 165:3; 175:25; 183:24; 184:3; 203:11; 226:18; 230:7; 241:8
I've [15] 141:19; 144:13; 151:19; 157:20; 166:3; 168:14; 178:2, 18; 180:23; 185:3; 202:11; 203:1; 214:3, 5; 222:6
i.e. [1] 226:7
IC-50 [1] 232:1
IC-90 [1] 232:1
IC-95 [1] 227:15
ID [1] 202:6
idea [3] 225:18, 19; 235:12
ideal [2] 58:16; 215:12
ideas [1] 191:9
identical [6] 71:7, 10; 83:15; 133:6; 155:24; 212:2
identified [5] 52:3; 62:25; 151:24; 153:16; 154:1
identify [3] 61:18; 150:15; 161:3
ignore [1] 135:23
II [5] 98:19, 24; 99:2, 18; 147:9
illnesses [2] 17:5; 236:5
illustrated [1] 40:14
imagine [2] 175:2; 232:14
imbalances [1] 34:17
immediate [3] 19:4; 201:15; 232:8
immediately [1] 24:22
immunity [1] 160:22
immunocompromise [1] 218:13
immunocompromised [2] 163:14; 233:19
immunoglycocide [1] 236:13
Immunologic [1] 15:23
immunologic [3] 73:22; 74:2; 168:2
Immunology [2] 18:21; 64:19
immunomodulating [1] 145:21
immunosuppression [1] 158:2
impact [6] 9:7; 79:11; 124:5; 178:23; 225:12; 232:13
impaired [1] 20:15
impairment [1] 46:16
impediment [1] 51:19
impediments [1] 10:12
implications [3] 54:16; 174:21; 184:15
implied [1] 189:21
Importance [4] 63:10, 13; 166:6; 240:14
important [43] 11:3; 14:25; 27:21; 45:25; 49:13; 50:7; 61:16; 78:2, 5; 95:5; 109:3; 127:13; 156:8; 158:17; 159:3; 160:9; 165:10; 167:5; 169:3, 4, 8, 22, 23; 170:2, 9, 24; 171:5; 172:6, 21; 174:18; 179:25; 185:14; 203:13; 206:17; 208:17; 209:9; 219:12; 221:21; 222:14; 225:9; 226:10; 239:19; 243:5
importantly [3] 169:24; 171:24; 200:20
imposed [1] 185:6
impossible [2] 106:6; 184:11
impression [3] 58:9; 194:10; 224:22
improve [3] 8:24; 63:16; 238:18
improved [3] 11:10; 60:10; 201:4
improvement [3] 10:6, 21; 230:12
improves [2] 14:20; 239:9
improving [5] 9:2; 10:22; 13:19; 52:5; 238:24
inability [1] 51:16
inactivation [1] 179:19
inadequate [1] 96:11
inadvertently [2] 48:13; 50:17
incarceration [1] 154:8
incentives [2] 200:15; 208:15
incidence [10] 16:1, 4; 48:23; 49:3, 12, 15, 17, 24; 50:7; 53:6
incidences [1] 48:7
incident [1] 152:4
include [15] 52:20; 70:6; 120:3, 5; 123:6; 128:23, 24; 133:21; 143:22; 145:14; 148:21; 158:1; 200:15; 216:22; 233:22
included [18] 25:22; 26:1; 28:12; 32:25; 35:7; 45:23; 66:7; 70:8; 90:3; 96:18; 110:8; 114:15; 120:2; 129:16; 209:18; 213:15; 231:16; 233:16
includes [2] 70:2; 126:13
Inclusion [1] 23:6
inclusion [4] 67:2, 24; 69:8; 119:16
incongruous [1] 59:3
increase [14] 8:1; 14:11; 16:4; 43:13, 22; 46:3; 51:4; 80:13; 166:12; 179:14; 197:25; 205:18; 236:1; 238:3
increased [14] 9:4; 14:3; 41:24; 42:24; 50:2; 51:25; 60:4; 73:15; 102:5; 117:25; 137:8, 12; 227:2; 236:9
increases [4] 14:4; 21:15; 38:20; 214:20
increasing [7] 14:8; 15:18; 42:6; 43:4; 61:5; 239:12
incredibly [1] 160:17
incurable [1] 52:2
independent [2] 33:8; 34:4
India [2] 109:6; 179:19
indicate [5] 44:19; 61:24; 74:22; 217:20; 218:3
indicated [5] 24:23; 56:18; 73:6; 232:5; 237:21
indicates [3] 127:3, 5; 145:1
indication [5] 99:23; 115:10; 182:23; 210:2; 225:14
indications [1] 213:14
indicative [1] 207:13
indicator [1] 225:24
indicators [3] 216:20; 218:8; 229:5
indinavir [19] 20:22; 21:25; 22:1, 4, 7, 9; 80:24; 81:1, 9, 11, 13, 17; 82:10; 159:25; 227:12, 13, 14, 16; 232:3
Individual [1] 52:14
individual [14] 138:13; 165:7; 170:8; 175:1; 176:9; 191:25; 198:10, 16, 21; 199:11, 14; 219:25; 224:10; 225:6
Individuals [1] 109:10
individuals [16] 25:15, 18; 49:22; 98:17, 24; 102:9; 138:9, 22; 158:19; 159:2, 24; 202:23; 203:2; 224:3, 5; 237:17
induce [2] 21:22; 85:14
inducer [2] 79:16; 81:12
induction [37] 117:5; 118:5; 120:11; 122:18; 146:16; 149:10, 12; 151:4; 155:3; 164:1; 214:7, 23; 215:10, 14, 15, 24; 216:2, 6, 21; 217:14, 15; 218:5, 20; 219:3, 8, 18; 221:10; 228:10; 230:2, 25; 232:9; 234:5; 236:11; 237:20; 241:1; 242:3, 10
industry [6] 14:13; 167:19; 169:1, 4, 6; 172:3
inexplicable [1] 72:13
infect [1] 13:24
infected [36] 14:4; 20:17; 46:16, 21; 49:22; 50:1; 81:3; 98:16, 24; 144:6, 15, 22, 25; 145:3, 6; 148:8; 149:18; 152:10, 12; 154:11; 158:19, 23; 159:1, 5; 161:4; 201:18; 202:23; 203:2; 224:3, 5; 226:20; 227:9; 228:3; 231:10; 235:16; 236:4
infection [11] 105:12; 123:19; 147:10; 153:1, 9; 154:25; 155:12; 158:8; 177:5; 218:12
Infectious [7] 5:6, 13; 18:19, 23; 64:5, 7; 151:23
infectiousness [1] 16:3; 240:11
inference [2] 79:20; 210:10
inferences [2] 208:5
inferential [1] 207:3
inferior [1] 230:14
inferiority [5] 189:10; 202:9, 19; 203:4; 243:22
infiltrate [1] 102:1
inflator [1] 89:15
influence [4] 9:22; 95:13; 171:25; 215:8
influenced [4] 55:11; 59:10; 69:13; 199:7
influences [1] 109:15
Information [1] 6:18
information [26] 10:2; 19:22; 34:23; 69:8; 70:7; 83:11; 84:9, 10; 100:5; 125:17; 129:18; 130:23; 143:11; 180:13; 195:24; 200:8; 211:13; 216:17, 19; 217:1; 221:24; 222:23; 223:2; 240:4, 12; 244:2
informative [2] 84:7; 137:10
infrequent [1] 11:6
INH [70] 24:16; 25:8, 9, 11, 13; 33:11; 35:12, 18, 23, 24; 36:25; 37:9, 12, 13; 38:6, 10, 15; 40:25; 41:5, 7, 9, 11; 45:10; 57:16; 60:7; 66:18; 67:3, 25; 69:10; 71:8; 76:2; 78:12; 88:8; 93:24; 94:25; 105:14, 19, 25; 106:5, 9, 21, 22; 107:4; 108:11, 19; 109:7, 12, 15; 117:10, 13; 134:21, 24; 135:2, 10, 16; 146:15, 17; 147:19, 20; 149:13, 14; 150:6; 160:19; 162:18; 197:14, 22; 203:23; 204:12, 20; 241:3
INH-PZA [1] 71:9
INH-rifampin [1] 78:21
inherently [1] 136:5
inhibitor [1] 20:22
inhibitors [8] 145:20; 159:9; 203:3; 227:10; 232:6, 15; 235:21; 237:4
initial [14] 15:10; 54:7; 59:24; 60:8; 69:19; 76:10; 104:3; 105:9; 196:25; 206:8; 214:18; 237:15; 238:24, 25
initially [6] 65:14; 109:6; 152:10, 12; 155:9; 203:13
initiate [1] 45:13
initiated [2] 96:9, 15
initiation [1] 238:12
initiative [1] 168:23
injections [1] 160:25
insert [2] 214:16; 233:17
instance [4] 210:22; 216:14; 240:24; 241:4
instances [1] 145:8
instructive [1] 151:21
insufficient [2] 57:23; 105:15
insure [1] 51:17
insuring [1] 179:4
integrated [2] 46:6; 49:14

intended [5] 12:11; 75:18; 109:13; 180:12; 242:21
 intense [1] 181:25
 intensity [4] 92:22; 102:1; 214:11; 238:25
 intensive [55] 15:7; 24:7, 11, 7; 25:1; 28:13, 21; 29:16; 33:12, 17; 34:21; 35:2, 11, 17; 36:6, 15, 19; 37:11, 15, 24; 38:21; 39:22; 40:11, 21, 24; 41:19, 24; 42:22; 44:6, 20, 24, 25; 45:4, 9, 12, 14; 46:2; 47:23; 48:14; 51:3; 57:11; 63:7; 66:17; 67:14; 69:20; 70:22; 71:6, 13; 105:10; 106:20; 110:25; 130:7; 136:14; 187:4; 238:24
 intent [13] 18:3; 25:25; 28:23; 84:22, 25; 86:8, 21; 90:16; 91:2; 120:5; 143:23; 173:15
 intentionally [1] 85:14
 interaction [7] 20:21; 21:25; 80:25; 158:20; 231:21; 235:22; 237:3
 interactions [3] 79:5; 219:11; 232:18
 interactive [1] 15:21
 interest [10] 5:24; 6:1, 12; 7:5, 10; 124:1; 144:23; 171:22; 215:4; 228:7
 interested [5] 204:10; 224:13, 19; 241:9, 13
 interesting [9] 86:2; 107:20; 109:18; 122:11; 155:20; 158:25; 188:7; 204:23; 227:4
 interestingly [1] 152:16
 interestingly [4] 153:8; 154:16; 155:6, 13
 interests [2] 6:6, 8
 interferes [1] 156:16
 interferon [1] 145:22
 interim [1] 17:9
 intermittency [1] 53:18
 intermittent [7] 60:7; 109:9; 146:17; 216:1; 218:19, 21; 222:7
 intermittently [1] 186:7
 International [1] 172:16
 international [2] 172:18; 238:23
 internationally [1] 168:6
 interpret [3] 57:14; 78:23; 87:2
 interpretation [9] 18:16; 50:6; 55:6; 58:6; 63:12, 19; 66:16; 91:17; 162:17
 interpreted [1] 183:3
 interpreting [6] 70:19; 71:2; 87:13, 20; 105:6; 195:5
 interval [9] 32:1; 85:2; 110:18; 126:11, 16; 127:2; 128:18; 217:9, 11
 intervals [12] 15:15; 29:25; 30:22, 25; 84:4, 21; 126:7; 128:20, 24; 140:11, 19; 188:22
 intervene [1] 179:24
 intervening [1] 118:21
 intimate [1] 197:19
 intravenous [1] 24:1
 intrigued [1] 231:11

intriguing [2] 72:13; 236:8
 intrinsic [1] 58:12
 introduce [3] 4:13; 62:9; 115:6
 introduction [4] 18:9; 114:24; 213:13; 214:11
 introductory [2] 7:15; 210:15
 invented [2] 75:8; 101:14
 investigate [1] 86:8
 investigated [2] 32:14; 39:1
 investigational [1] 157:23
 investigator [13] 29:3; 47:13; 89:1, 5, 9, 11, 12, 17, 21; 90:2, 10; 155:8; 168:23
 investigators [7] 35:14; 47:15; 148:24; 155:7, 9; 162:7; 168:15
 invited [1] 7:19
 involve [1] 7:3
 involved [1] 170:9
 involvement [2] 7:7, 11
 irrelevant [1] 201:17
 irrelative [1] 237:19
 ISEMAN [8] 51:11; 78:9; 79:15; 93:15; 101:18; 109:2; 176:3, 7
 Iseman [21] 18:16, 18; 51:10; 63:4, 11, 24; 77:23; 93:10; 98:11; 101:9; 109:4; 167:8; 184:24; 189:11; 190:5; 191:24, 25; 197:20; 206:16; 236:8; 239:11
 isolate [9] 23:17; 24:18, 20, 24; 26:6; 115:13; 123:14, 20; 155:19
 isolated [1] 130:18
 isolates [2] 69:20; 150:10
 Isoniazid [1] 24:13
 isoniazid [22] 55:19; 56:7, 13, 16; 58:4, 19; 77:24; 95:6; 104:14; 105:6; 109:4, 11, 20; 124:2; 159:19; 163:2, 5, 9, 16; 179:15, 16, 20
 Israel [1] 5:9
 issue [25] 6:1; 10:22; 60:25; 70:4; 73:5; 101:18; 110:6; 117:12, 14; 119:21; 141:4; 142:5; 145:20; 160:9, 14; 201:16; 206:25; 207:11, 18; 208:14, 23; 224:4; 227:9; 240:23; 244:14
 issues [33] 9:13; 12:13; 14:12; 49:13; 50:8; 54:15; 59:16; 92:2; 95:2; 109:25; 116:22; 124:12; 145:10, 12, 23, 25; 168:7; 182:22; 194:24; 198:5; 206:1, 11, 16; 207:10; 208:21; 209:21; 213:13; 214:10; 221:16; 222:21; 223:8; 234:8; 240:5
 it'll [1] 114:22
 itching [1] 48:16
 item [2] 114:5; 144:5
 iteration [1] 30:7
 ITT [14] 25:25; 26:4, 8, 9, 17; 28:23; 29:13; 31:3, 6, 19; 36:4; 66:7; 120:2; 129:16

- J -

jail [1] 90:8

Jefferson [1] 5:13
 Jersey [2] 65:1, 3
 Jewish [2] 18:20; 64:18
 Jim [1] 5:15
 job [2] 200:20, 22
 John [10] 4:16; 5:6; 6:14; 65:4; 178:14; 187:7; 189:6; 218:11, 17; 223:9
 jokes [1] 168:14
 Joseph [1] 4:22
 Journal [2] 146:12; 147:15
 Joyce [3] 5:19; 114:6; 223:13
 judge [1] 148:18
 judgment [1] 47:13
 Judith [2] 5:4; 107:25
 July [2] 22:25; 35:6
 jump [1] 217:3
 jumping [1] 72:25
 June [1] 17:19
 justified [1] 217:23
 Juzar [1] 64:14

- K -

K-19 [2] 110:19; 113:17
 K-22 [3] 111:15, 16
 K-25 [1] 113:3
 Kaplan-Meier [2] 127:15; 129:20
 Kaplan-Meiers [2] 122:4; 198:1
 Karnofsky [1] 26:20
 keep [9] 9:7; 12:21; 78:18; 93:18; 179:17; 200:18; 205:25; 229:12; 244:11
 keeping [1] 205:14
 KENNY [2] 97:1, 5
 Kenny [2] 64:8; 97:5
 KEUNG [1] 108:3
 Keung [1] 108:3
 key [1] 183:16
 kidneys [1] 177:4
 killed [1] 57:22
 Killing [1] 56:14
 killing [1] 57:7
 kills [1] 13:22
 kilogram [1] 179:18
 kinds [5] 68:5; 74:4; 76:13; 206:22; 221:24
 kinetics [4] 112:25; 113:11, 13; 231:2
 KMs [1] 122:4
 knowing [5] 99:3; 173:23; 202:13; 216:15, 22
 knowledge [3] 97:24; 167:16; 218:22
 knowledgeable [2] 94:20; 233:14
 KORVICK [5] 5:19; 114:8; 136:20; 142:4; 143:21
 Korvick [4] 5:19; 114:6; 130:9; 136:19
 Kumi [1] 114:19
 Kuzick [1] 109:22

- L -

label [13] 12:16; 22:16; 104:10; 115:14; 180:22; 182:1; 211:10; 213:14, 15; 216:18; 217:20; 226:20; 238:5
 labeling [6] 12:22; 63:9; 73:1;

181:7; 210:17; 228:2
 laboratories [1] 27:24
 Laboratory [1] 64:18
 laboratory [2] 49:20; 61:9
 laborious [1] 226:13
 lack [2] 168:13; 169:25
 Ladies [1] 51:11
 ladies [1] 19:9
 Lady [1] 13:4
 laid [1] 156:15
 language [1] 63:8
 large [6] 16:8; 17:7; 22:11; 105:19; 141:25; 230:11
 largely [5] 57:3; 58:11; 141:7; 145:7; 177:11
 larger [2] 189:11; 222:19
 largest [2] 55:12; 91:3
 Last [1] 172:7
 last [18] 57:18; 60:2; 75:18; 87:1; 110:11; 121:1, 7, 8; 133:7; 135:3; 153:13; 154:20; 166:21; 167:7; 169:3, 13; 170:13
 lasting [3] 19:23; 24:7, 8
 Lastly [2] 6:23; 240:1
 late [22] 40:9, 12; 41:17, 22, 24; 42:6, 12; 43:8, 16, 19; 44:7, 13; 59:25; 66:6; 68:15, 20; 93:16, 20; 100:5, 8; 165:19; 205:19
 latter [1] 223:18
 Laughter [9] 143:3; 144:12; 168:17; 176:6; 202:3; 214:2, 14; 229:20; 234:1
 lead [3] 78:15, 20; 114:6
 leading [4] 26:3; 56:5, 12; 118:17
 leap [1] 211:22
 leaps [1] 195:21
 learned [1] 239:3
 learning [1] 237:10
 leave [7] 90:11; 180:17; 183:12; 197:23; 213:7; 220:8; 223:7
 leaving [1] 9:1
 Lee [1] 64:25
 legitimate [1] 12:2
 length [3] 166:24; 171:2; 214:11
 Leonid [1] 64:17
 lesser [4] 76:11; 92:22; 198:9; 243:8
 level [4] 53:17; 135:22; 151:10; 218:25
 levels [5] 48:1; 75:23; 95:8; 99:24; 235:24
 liberal [1] 235:13
 licensure [1] 223:2
 lie [1] 127:18
 life [5] 10:4; 17:4; 160:14; 178:10; 236:4
 light [2] 168:14; 200:7
 lights [2] 138:2; 158:13
 liked [1] 202:7
 likelihood [3] 214:20; 238:3; 242:12
 limit [6] 23:13, 15; 30:24; 60:23; 181:6; 241:20
 limitations [3] 185:5, 6, 16
 limited [2] 82:17; 208:8
 limiting [1] 53:8

limits [2] 187:8, 10
 line [5] 164:10; 171:5; 196:3;
 198:13; 241:6
 lines [5] 21:8; 56:24, 25;
 168:21; 243:12
LIPSKY [21] 5:15; 103:22;
 105:1; 106:3, 8, 13, 16; 107:2,
 6, 10, 14, 18; 109:1, 17;
 162:17; 163:4, 18, 21, 25;
 203:10; 234:16
Lipsky [7] 5:15; 102:15;
 103:21; 162:16; 203:9; 212:14;
 234:15
 list [1] 180:19
 listed [7] 49:7; 122:7; 138:22;
 145:11, 13; 157:12; 211:12
 listen [1] 174:1
 listening [1] 100:22
 listing [1] 91:4
 lists [1] 102:18
 literature [8] 11:19; 12:4;
 17:20; 97:8; 101:13; 116:9;
 151:19; 159:17
 liters [2] 111:4, 22
 live [1] 193:12
 liver [1] 179:20
 load [2] 34:14; 74:23
 loaded [1] 78:24
 loads [1] 227:18
 local [3] 55:11, 25; 56:2
 located [1] 55:9
 log [2] 108:20; 130:1
 logically [1] 106:8
 logistical [1] 196:6
 logistics [1] 230:17
 London [1] 170:16
 long-term [1] 14:23
 longest [1] 129:22
 looks [7] 91:13, 15; 104:2, 7;
 107:19; 141:14; 193:22
 lose [2] 90:15; 176:9
 loss [10] 27:6; 124:14; 125:11,
 15; 128:6, 8; 138:8; 139:15;
 143:12; 178:10
 lost [9] 94:11; 120:10, 23;
 124:25; 127:20; 140:8; 142:20,
 23; 211:2
 lot [27] 12:24; 67:17; 72:14,
 15; 75:19; 79:7; 105:4, 22;
 121:1; 142:22, 23, 24; 146:4;
 160:23; 168:22; 188:3; 189:17;
 198:25; 199:4; 213:25; 218:16;
 226:23; 232:20; 235:6; 240:12;
 242:7
 lots [2] 222:21; 232:14
Louisiana [1] 64:15
 low [42] 33:10; 37:18, 25;
 38:6, 14, 23; 41:3, 10, 23;
 42:1, 8, 20; 43:6, 14, 23; 44:5,
 10, 12, 20; 50:9; 67:7, 18, 20;
 68:13, 16, 19, 21, 23, 25; 69:2,
 4; 77:16, 21; 88:8; 98:3, 17;
 105:20; 134:18; 151:12; 155:6,
 7; 172:8
 lower [14] 20:9; 68:14; 127:1,
 2, 5; 131:16; 133:9; 140:19;
 151:1, 8; 156:1; 209:16; 239:6;
 241:19
 lowest [4] 44:23; 85:20, 23;
 135:15
 lump [1] 142:10

lumped [1] 143:6
 lunch [2] 164:10, 14
 lunchtime [1] 204:11
Lung [1] 172:16
 lung [6] 34:12; 101:24;
 176:21, 25; 177:10, 12
 lungs [1] 177:4
 lymph [1] 72:7
Lynch [4] 34:1; 75:8; 101:15,
 22

- M -

MAC [6] 96:3, 11, 15, 21;
 153:1; 167:13
 macho [1] 225:3
Madras [1] 109:6
 magnitude [4] 14:7; 30:15;
 141:21
 main [2] 98:9; 229:21
 mainly [5] 51:18; 56:15;
 67:24, 25; 69:8
 maintain [2] 45:25; 243:5
 maintained [1] 171:22
 major [13] 11:24; 13:12;
 15:13; 23:16, 23; 51:19; 58:21;
 62:6; 90:23; 98:23; 169:11, 16;
 172:17
 majority [3] 116:9; 122:9;
 213:10
 male [8] 33:8; 76:12; 92:17;
 111:11; 153:7; 154:7; 198:24;
 225:3
 males [5] 23:7; 27:3; 33:16,
 19; 111:1
 manage [2] 14:14; 232:12
Management [1] 64:11
 manager [1] 114:18
 managing [2] 232:9, 10
Mann [2] 114:15, 16
 manner [2] 16:12; 57:15
 manufactured [1] 17:21
 manufacturer [1] 17:23
March [1] 17:11
 margin [6] 187:1, 13, 19;
 194:17; 219:15; 228:24
Marianne [1] 114:16
Mario [1] 74:7
Marion [26] 4:7; 11:13; 13:8,
 18; 15:22; 16:5, 14, 22; 17:1,
 23; 18:11; 19:20; 46:5; 51:13;
 63:25; 64:24; 69:25; 95:25;
 97:5; 99:5; 108:4; 169:2;
 170:17, 18; 171:20; 244:19
Mark [7] 5:20; 7:14; 64:2;
 81:25; 95:24; 168:5; 223:24
 marked [1] 43:13
 marker [2] 10:7; 59:20
 markers [1] 221:7
 market [5] 171:7, 15; 190:9;
 222:24, 25
 marketed [1] 19:25
 marketing [5] 171:10; 221:4,
 14; 229:9; 240:4
 match [1] 123:17
 matched [1] 153:20
 material [3] 8:9; 141:12;
 204:11
 materials [1] 115:19
 matrix [1] 179:15
 matter [2] 113:24; 192:20

matters [2] 6:15; 87:25
 mature [2] 229:22; 230:5
 maturing [1] 234:3
 maximizes [1] 187:18
 maximum [6] 21:2, 7; 22:3, 6;
 85:11; 140:3
Mayer [1] 64:22
Mayo [2] 5:16; 236:16
MCCLS [1] 123:11
McMaster [1] 114:20
MDR [1] 166:13
 meal [1] 227:2
 mean [34] 34:9; 39:1, 10, 12,
 14, 16; 74:11; 80:24; 87:10;
 95:4; 104:16; 105:6; 106:13;
 107:14; 155:5; 175:9, 18;
 177:21; 192:21; 193:9, 17;
 194:2, 4; 202:15; 205:4; 209:8;
 215:16; 223:24; 228:21;
 229:11; 236:5; 241:25; 242:2,
 4
 meaningful [4] 127:17; 183:1;
 207:20; 230:8
 means [9] 52:5; 130:12, 15;
 131:4; 175:1; 176:1, 3; 235:1;
 244:9
 meant [2] 32:17; 35:13
 meantime [1] 84:3
 measure [1] 195:8
 measured [4] 111:18, 19;
 129:25; 133:9
 mechanism [3] 20:1; 156:15;
 188:12
 mechanistic [1] 188:10
 median [3] 47:2, 7, 10
 mediated [1] 55:25
Medical [8] 5:9, 10; 18:10, 20;
 64:15, 18; 65:1, 3
 medical [1] 169:9
 medication [2] 26:1; 47:1
 medications [13] 33:11, 18;
 34:20; 40:20, 24; 45:4; 46:1;
 51:3; 52:22; 77:21; 105:11, 23;
 215:7
Medicine [5] 18:21, 22, 23;
 64:20; 147:15
 medicine [7] 64:15; 65:2, 5;
 174:23; 234:20
 medium [3] 20:7; 68:12;
 243:6
 meet [3] 169:9; 180:11; 230:7
 meeting [16] 6:2, 4, 6, 12; 8:5;
 15:24; 153:14; 154:21; 164:13;
 166:6; 167:15; 170:16; 171:21;
 172:2; 244:20, 22
 meetings [1] 166:14
 member [2] 167:22; 232:25
 members [24] 4:6, 12; 7:19;
 20:2; 65:10, 12, 14; 114:10,
 14; 138:4; 164:9; 173:8;
 183:12; 190:2; 197:9; 204:8;
 206:2; 207:16; 212:13, 22;
 213:5, 7; 244:17
 men [10] 20:14; 80:13;
 111:10, 22; 112:2, 10, 22;
 233:1, 4
 mention [6] 8:25; 96:1;
 149:25; 154:19; 183:6; 208:19
 mentioned [18] 77:15, 23;
 * 84:19; 130:9; 153:8; 155:15;
 169:8; 181:19; 188:3; 189:6;

191:25; 195:4; 202:22; 206:17;
 207:9; 239:11, 24
 mergers [2] 170:12, 21
 merits [1] 165:22
Merrill [2] 170:16, 17
 message [1] 169:20
 metabolic [2] 55:10; 79:8
 metabolism [4] 21:23; 55:10;
 94:22; 109:22
 metabolite [1] 15:4
 method [1] 30:13
 methodologies [1] 14:14
 methodology [1] 75:7
 methods [1] 30:3
MIC [6] 20:5; 21:11, 12; 95:8;
 97:7; 107:1
Michael [4] 18:15; 51:9;
 60:17; 64:8
 micro [1] 55:23
Microbacteriology [1] 64:18
 microbacterium [1] 101:24
 microbial [1] 55:10
 microbiologically [1] 15:4
 microbiologist [1] 64:9
Microbiology [3] 64:20, 22,
 23
 microbiology [2] 19:14;
 114:19
 micrograms [1] 97:8
 microphage [1] 56:1
 microphone [2] 97:4; 176:4
MICs [3] 21:7; 96:6; 97:2
 mid-1980s [1] 167:8
 middle [2] 81:10, 15
Mike [6] 77:23; 89:23; 97:5;
 109:4; 167:8; 176:2
 mild [1] 48:16
 milestone [1] 35:9
 milieu [1] 56:1
 milligram [11] 19:25; 21:1;
 25:5, 13; 45:18; 46:19, 20;
 47:3; 50:14; 108:7, 8
 milligrams [12] 20:13, 14;
 46:14, 23; 47:7, 10; 78:12;
 104:13, 14, 15; 160:2; 179:18
 millimeter [1] 144:11
 million [7] 13:24, 25; 145:2;
 171:7, 12, 15; 172:13
 mind [8] 9:7; 197:10; 198:3,
 19; 199:16; 200:10; 203:20;
 224:18
 minds [1] 12:22
 mingling [1] 192:4
 minimize [3] 187:19; 207:4;
 242:2
 minimum [3] 45:9; 217:6;
 226:8
Minnesota [1] 5:16
 minus [6] 29:25; 30:25; 32:1;
 126:8, 11; 127:9
 minutes [2] 151:15; 173:8
 miss [2] 58:3; 219:14
 missed [7] 57:16; 75:11;
 97:11; 99:19; 110:3; 239:18,
 19
 missing [17] 29:4; 30:3, 4, 6,
 7, 10, 14; 83:18; 84:2, 14, 21;
 85:9, 15; 88:15; 138:14;
 139:19; 142:10
 mistake [1] 153:16
Mitchison [3] 55:3; 57:4, 14

mitigate [1] 32:17
 mix [1] 26:24
 mixed [1] 192:15
 mL [1] 97:9
 Mobile [1] 4:17
 mode [1] 154:2
 model [12] 52:10; 55:4, 5;
 56:12, 18; 57:14; 60:17; 61:6;
 63:4; 76:19; 225:8; 241:5
 modeled [1] 240:25
 modeling [6] 53:12; 195:23;
 196:10; 230:10, 19; 236:1
 models [4] 53:11, 22; 57:6;
 230:24
 moderate [9] 19:1; 38:4, 9;
 41:2, 6, 23; 42:20; 67:7, 18
 modern [1] 53:14
 modest [2] 176:18; 177:16
 modification [2] 67:10;
 195:25
 modified [10] 25:24; 26:4, 8,
 9; 28:23; 36:3; 55:3; 102:2;
 120:4; 179:15
 modify [1] 230:1
 modifying [1] 79:23
 molecular [3] 19:24; 156:8;
 202:1
 moment [9] 81:6; 82:14; 83:1;
 114:13; 120:22; 150:1; 210:2;
 231:8; 240:7
 moments [1] 7:25
 money [2] 160:5; 201:3
 monitor [1] 233:8
 Monitoring [1] 149:24
 monitoring [4] 81:1; 145:16;
 173:14; 239:25
 nonresistance [7] 152:7;
 154:15; 155:15, 17; 156:7;
 162:1, 23
 monoresistant [17] 151:17,
 25; 152:3, 10, 19, 21, 25;
 153:4, 15, 17, 21; 154:5, 10;
 157:10, 21, 23; 158:7
 monotherapy [2] 78:14;
 211:9
 month [4] 45:15; 147:19;
 179:9; 218:7
 months [68] 10:14; 11:14, 22,
 25; 22:22, 24; 24:7, 8, 10;
 27:17; 28:14, 15; 29:20; 39:21,
 24; 40:4; 43:10; 46:19, 20, 24;
 53:17, 18; 54:7, 23; 57:19, 21,
 25; 59:20; 60:2, 8; 77:6, 7;
 93:12, 13, 19; 105:25; 106:20;
 110:2; 116:11, 13; 121:10,
 23, 24, 25; 122:10, 13; 129:7,
 8, 9; 147:7, 16, 22, 23, 24;
 148:1; 149:13, 14; 154:23;
 155:2, 10, 16; 159:20; 160:24;
 181:12; 186:4, 10, 25
 mopping [1] 78:22
 morbidity [2] 11:6; 178:10
 morning [11] 13:5; 19:9;
 51:12; 65:16; 75:14, 15; 86:11;
 138:21; 164:7; 201:11; 210:15
 mortality [2] 11:7; 52:1
 mostly [3] 119:15; 153:6;
 188:21
 motivates [1] 88:19
 mount [1] 194:4
 mouth [1] 201:3

Move [1] 68:9
 move [4] 68:10; 180:3;
 183:13; 243:11
 moves [1] 239:1
 MS [2] 5:11, 25
 MTB [1] 156:18
 multi-center [2] 22:17; 172:19
 multi-drug [7] 19:17, 18;
 22:17; 23:19; 32:23; 34:24;
 53:3
 multi-racial [1] 26:23
 multifactorial [1] 244:14
 multiple [8] 11:4; 20:13;
 21:18; 33:6; 46:18, 19; 47:6;
 50:3
 multiplication [1] 55:14
 multiplying [1] 162:24
 multivariate [7] 76:17, 19, 25;
 77:10; 80:21; 224:15; 229:4
 MURPHY [10] 5:21; 143:4, 18;
 180:8; 210:13; 212:3; 215:11,
 17, 20; 243:23
 Murphy [6] 5:21; 180:7;
 210:1, 10; 213:12; 240:16
 mutants [1] 156:22
 mutation [1] 156:23
 mutations [4] 157:3, 8, 16, 17
 Mya [1] 99:4
 mycobacteria [2] 170:5;
 211:23
 mycobacterial [4] 167:17, 25;
 170:21; 211:20
 Mycobacteriology [1] 18:19
 mycobacterium [3] 46:22;
 49:23; 211:6
 myself [5] 69:6; 114:15;
 197:24; 202:14; 204:7

- N -

name [2] 95:23; 204:2
 namely [1] 221:11
 National [3] 18:20; 64:18;
 65:1
 naturally [1] 156:12
 nature [5] 14:7; 19:14; 49:2;
 92:13; 236:18
 NDA [7] 8:19; 17:1, 6, 8, 16;
 58:22; 166:19
 needs [3] 169:9; 174:19;
 191:19
 negative [49] 26:4; 27:19;
 28:5, 7, 18; 30:5; 38:25; 39:21,
 24; 57:20; 78:19; 90:18, 23;
 93:18; 118:8, 10, 14, 17, 20,
 23; 119:4, 22; 121:2; 125:5;
 126:22; 127:24; 128:2; 130:13,
 18, 25; 131:21, 25; 132:12, 25;
 133:3; 140:24; 143:16; 146:13,
 20, 24; 147:5, 13; 148:15, 19;
 159:23; 172:3; 216:16; 236:25
 negatives [6] 118:18, 22;
 130:22; 132:5, 6, 14
 negativity [3] 54:22; 56:20;
 93:13
 Neil [1] 144:6
 nelfinavir [1] 160:1
 net [2] 60:4; 178:10
 nice [8] 139:10; 140:13, 14;
 143:6; 186:11; 234:23; 236:12,
 13

nicely [1] 198:14
 nicer [1] 139:24
 niceties [1] 175:22
 niggling [1] 197:9
 NIH [3] 11:16; 37:23; 166:15
 Nine [1] 119:18
 nine [18] 58:23; 66:5; 120:15;
 121:7; 122:16; 125:4; 129:11;
 132:22, 23; 133:2, 3; 148:2;
 154:2; 155:2, 16; 159:20;
 160:24; 186:25
 nine-month [3] 94:9, 12;
 155:17
 NNRTIs [1] 227:20
 nodes [1] 72:7
 non [2] 112:25; 233:10
 non-egg [1] 20:7
 non-HIV [2] 226:20; 228:3
 non-nucleocides [1] 232:5
 non-rifampin [1] 159:15
 non-rifamycin [29] 33:10, 17;
 34:19; 37:12; 38:20; 40:12, 20,
 24; 41:17, 25; 42:7, 22; 43:5;
 44:6, 20, 23; 45:4, 9; 46:1;
 51:3; 63:6; 69:2; 71:6, 14;
 77:21; 87:15; 105:11, 22;
 145:19
 non-rifapentine [2] 62:25;
 76:10
 non-veterans [1] 182:19
 nonadherence [10] 51:18;
 60:10; 66:18, 23; 67:3; 69:10,
 13, 16; 76:9; 78:1
 Noncompliance [2] 36:2, 11
 noncompliance [18] 33:17;
 35:4; 36:7, 14, 15, 19, 21, 25;
 37:3, 4, 5, 8; 67:17; 70:4;
 78:20; 87:8, 18; 231:15
 noncompliant [3] 124:3;
 136:3, 5
 nonconversion [1] 77:2
 nonconvertors [3] 131:13,
 17; 140:2
 nongovernmental [2] 172:17;
 179:3
 noninfectious [1] 53:5
 nonsuccess [2] 31:14, 15
 nonsuccesses [4] 28:1; 31:3,
 9; 83:24
 nonunilateral [1] 102:24
 noon [1] 164:13
 normal [8] 21:24; 23:13, 15;
 111:5; 112:13; 175:15; 177:3,
 8
 normally [2] 140:5; 212:4
 normals [1] 112:8
 North [11] 13:7; 16:9; 18:10;
 27:25; 64:11; 92:9, 16, 18, 22,
 25
 notable [1] 148:2
 notably [3] 51:21; 169:13;
 171:20
 Note [2] 31:4; 131:15
 note [7] 9:21; 27:21; 58:6;
 117:9; 119:20; 122:11; 125:10
 noted [5] 7:8; 21:14; 41:1;
 44:9; 47:15
 notes [2] 86:8; 125:19
 noteworthy [1] 32:8
 Notice [2] 126:11; 133:5
 notice [4] 125:12; 129:9;
 134:9; 231:25
 noting [1] 132:8
 notion [1] 94:25
 notoriously [1] 75:5
 notwithstanding [1] 12:3
 novel [1] 167:2
 nowadays [1] 158:23
 Number [2] 58:14; 68:8
 number [64] 9:5; 10:25;
 22:15; 25:19; 31:4, 6, 9; 32:16;
 33:10; 37:21; 38:19, 20; 39:1,
 7; 40:20; 41:24; 42:7, 22;
 43:5; 44:5, 20, 23; 45:9; 50:2;
 55:12; 57:20; 67:8, 13, 16;
 83:25; 84:1; 86:3; 100:25;
 104:16; 105:19; 108:24; 113:5;
 116:2;
 118:19; 121:6; 128:13; 129:6,
 15; 133:22; 134:17; 141:11;
 144:17; 145:15; 149:25; 150:1;
 166:14; 168:10; 169:6, 18;
 171:3; 181:3; 186:19; 187:3;
 197:6; 219:6, 10; 225:17;
 241:23; 243:4
 numbers [19] 69:2; 90:14;
 91:12; 92:11; 93:5, 6, 22;
 97:15; 110:7; 133:19, 20;
 140:6, 18; 141:25; 156:1, 2;
 176:9; 222:19; 239:16
 numerator [1] 139:4
 nursing [1] 24:3
 NYU [2] 144:7; 153:13

- O -

O'BRIEN [2] 165:12; 168:18
 O'Brien [3] 165:7, 13; 173:21
 object [1] 160:24
 objective [1] 112:19
 observation [1] 94:4
 observations [2] 115:5; 184:8
 observe [1] 131:5
 observed [24] 10:23; 14:15;
 15:15; 32:17; 43:22; 52:4, 9,
 12; 63:14; 70:3, 9, 11; 115:25;
 125:11, 14; 127:22; 128:3, 10;
 140:4; 215:3; 216:3; 218:19;
 219:13; 242:24
 obtained [3] 6:17; 20:6; 112:1
 obvious [2] 157:3; 220:5
 Obviously [2] 152:1; 179:9
 obviously [7] 9:7; 98:9;
 159:22; 210:4, 16; 230:2;
 244:13
 occasionally [1] 204:7
 occasions [1] 168:12
 occur [9] 48:25; 53:2; 109:21;
 122:9; 157:5; 188:23; 201:1;
 221:17, 18
 occurred [16] 15:25; 44:16;
 47:20; 48:4, 6, 8; 49:4; 116:10;
 121:9; 122:12; 150:10; 157:17,
 22; 170:12; 188:21; 211:18
 occurrence [1] 47:17
 occurring [3] 28:9; 125:18;
 156:13
 odds [1] 220:2
 offer [2] 216:2; 219:24
 offering [1] 59:12
 offers [2] 50:23; 53:23
 Office [1] 6:18

official [1] 184:5
 offset [2] 179:19; 196:6
 Oh [3] 102:21; 103:13; 231:6
 Okay [24] 70:12; 73:8; 77:22;
 80:9, 20, 23; 82:23; 86:12;
 93:9; 99:15; 100:11, 14;
 103:18; 113:20; 114:13;
 144:13; 145:5; 153:13; 156:4;
 165:3; 175:3; 180:18; 213:3;
 226:17
 okay [3] 183:9; 206:7; 230:16
 old [1] 163:10
 ominously [1] 52:1
 omitted [2] 30:6, 9
 ones [7] 68:9; 78:25; 84:8;
 98:14; 99:22; 225:8; 229:24
 ongoing [4] 30:8; 32:13; 92:4;
 200:6
 open [7] 22:16; 65:9; 104:10;
 165:4, 6, 11; 173:3
 operating [1] 189:15
 opinion [4] 63:11, 20; 145:7;
 184:4
 opinions [2] 183:13; 207:16
 opportunities [1] 179:21
 opportunity [3] 94:3; 215:17;
 239:7
 opposed [3] 87:21; 132:13;
 134:6
 opposite [1] 85:10
 optimal [5] 55:15; 61:2, 19;
 145:14; 172:20
 option [3] 159:14, 15, 25
 options [2] 61:19; 159:8
 oral [1] 21:1
 orange [2] 47:16; 84:25
 order [11] 4:4; 36:13; 37:11;
 42:10; 55:19; 65:14; 115:24;
 121:12, 14; 226:13; 230:7
 organism [3] 100:13; 156:25;
 231:1
 organisms [8] 46:22; 57:8,
 24; 78:22; 93:25; 156:11;
 162:25; 195:23
 Organization [6] 14:9; 52:11;
 65:7; 145:1; 169:14; 178:17
 organization [2] 172:17;
 179:25
 organizations [1] 200:16
 organs [1] 177:7
 original [1] 192:17
 Originally [1] 55:25
 originally [3] 8:10, 17; 12:11
 orphan [2] 17:17, 18
 ought [7] 211:11; 212:1;
 217:19; 221:3; 231:24; 232:19;
 233:2
 ourselves [6] 190:1; 193:17;
 200:14, 19, 21; 212:13
 out-patient [1] 186:6
 outbreaks [1] 166:13
 outcome [15] 9:22; 10:8;
 27:16; 58:16; 59:9; 116:22;
 117:17; 118:3, 4; 124:6, 21;
 172:2, 3; 187:5; 195:8
 outcomes [13] 29:19; 32:21;
 115:1; 116:6; 117:21; 119:20;
 120:8, 21; 121:5, 13; 122:15;
 189:14; 239:9
 outline [2] 173:11; 175:20
 outlined [3] 63:13, 15; 183:23

outnumber [2] 135:14, 19
 outstanding [1] 191:10
 outstrip [1] 230:18
 outweigh [1] 205:20
 oval [1] 55:13
 Overall [2] 58:9; 117:22
 overall [13] 10:16; 37:2;
 60:22; 80:12; 111:3; 135:11;
 187:5; 195:3; 198:15; 205:5;
 206:7; 214:21
 overcame [1] 204:6
 overcome [1] 78:3
 overdoses [2] 48:9; 49:7
 overdosing [1] 49:17
 overseas [1] 9:15
 overwhelmed [1] 178:20

- P -

p.m. [5] 164:8, 11, 14; 165:2;
 244:21
 package [3] 87:7; 214:16;
 233:16
 packet [1] 101:3
 page [10] 77:4; 80:10; 90:2;
 91:12; 100:16; 102:18; 104:4,
 25; 105:1; 108:2
 paid [2] 51:2; 187:15
 pains [1] 202:25
 pair [2] 157:14, 15
 pairs [1] 157:6
 pan [1] 11:22
 panel [9] 4:5; 13:9; 63:20;
 65:14; 142:17; 197:9, 23;
 206:2; 232:25
 paper [3] 58:20; 60:16;
 190:22
 par [1] 94:12
 paradox [1] 54:19
 paradoxes [1] 199:24
 parallel [1] 104:10
 parameter [2] 27:17; 29:18
 parameters [1] 28:11
 Parklawn [1] 6:19
 Part [1] 213:16
 part [17] 6:2; 10:2; 32:13, 23;
 34:24; 69:10; 70:9, 12; 76:23;
 87:11; 165:10; 174:4; 206:8;
 207:6; 210:9; 213:16; 237:15
 PARTICIPANT [1] 104:25
 participant [1] 7:5
 participants [9] 6:7, 10, 11;
 7:6, 9, 21; 65:21, 23, 25
 participate [2] 6:15; 168:16
 participated [1] 170:15
 participating [1] 6:21
 partly [1] 79:18
 partnership [1] 169:1
 parts [1] 19:13
 Parviz [1] 64:6
 PAS [3] 109:7, 11; 197:19
 pass [1] 71:19
 Pathogens [1] 15:23
 pathogens [1] 168:2
 patient [54] 9:19, 20; 12:18;
 14:18, 20; 24:13, 18, 21; 28:2;
 31:16; 38:2; 47:7, 11; 70:6;
 79:1; 89:11; 90:1, 6, 7, 11;
 92:13; 110:24; 114:25; 118:10;
 119:3, 6; 123:13, 16, 21;
 152:9, 12, 25; 155:18, 19;

159:8; 175:1, 2, 18; 176:10,
 19; 191:25;
 192:1; 197:7; 198:16, 21;
 199:11, 14; 213:10, 13; 232:8;
 233:16; 234:7; 236:23; 243:4
 Patients [5] 23:8; 52:22;
 149:5; 150:18, 23
 pattern [5] 24:24; 43:3;
 131:23; 132:8, 19
 patterns [2] 37:16; 77:12
 Paul [1] 5:17
 pay [4] 160:5; 168:15; 175:24;
 214:6
 pediatric [2] 20:18; 46:15
 pentoxifyline [1] 145:22
 people [31] 13:22, 24; 63:25;
 103:11; 130:17; 142:6, 19;
 145:2; 160:14, 21; 163:6;
 171:10, 16; 172:13; 175:16;
 178:3, 8, 20; 192:4; 198:4;
 202:25; 204:19; 209:22;
 219:13, 21; 226:11; 231:10,
 18; 235:16; 241:14; 242:5
 percentage [1] 43:25
 percentages [3] 103:1; 125:8;
 128:13
 perception [1] 9:1
 perceptions [1] 9:19
 perfect [1] 8:13
 perfectly [1] 161:7
 performance [1] 60:11
 performed [4] 27:16, 23;
 29:13; 213:17
 period [27] 19:2; 22:22; 24:6;
 28:10, 22; 59:25; 65:9; 95:9;
 97:16; 121:20; 122:7, 23;
 123:25; 124:24; 152:5; 153:23;
 159:18; 166:16; 168:8; 176:20;
 179:10; 205:2; 219:18; 232:24;
 241:10; 242:10
 periods [6] 48:14; 129:7, 11,
 15; 186:5; 241:11
 permits [1] 6:15
 permitted [2] 149:18; 212:13
 permutations [1] 128:5
 Perriens [1] 147:14
 persist [2] 78:13; 170:1
 persistent [2] 57:7; 78:22
 persisting [1] 93:25
 person [6] 23:19; 144:10;
 200:11; 218:6; 224:25; 226:12
 personal [2] 160:16; 166:1
 personally [6] 190:3; 206:4;
 207:15; 215:10, 19; 244:16
 personnel [1] 216:4
 persons [8] 144:15, 22;
 145:6; 149:18; 154:11; 159:23;
 186:22; 218:12
 perspective [8] 9:8; 12:15;
 51:14; 101:19; 166:2, 5; 169:6;
 178:17
 pertinent [1] 110:6
 perturbations [1] 140:21
 pharmaceutical [1] 169:18
 Pharmaceuticals [1] 13:17
 pharmacodynamic [1]
 234:10
 pharmacodynamics [1]
 106:16
 pharmacokinetic [7] 47:5;
 75:20; 95:11; 112:18, 23;

162:4; 232:22
 pharmacokinetics [13] 19:15;
 20:10, 11, 20; 21:17, 19, 20;
 22:2; 33:4; 75:22; 79:5; 95:14;
 222:13
 pharmacologic [1] 62:5
 pharmacological [1] 13:13
 Pharmacology [2] 4:23; 5:16
 pharmacology [4] 47:4; 50:8;
 103:25; 104:11
 Phase [4] 166:23, 24; 170:18,
 20
 phases [5] 28:21; 35:3; 36:5;
 57:11; 238:25
 phenomenon [3] 51:20;
 56:18; 203:16
 phenotype [1] 109:5
 Phil [2] 4:18; 218:17
 Philadelphia [3] 5:14; 202:15,
 16
 philosophy [1] 14:18
 phonetic [8] 99:4; 101:24;
 108:15; 109:22; 152:23;
 167:12; 235:23
 physical [1] 74:5
 physician [3] 198:10, 21;
 225:4
 physicians [1] 160:24
 physiologic [1] 118:9
 pick [7] 99:2, 17, 23; 164:10;
 198:20; 215:18; 244:4
 picked [3] 99:3; 184:14, 16
 picking [1] 244:11
 pictorial [1] 77:9
 picture [1] 205:17
 pieces [1] 69:8
 pink [1] 55:13
 pipeline [1] 167:3
 pivotal [8] 16:8; 17:7; 18:12,
 16; 19:19; 22:11, 13; 53:25
 PK [9] 50:8; 95:11; 110:12, 16,
 22; 112:2; 113:16; 208:11;
 238:15
 place [2] 222:1; 230:3
 placebo [1] 193:14
 plan [4] 16:7; 22:21; 52:16;
 175:21
 planned [3] 81:6; 162:4;
 239:14
 planners [1] 14:13
 planning [1] 238:24
 plans [2] 80:23; 173:12
 plasma [2] 20:24; 21:10
 play [7] 56:12; 57:7; 189:18;
 194:21; 209:22; 210:10;
 223:11
 player [1] 169:3
 playing [1] 56:5
 Please [3] 97:3; 174:12;
 240:20
 please [29] 65:12; 93:10;
 95:22; 108:13; 111:9; 115:16;
 116:18; 124:11, 22; 125:16;
 126:4; 127:12; 128:9, 16;
 129:5, 17; 130:2; 131:2, 20;
 132:17; 133:13; 134:13; 136:6;
 138:2; 158:13; 180:20; 181:9;
 212:22; 223:6
 pleasure [1] 13:8
 plus [4] 29:25; 35:23, 24;
 45:10

pneumonic [1] 102:6
 podium [1] 18:25
 poignant [1] 176:7
 point [30] 72:24; 78:10; 81:17;
 85:12, 13; 91:14; 94:7; 95:5;
 9:1; 98:10; 101:2; 116:25;
 35:24; 141:17; 143:16, 17,
 24; 151:3; 155:20; 157:16;
 165:5; 177:3; 187:2; 202:19;
 216:14; 223:19, 23; 227:25;
 234:10
 pointed [1] 77:11
 pointing [1] 189:12
 points [8] 28:25; 97:12, 21;
 142:5; 184:6; 201:10; 235:14;
 240:17
 polymerase [2] 156:17, 19
 polymorphism [1] 109:21
 POMERANTZ [17] 5:12; 98:6,
 22; 99:9, 13, 15; 100:11, 14;
 102:14, 21; 103:5, 16; 158:15;
 160:7; 161:8; 201:25; 202:4
 Pomerantz [5] 5:12; 98:5;
 201:24; 212:15, 24
 pontification [1] 234:19
 poor [8] 18:2; 34:19; 134:21,
 24; 135:2, 9, 16; 229:5
 poorly [1] 204:22
 pop [1] 112:17
 Population [8] 55:13, 18, 22;
 56:8, 10, 13, 15; 57:2
 population [38] 9:20, 21;
 25:25; 26:4, 8, 14, 17; 28:23;
 30:13, 14; 31:6; 36:4; 56:4, 9;
 57:22, 24; 86:22; 92:1; 94:17,
 8; 95:11; 110:12, 22; 112:2,
 8; 113:15; 137:18; 162:25;
 182:8; 189:23; 196:10; 197:2;
 198:25; 209:20; 212:4; 215:4;
 231:19;
 232:22
 population-wide [1] 189:21
 populations [22] 12:18;
 21:21; 55:8; 56:21; 57:10;
 74:13; 78:25; 84:22; 92:13;
 93:22; 95:16; 110:17; 146:9,
 21; 184:23; 185:13; 195:23;
 201:13; 220:25; 228:13;
 233:16; 234:7
 portion [4] 36:23; 86:4, 5;
 230:25
 posed [1] 94:16
 positive [66] 23:9; 24:2; 28:9;
 29:6; 30:10; 32:11; 38:25;
 40:4; 60:2; 66:2; 74:11; 75:19;
 80:6, 8; 82:15; 83:24; 96:10;
 100:4; 108:12; 118:8, 21;
 119:2, 3, 19; 120:16; 121:8;
 122:16; 123:4; 125:3; 127:21,
 25; 130:17; 132:21; 133:1, 4;
 140:24;
 142:10, 11; 144:18; 146:13,
 20, 23; 147:5, 16; 148:3, 22;
 149:2, 17, 21; 151:1; 152:17;
 158:6; 159:24; 160:20; 161:2,
 12; 172:2; 190:14; 192:14;
 14:4; 223:17, 22; 224:10;
 228:9; 231:16; 237:1
 positives [2] 119:22; 131:5
 positivity [1] 96:8
 possibilities [2] 173:23;

211:12
 possibility [5] 60:20; 74:22;
 145:21; 194:13; 219:2
 post [12] 32:19; 66:12; 94:1;
 110:15; 129:7, 24; 141:14;
 142:2; 221:4, 14; 229:9; 240:4
 postulated [1] 116:7
 pot [1] 157:5
 potency [2] 56:22; 61:5
 potent [5] 55:20; 57:19;
 60:19; 79:16; 160:17
 Potential [1] 23:21
 potential [28] 6:11; 15:17;
 32:20; 46:2; 51:4; 52:1, 18;
 62:6; 81:4, 5, 8; 85:10; 90:12;
 112:21; 113:12; 136:13;
 168:23; 170:2, 6; 183:4; 198:9;
 217:16; 219:5, 22; 222:16;
 234:4; 240:6; 242:19
 potentially [8] 53:23; 76:2;
 115:23; 199:13; 200:25;
 218:18; 239:10; 240:23
 potentials [1] 190:6
 power [2] 148:18; 149:1
 practical [3] 92:3; 205:18;
 237:23
 practicality [1] 205:20
 practice [7] 145:8; 174:22;
 194:1; 202:13, 18; 213:20;
 229:25
 practiced [1] 101:22
 practices [1] 202:14
 practitioner [2] 14:22; 15:16
 practitioners [1] 63:9
 pragmatic [1] 224:18
 pre-clinical [1] 19:11
 pre-dose [1] 110:15
 pre-follow-up [2] 126:6, 20
 precedent [1] 141:1
 precedents [1] 197:21
 preceding [1] 211:18
 precisely [1] 158:5
 preclude [1] 6:3
 precluded [1] 223:17
 predecessor [4] 13:17; 64:24;
 113:12; 168:9
 predict [4] 10:8; 21:18; 102:5;
 206:23
 predictable [1] 94:21
 predictably [1] 52:22
 predicting [2] 12:8; 182:25
 predictive [3] 88:11; 225:7;
 237:21
 predictor [1] 33:10
 predictors [4] 32:20; 33:7;
 206:21; 237:19
 predominance [2] 26:23;
 27:2
 predominant [1] 162:13
 predominantly [2] 73:9;
 92:17
 prefer [1] 190:11
 preferable [1] 160:18
 pregnant [1] 24:3
 preliminary [1] 82:13
 prepared [4] 63:23, 25; 64:13;
 174:1
 preparing [1] 8:5
 preplanned [1] 32:19
 preponderance [1] 33:19
 prescriber [1] 199:9

prescriptions [1] 198:12
 presence [1] 162:8
 present [15] 6:10, 11; 13:9;
 18:4, 11; 46:4; 114:14; 115:4;
 152:5; 166:1; 181:13; 182:9;
 186:21; 220:23; 233:13
 presentation [17] 13:2; 18:8;
 19:11; 22:13; 76:14; 77:11;
 84:20; 86:25; 96:18; 114:6, 24;
 123:6; 136:18; 137:24; 141:1;
 144:5; 196:8
 presentations [5] 19:5; 37:14;
 71:21; 167:9; 196:14
 presented [25] 26:18; 33:20;
 35:1; 53:23; 61:11; 74:15;
 86:24; 117:19; 143:20; 153:14;
 161:12; 169:10; 180:13; 182:5;
 185:3; 189:1; 192:9; 195:2;
 196:2, 23; 203:17; 212:7;
 237:12, 18; 238:11
 presenter [1] 51:9
 presenters [2] 138:5; 199:5
 presenting [2] 122:4; 123:3
 presents [13] 20:4, 24; 24:5;
 31:2; 39:1, 19; 46:25; 47:12;
 48:20; 49:2, 12; 185:23;
 186:11
 preserved [1] 160:22
 President [4] 13:6; 18:10;
 64:6, 10
 press [1] 221:17
 pressing [1] 65:13
 presumably [4] 55:24; 56:8;
 81:20; 93:25
 presume [1] 163:21
 pretty [8] 94:12; 128:7;
 195:17; 201:19; 209:14, 15;
 221:12; 225:16
 prevalative [1] 74:11
 prevalent [1] 33:14
 prevent [1] 45:6
 Prevention [3] 6:25; 16:16;
 52:8
 preventive [2] 65:2, 5
 previous [8] 7:11; 61:9; 90:2;
 127:25; 129:19; 132:9; 133:24;
 204:22
 previously [11] 23:8; 49:9;
 58:5; 59:3; 61:21; 121:15;
 126:6; 157:8, 18; 163:17;
 196:25
 Priftin [9] 6:16, 22; 7:2; 13:10,
 12; 17:24; 18:1, 5; 19:12
 Primarily [1] 73:12
 primarily [7] 9:15; 58:17;
 76:9; 92:7; 121:9; 148:14;
 211:22
 primary [12] 27:15, 17; 29:18;
 30:11; 52:13; 62:14; 114:14;
 117:17; 149:15; 152:9; 154:1;
 157:24
 prior [7] 31:8; 96:8; 98:2;
 104:3; 152:19; 154:15; 223:2
 priori [1] 199:9
 prioritize [1] 65:12
 probability [2] 98:3; 243:20
 probe [1] 241:22
 problem [11] 9:3; 84:6, 8;
 98:23; 105:7; 106:3; 142:21;
 163:13; 178:19; 236:17
 problematic [2] 135:25; 220:7

problems [5] 99:16; 136:3;
 188:11; 206:22; 225:15
 proceed [1] 114:23
 process [4] 25:17; 167:24;
 205:5; 235:13
 proclaimed [1] 169:15
 produce [1] 142:14
 produced [2] 17:22; 30:17
 product [13] 12:22, 23; 16:12;
 17:22, 24, 25; 63:8; 167:1;
 171:7, 11; 211:10; 212:1, 4
 productive [1] 98:4
 Products [1] 15:23
 products [5] 7:4, 12; 8:2;
 9:25; 168:3
 Professor [1] 18:22
 professor [4] 64:14, 20; 65:2,
 4
 profile [12] 50:11; 51:6; 62:21,
 23; 110:16; 137:2; 191:16;
 196:1; 208:11; 230:18; 238:15
 profiles [1] 20:25
 program [8] 13:16; 62:12;
 178:5, 6, 9; 187:18; 189:15;
 244:8
 programs [5] 52:19; 60:5;
 62:8; 219:22; 243:11
 progress [2] 166:17; 167:4
 progression [1] 53:4
 progressive [1] 176:24
 progressively [4] 133:16;
 185:25; 186:9; 187:1
 project [1] 114:18
 projected [2] 13:23; 171:11
 projections [1] 14:8
 prolonged [1] 51:25
 promoted [1] 57:24
 promoting [2] 10:9; 169:19
 pronounced [2] 42:5; 112:13
 proof [1] 181:15
 properly [1] 240:3
 property [1] 62:14
 prophylaxis [1] 153:1
 proportion [12] 27:4; 33:15;
 41:16, 23; 42:12, 15, 23; 43:2,
 4, 15; 92:16; 122:12
 proportionally [1] 81:23
 proposals [1] 59:17
 Proposed [1] 15:6
 proposed [5] 34:23; 63:16;
 115:10; 116:2; 242:15
 proposing [1] 181:13
 prospective [2] 154:22; 234:3
 protease [9] 20:22; 145:20;
 159:9; 203:3; 227:10; 232:6,
 15; 235:20; 237:4
 proteases [1] 227:20
 protein [2] 61:3; 156:24
 proteinuria [2] 48:7; 72:15
 Protocol [14] 16:8; 18:12;
 22:14, 21; 59:7; 62:17; 95:12;
 107:22; 110:12, 22; 111:25;
 112:1; 173:16; 198:18
 protocol [31] 22:15; 26:2, 13,
 14; 30:12; 32:20; 35:4, 10, 25;
 36:2, 6; 37:19; 40:18; 62:3;
 65:19; 67:17, 19; 69:14; 70:2,
 12, 18; 75:11; 84:5, 22; 85:1;
 94:11, 12; 110:21; 117:18;
 163:23; 167:11
 prove [2] 81:16; 199:14

Proven [1] 52:20
proven [2] 149:5, 8
provide [16] 12:10; 16:24; 17:14; 18:16; 34:22; 51:14; 72:23; 116:16; 148:16, 17, 25; 172:19; 182:11; 210:17; 211:25
provided [7] 10:1; 63:4, 11; 100:17; 115:18; 188:24; 207:12
provides [1] 183:1
providing [2] 17:12; 233:14
provisions [1] 116:15
psychological [1] 203:16
psychologically [2] 203:25; 204:4
Public [3] 94:8; 148:11; 165:18
public [10] 51:15; 165:6, 11; 173:3; 174:21; 197:4; 198:7, 15; 199:10; 200:16
publicly [1] 16:23
published [7] 20:4; 59:3; 97:8; 123:4; 146:10, 11; 151:23
pull [4] 86:2, 10; 87:3; 139:20
pulling [1] 139:17
Pulmonary [2] 18:22; 149:6
pulmonary [70] 4:11; 12:14; 13:11, 13, 20; 17:19; 18:13; 20:16; 22:18; 23:9; 33:16, 24; 45:21; 46:17; 50:14, 24; 55:16; 61:13; 62:13; 63:22; 64:15; 71:23, 24; 72:1, 3, 4, 9; 73:2, 6; 74:21; 96:11; 115:11; 137:17; 149:6, 7, 8; 151:2, 12; 154:17, 18; 158:2; 161:5; 163:6; 167:13; 183:18; 188:2; 197:1, 2; 210:4; 212:20; 220:6, 9, 10, 13, 17, 19, 21, 22; 222:8; 226:9, 11, 12, 15, 21; 236:25; 237:6; 239:22
purely [1] 203:16
purpose [1] 109:13
purposes [1] 182:24
pursuit [1] 176:14
push [2] 140:10; 192:21
pushes [1] 177:14
putative [4] 55:6; 78:25; 93:21; 200:15
puts [1] 238:4
putting [2] 7:23; 225:3
pyrazinamide [7] 24:13; 56:5; 58:4; 67:4; 68:1; 146:16; 147:20
Pyuria [1] 48:6
pyuria [1] 72:15
PZA [34] 24:15, 16; 33:11; 35:12, 19; 36:25; 37:12, 13, 23; 38:6, 10, 15; 40:25; 41:5, 7, 9, 11; 45:10; 47:24; 56:16; 57:16; 58:19; 60:7; 66:18; 71:9; 79:17; 88:8; 105:19; 134:21, 24; 135:10, 16; 159:19; 160:19

- Q -

qualify [1] 11:9
qualitatively [1] 117:23

quality [1] 214:17
quantitate [1] 101:12
quantitative [5] 34:4; 73:17; 74:10, 19; 101:23
quarter [1] 8:20
Question [2] 213:9; 236:23
question [74] 12:21; 19:1; 65:9, 18; 66:11; 69:23; 73:8; 75:17; 76:16; 77:22; 78:2; 79:5; 84:2; 86:19; 87:2, 4, 15; 90:13; 91:22; 93:10; 94:16; 100:15; 107:17; 109:3, 23; 110:11; 127:13; 138:21; 143:4; 160:15; 173:10, 24; 175:8; 176:8; 178:11; 180:5; 183:15, 16, 20; 184:12; 185:4; 190:22, 24; 191:23; 192:19; 193:4, 24; 194:18, 20; 200:7; 202:1; 203:7; 209:7, 10, 18, 23; 212:17, 18, 21; 213:4; 216:11; 217:8, 18; 218:1; 226:1, 9; 229:10, 18; 230:16; 232:23; 233:25; 237:22
questioning [1] 65:15
questions [46] 12:13; 19:3, 7; 63:23; 64:13; 65:11, 12, 13; 73:21; 79:12; 83:6; 91:11, 20; 98:10; 115:6; 116:17; 137:14, 25; 138:4; 144:2; 158:11, 14, 15; 164:4; 173:9; 174:11, 14; 180:5, 17, 19; 181:11; 183:23; 184:18, 22; 185:7; 190:21, 25; 191:10; 196:15; 197:12, 15; 199:16; 214:25; 215:2, 25
quickly [1] 228:11
Quint [1] 235:22
quo [1] 233:10
quote [2] 59:25; 182:23

- R -

race [4] 26:22; 94:22; 95:13; 154:7
racial [1] 26:24
radical [1] 175:11
radio [1] 126:8
radiograph [1] 225:19
radiographic [1] 73:10
radiologist [4] 34:2; 101:9, 11, 17
raise [1] 212:22
raised [6] 142:5; 201:10; 209:22; 220:16; 237:22; 240:22
raises [3] 60:20; 79:12; 197:11
Ralph [1] 4:25
randomization [1] 25:1
randomized [10] 22:16; 25:19, 20; 90:15; 104:12; 119:11; 147:16; 148:12; 149:12; 154:22
range [8] 20:4, 8; 30:19; 60:23; 97:1, 7; 113:9, 10
ranged [2] 147:11; 155:22
ranging [4] 20:13; 42:7; 47:6, 9
rank [1] 130:1
rapid [8] 14:11; 55:14; 56:23, 24; 95:7; 109:12; 179:19; 204:21
rapidly [1] 65:24
rare [3] 53:3; 145:8; 175:22
rarely [1] 188:21
rarified [1] 174:23
rate [48] 11:14; 29:20; 31:1; 38:16; 40:1, 2, 5, 7; 54:20; 56:22; 59:1; 63:2; 68:19, 20, 24; 85:19; 88:4; 91:16, 18; 93:13, 14; 125:13; 126:5, 6, 23; 128:11; 136:17; 146:22; 147:8, 13; 148:3; 149:16; 150:7; 156:1; 159:22; 192:6; 195:11; 196:5; 197:25; 206:25; 207:5, 22; 215:8; 219:17, 23; 238:10
rates [77] 11:24; 12:8; 16:1, 4; 28:20; 29:11, 15, 24; 30:17, 19, 22; 31:22; 37:25; 38:2, 6, 12; 40:8; 44:2; 45:22; 49:4; 50:6; 51:21; 54:2, 3, 21, 25; 57:24; 58:10, 15, 24, 25; 77:2, 15; 88:5, 10; 93:3; 94:4; 105:20; 117:24, 25; 124:13, 16; 125:14; 126:2, 3, 9, 10, 12, 14, 19; 128:12, 18, 21; 134:14; 136:8, 10; 137:6, 10; 139:18, 25; 141:7; 146:8, 19; 147:11, 12; 148:7; 155:7, 22; 191:24; 192:10; 195:6, 15; 207:13; 228:25; 230:13, 15; 239:5
ratio [2] 126:14; 127:5
rational [1] 200:11
rationale [1] 169:24
raw [2] 146:22; 150:7
reach [2] 31:7; 151:10
reactions [2] 61:6; 191:21
reactivation [3] 79:1; 94:1; 177:16
read [9] 5:24; 102:9, 11, 12; 103:5, 6; 104:9, 10; 212:17
readily [1] 26:19
reading [4] 34:2; 101:10; 104:22; 105:1
real [14] 142:1, 2; 145:20; 175:16; 176:13, 22; 177:18; 198:14; 218:18; 219:12, 13; 222:14; 228:18, 19
realize [6] 61:17; 106:3, 5; 107:6; 206:19; 208:9
reason [12] 10:9; 23:2; 26:3; 28:3; 29:7; 31:15; 96:17; 137:11; 155:11; 174:4, 19; 195:12
reasonable [5] 60:14; 92:6; 211:19; 237:14; 243:17
reasonably [6] 10:7; 12:23; 21:19; 160:22; 234:11; 242:12
reasons [18] 18:3; 26:7; 29:2; 31:13; 47:21; 88:18, 23; 90:9, 21, 23; 94:6; 98:12; 119:15; 169:6; 224:13; 225:5; 236:9; 237:2
reassurance [1] 96:13
Recall [2] 128:10; 129:23
recall [5] 110:1; 117:4; 119:21; 120:24; 127:7
receipt [2] 36:1; 40:23
receive [5] 25:1; 70:22, 25; 149:12; 181:25
received [24] 25:8, 9, 11, 21;

26:1; 41:7; 47:2, 5, 9; 48:13; 50:18; 67:16; 119:11, 12; 147:25; 149:9, 10; 150:19, 20, 23; 151:6, 7; 152:2; 154:25
receiving [5] 38:14; 44:5; 104:17; 109:10; 199:8
recent [2] 53:7; 151:22
Recently [1] 52:3
recently [2] 52:6; 123:3
recessed [1] 164:14
recognition [1] 201:5
recognize [3] 173:18; 208:21; 221:3
recognized [2] 47:25; 148:23
recollection [1] 89:7
recommend [11] 96:22; 171:10; 175:17; 181:2; 202:13; 203:1; 212:10; 216:10; 217:9, 10; 239:13
recommendation [4] 82:9, 22; 149:23; 182:5
recommendations [3] 116:18; 174:1; 191:6
recommended [9] 15:9; 63:17, 21; 137:19, 20; 173:25; 213:11; 228:10; 236:7
recommending [1] 236:17
reconstitutes [1] 177:6
reconvene [2] 113:23; 164:14
reconvening [1] 164:11
record [9] 4:14; 6:3; 7:8; 109:18; 113:25; 114:1; 184:6; 221:9; 222:3
recorded [2] 27:12; 130:23
records [1] 153:19
recruit [1] 168:10
recruited [1] 171:3
recurrence [2] 89:13; 90:12
red [1] 113:7
reduce [11] 10:24; 60:22; 78:24; 81:13; 179:11, 22; 219:10, 23; 241:23; 242:9; 243:3
reduced [5] 60:9; 78:16; 81:19, 20; 187:12
reduces [1] 116:2
reducing [3] 53:6; 81:10; 187:19
reduction [2] 53:16; 82:5
reductions [1] 52:21
reference [1] 144:16
referred [5] 22:13; 41:2; 104:1, 4; 173:21
Referring [1] 116:14
referring [1] 176:11
refers [1] 207:7
reflect [5] 54:4; 55:15; 57:3; 62:2; 102:23
reflects [1] 26:24
regard [14] 6:2; 79:6; 81:10; 95:3, 5; 96:5; 102:17; 116:19; 131:22; 186:24; 188:6; 220:15, 24; 237:18
regarded [2] 52:12; 56:17
regarding [4] 84:20; 119:23; 123:4; 137:1
Regardless [1] 30:13
regardless [7] 30:20; 47:13; 128:7; 131:1; 133:8, 12; 135:6
regimens [42] 8:9; 11:3; 15:10; 53:14; 58:15, 18, 22,

- 24; 61:20; 66:24; 76:9;
116:24; 117:6; 144:17; 145:16;
18, 19; 149:3; 160:18; 161:2;
181:2, 3; 184:14; 187:14;
189:7; 192:15, 16; 204:13;
207:4; 213:19; 215:22; 219:9;
22:8; 229:10, 23;
237:8, 10, 15; 238:18; 239:18;
242:1; 243:17
region [2] 157:5, 17
regulated [1] 6:8
regulations [10] 9:25; 10:3;
11:11; 17:3; 73:1; 115:18, 22;
116:15; 137:21; 211:4
Regulatory [1] 13:7
regulatory [3] 73:5; 127:10;
168:7
Reichman [1] 64:25
reiterate [4] 62:1; 203:6, 12;
234:18
reiterating [2] 105:9; 106:1
Relapse [2] 40:8; 137:7
relapsed [21] 39:3, 11, 13, 15;
42:18, 20; 100:10; 122:7, 24;
123:14; 125:20; 150:19, 21,
24; 151:6, 9, 12; 155:18, 19;
192:3; 193:10
relapser [3] 43:12, 22; 105:21
relapsers [8] 43:2, 4, 16, 23,
25; 44:7, 10; 69:1
Relapses [1] 32:5
relapses [59] 14:24; 28:2;
29:9; 31:13; 32:8; 38:20, 24;
39:7, 8; 40:11; 42:12, 15, 23;
43:13; 44:14, 15, 16, 18; 53:1,
2; 59:10; 66:12; 67:13; 105:4;
107; 111:14; 113:7, 13;
116:10; 119:1, 5; 122:8, 9, 12,
25; 124:17; 125:17; 126:20;
129:6,
10, 12; 133:20, 22; 137:12;
150:1, 5, 6, 9, 10, 12; 155:10,
14; 176:24; 177:14; 182:2;
201:1, 6; 206:14; 233:9
relate [2] 57:10; 175:23
related [21] 15:14; 32:24;
40:8; 44:21; 46:10; 48:21, 24;
49:5, 11; 61:21; 70:11; 72:18,
21; 76:9; 90:11; 124:20;
130:4; 145:23; 190:25; 191:20;
225:6
relates [1] 188:18
relating [2] 95:13; 209:19
relation [3] 40:11; 109:5;
174:6
relationship [9] 34:20; 38:24;
42:11; 47:14; 59:3; 79:25;
112:5; 133:14; 169:2
Relative [1] 187:25
relative [26] 79:13; 127:6;
128:19, 23, 25; 131:15, 18;
132:9, 10; 133:5, 25; 134:4, 5,
6; 135:5, 8, 11, 15, 17, 21;
136:12; 141:22; 174:15;
193:11; 195:12; 198:2
relatively [22] 11:25; 54:3;
79:19; 108:24; 149:4; 151:20;
153:6; 155:6; 157:5; 159:18;
160:22; 161:5; 166:16; 167:4;
187:3; 199:20; 205:3, 25;
241:4, 8; 243:13
releases [1] 129:10
relevance [1] 51:15
relevant [1] 65:11
reliable [1] 35:15
relieved [1] 231:25
remain [3] 165:23; 199:16;
234:8
remainder [1] 178:25
remained [4] 21:12; 39:8;
40:4; 227:14
remaining [1] 25:17
remains [1] 124:19
remarkable [1] 8:15
remember [6] 9:3; 71:7;
113:18; 167:8; 206:13; 238:10
remove [1] 202:25
renal [2] 79:23; 188:19
reoccurrence [1] 90:6
reorganized [1] 168:20
repeated [1] 51:24
repeats [1] 126:5
replace [1] 219:4
replicate [1] 56:10
replicating [2] 55:23; 57:2
report [6] 47:15; 90:10;
124:10; 152:20, 22; 176:15
reported [18] 6:6, 9, 10; 18:6;
21:7; 22:6; 30:18; 48:21;
123:16; 146:6, 13; 147:1, 4,
15; 148:8; 154:20; 162:13;
172:7
reports [1] 204:12
represent [11] 31:22; 38:2;
41:21; 42:18, 19; 43:2; 55:22;
56:1, 2, 9; 186:17
representative [3] 111:6;
144:10; 201:13
representatives [1] 4:6
represented [7] 55:13; 56:14,
23; 93:22; 123:19; 153:9;
171:21
representing [2] 77:20; 101:5
represents [3] 29:10; 70:5;
168:3
reproducibility [1] 97:24
request [3] 6:17; 164:9;
181:12
requested [1] 17:2
requesting [1] 17:13
requests [1] 116:15
require [3] 45:8; 130:22;
243:18
required [14] 10:13; 35:16;
39:2; 40:19; 70:25; 117:1;
137:23; 158:4; 168:10; 186:8,
19; 200:17; 229:19; 241:24
requirements [1] 35:18
requires [2] 118:13; 179:23
rereading [1] 100:22
Research [6] 4:23; 6:9; 18:20;
64:5, 19; 165:14
research [9] 64:8; 116:16;
137:22; 166:4; 169:21; 191:9;
208:6; 226:23; 229:19
researchers [2] 14:13; 169:17
reservations [1] 214:4
reserve [1] 177:6
resistance [28] 14:12, 24;
24:24; 32:9; 51:22; 52:24;
53:3; 69:19; 78:15; 81:4;
107:6; 119:24; 120:1; 123:9,
25; 124:2; 152:8, 14; 154:1, 3;
156:10; 157:4; 162:18; 181:23;
182:3; 206:15; 233:10; 239:25
resistances [1] 156:13
resistant [17] 23:18, 19;
24:21; 26:6; 90:24; 100:13;
123:14; 145:23; 150:2, 11, 12,
16; 152:13; 156:22; 157:7;
220:6; 224:8
resistent [2] 11:4; 123:20
resolve [1] 201:8
resolved [3] 48:17; 229:13, 14
resource [1] 243:2
resources [10] 15:16; 179:6,
7; 186:1; 189:18; 200:17, 21,
23, 25; 216:4
respect [9] 7:9; 125:23, 25;
126:17; 134:17, 25; 206:20;
236:23; 238:7
respectively [2] 21:9; 44:8
Respiratory [3] 18:21; 64:19;
146:12
respiratory [1] 177:12
respond [3] 64:1, 13; 221:11
response [11] 90:10; 125:9;
144:3; 145:16; 164:5; 173:5;
191:24; 224:15, 19; 228:11;
229:6
responses [2] 75:19; 125:8
responsibilities [1] 208:23
responsibility [2] 179:4;
201:7
responsible [2] 56:19; 113:13
responsiveness [1] 73:25
rest [4] 90:19; 197:24; 209:3;
233:15
restate [1] 93:10
restored [1] 177:8
restrictive [1] 26:13
rests [1] 145:8
result [10] 13:15; 44:4; 47:17;
48:3; 60:4; 61:22; 178:9;
188:12, 14; 201:4
resulted [3] 54:8; 60:11;
69:16
results [50] 12:5; 17:6; 18:6,
12, 17; 27:22; 28:12; 29:4;
45:16; 50:20; 53:25; 57:14;
58:2; 62:1, 2, 12; 63:13, 18;
66:1, 6; 68:4; 69:14; 72:14;
87:3; 91:17, 18, 25; 92:9, 10;
95:12; 101:20; 102:13; 108:14;
111:3, 21; 123:22; 124:23;
126:23;
129:14; 131:1; 132:19; 142:10,
13; 144:20; 162:3; 165:24, 25;
176:16; 185:24; 187:5
resume [1] 164:8
return [3] 18:25; 136:18;
177:3
reversed [1] 132:10
review [10] 8:7, 20; 114:14,
16; 116:21; 117:18; 136:22;
146:5; 153:20
reviewed [2] 124:5; 151:19
reviews [1] 118:2
revise [1] 177:25
revolve [1] 200:14
revolves [1] 10:22
rewife [1] 103:16
RFLP [2] 123:15, 22
Rhonda [2] 5:11, 23
rhythm [1] 60:20
Richard [1] 165:7
Rick [2] 165:13; 173:21
rif [1] 161:25
rifabutin [8] 22:8; 81:15;
152:18, 20; 153:1; 160:1;
162:20; 167:12
Rifampin [4] 13:14; 156:10,
16; 157:23
rifamycin [13] 19:23; 20:2;
36:23; 37:9; 51:7; 56:16; 57:4;
71:15; 107:11; 158:18; 161:2;
162:18; 166:23
rifamycins [17] 32:9; 46:11;
47:18; 55:21; 56:6, 11, 12;
57:6; 61:4; 157:19, 22; 158:8;
159:1; 160:17; 161:6; 185:12;
188:15
Rifapentine [8] 17:17; 19:23;
21:5; 25:4, 9, 12; 81:12;
135:19
rifapentine-INH [1] 57:18
Right [8] 74:6; 84:14; 86:7;
95:20; 100:11; 107:2; 140:15;
164:2
right [19] 66:11; 77:20; 81:15;
82:4, 19; 86:2; 90:15; 93:4;
96:9; 103:14; 106:7; 114:23;
163:24; 164:2; 175:13; 183:11;
216:25; 242:1, 6
rights [1] 92:6
rigor [1] 194:12
rising [1] 16:2
risk [36] 27:11; 33:3; 59:20;
78:20; 79:1; 124:18; 128:19,
23, 25; 130:4; 131:6, 11, 15,
24; 132:3, 10, 20, 24; 133:9,
10, 15, 25; 134:4; 135:8, 11,
17, 21; 141:22; 154:4; 157:25;
158:5; 175:5; 177:21; 193:11;
198:2, 22
risks [9] 131:18; 132:9; 133:5;
134:5, 7; 135:5, 11, 15; 195:13
ritonavir [1] 158:21
RMP [1] 25:3
RNA [6] 99:24; 156:16, 17, 19,
20, 25
Rochester [1] 5:16
Roger [1] 5:12
role [5] 56:6, 12; 57:7; 63:6;
223:11
Room [1] 6:18
room [2] 114:11; 239:10
rough [1] 225:19
roughly [3] 149:22; 157:7;
230:13
Roussel [25] 4:8; 11:13; 13:8,
18; 15:22; 16:5, 14, 22; 17:1,
24; 18:11; 19:20; 46:5; 51:14;
63:25; 64:24; 69:25; 95:25;
97:6; 99:5; 108:4; 169:2;
170:18; 171:20; 244:19
routinely [2] 65:20; 226:14
row [4] 134:20, 23; 135:1, 3
rows [3] 131:10; 132:3;
133:16
RPOB [2] 156:18, 23
RPT [3] 25:2; 87:8, 18
RUBERG [15] 69:24; 76:23;
80:16, 22; 83:25; 84:14; 85:13,

21, 24; 86:7, 12, 17, 24; 87:14, 23
Ruberg [2] 64:10; 69:24
rudimentary [1] 230:10
running [3] 113:21; 114:2; 138:3

- S -

safe [13] 61:12; 137:16; 183:17; 188:1; 191:15; 196:24; 199:19; 201:22; 205:7; 209:1, 11; 212:19; 244:3
safely [4] 46:14, 18, 22; 50:14
safer [1] 188:18
Safety [2] 149:23, 24
safety [31] 12:13; 16:18; 19:20; 25:23; 46:5, 6, 8; 49:13, 14; 50:7, 11; 51:6; 62:21; 95:2; 96:19; 114:16; 136:22; 137:1, 2; 181:15, 22; 187:1, 13, 20, 22; 188:6; 191:21; 194:17; 206:4; 209:14; 210:6
sake [1] 213:6
sales [2] 171:11, 14
sample [4] 26:6; 43:11, 21, 24
sampled [1] 113:15
samples [1] 110:23
San [1] 4:19
sat [1] 235:4
satisfactory [1] 89:22
satisfying [1] 185:24
save [1] 200:24
savings [1] 222:18
saying [11] 87:12; 104:20; 138:9; 143:5; 179:2; 187:8; 206:24; 207:24; 212:6; 233:8; 244:1
SBARBARO [1] 178:14
Sbarbaro [3] 65:4; 178:14; 189:11
scale [1] 108:20
scenario [2] 29:10; 143:7
schedule [5] 36:3; 136:4; 145:14; 195:25; 197:13
scheduled [5] 22:23; 24:9; 70:23; 71:1; 116:12
SCHLUGER [13] 144:8, 13; 159:4; 160:16; 161:14, 17, 21; 162:2, 21; 163:8, 20, 24; 164:2
Schluger [3] 123:3; 144:6; 158:14
School [3] 5:10; 65:1, 3
Science [2] 4:21; 6:24
Sciences [2] 64:21; 65:6
scientific [2] 169:24; 182:15
scientifically [1] 186:12
scores [2] 26:20; 73:10
scoring [2] 75:1, 4
Scott [2] 5:8; 223:5
screen [2] 98:25; 114:22
screened [1] 25:16
screening [1] 25:17
se [1] 113:11
Second [7] 46:13; 125:2; 130:21; 131:10; 132:3, 24; 136:10
second [18] 8:18; 9:23; 26:13; 30:6; 66:11; 73:8; 77:22; 93:9; 96:1; 97:19; 99:22; 114:9; 134:23; 183:1; 207:19; 211:11;

230:7; 243:16
Secondary [1] 28:11
Secondly [3] 54:10; 60:6; 124:15
secondly [1] 200:20
seek [1] 9:15
seemingly [1] 72:13
sees [2] 129:21; 131:10
selecting [1] 223:11
selection [1] 233:15
SELF [8] 5:2; 88:14; 89:25; 90:13; 91:8; 195:2; 229:17, 21
Self [5] 5:2; 88:13; 195:1; 212:15; 229:16
send [1] 191:3
sends [2] 208:14, 15
Senior [1] 64:4
senior [1] 64:8
sense [8] 77:3, 9; 85:14, 19; 141:6; 172:5; 197:10; 229:5
sensitive [2] 24:19; 38:22
sensitivity [3] 96:24; 139:2; 195:7
separate [7] 87:20; 105:14; 106:11, 23; 184:11; 203:14; 235:15
separately [5] 36:16; 37:13, 16; 92:25; 119:20
separates [2] 36:17; 134:18
separating [2] 71:14; 100:1
separation [2] 85:11; 88:10
sequelae [1] 48:18
sequence [4] 68:9; 71:17; 130:13; 185:24
sequenced [1] 157:12
sequences [1] 118:3
sequencing [1] 170:4
series [2] 67:9; 165:17
serious [10] 10:4; 17:4; 49:3, 8, 9, 15, 24; 50:19; 175:10; 188:15
seronegative [2] 147:25; 197:1
seropositive [2] 153:11; 231:19
serum [5] 21:3; 22:4, 7; 23:12; 47:25
served [3] 167:22; 178:7; 183:7
serves [1] 65:6
Service [4] 18:19; 94:8; 148:11; 165:18
Services [1] 64:23
session [6] 4:4; 164:7, 8, 12; 165:4, 6
sets [1] 143:22
setting [1] 176:18
settle [1] 228:18
seven [18] 32:1; 38:18; 91:6; 127:4, 9; 129:8, 11; 131:9, 12; 132:1, 2, 5, 7; 135:10; 140:19; 147:11; 192:24; 193:19
seven-day [1] 106:24
Seventy [1] 82:3
severe [2] 74:23; 218:13
severely [1] 163:14
severity [10] 33:9, 16; 34:17; 73:9; 76:12; 223:10; 224:12, 14; 225:14, 23
sex [2] 112:10; 191:20
SGPT [1] 23:14

shallow [1] 56:25
shape [1] 221:12
share [2] 124:18; 231:20
sharpen [2] 147:2; 150:3
shed [1] 200:7
shortcomings [1] 62:2
shorten [2] 238:18; 239:3
shortened [1] 186:9
shortening [1] 186:24
shot [1] 210:13
Show [3] 84:6; 212:23; 213:2
show [15] 53:11; 61:6, 12; 67:12; 76:19; 84:3, 4; 85:3, 8; 107:23; 124:13; 128:21; 191:15; 195:2; 242:21
showing [4] 45:21; 77:3; 140:18; 243:8
shows [17] 27:2; 41:16; 42:25; 43:7; 67:6, 7; 68:12; 110:21; 120:25; 122:15; 124:23; 128:12; 129:2, 6, 18; 135:8, 13
sicker [1] 92:15
sides [1] 66:13
sight [1] 176:9
signal [1] 191:4
signals [1] 208:14
signed [2] 165:7; 173:2
significance [6] 141:19, 20, 24; 146:25; 151:10
significant [25] 23:23; 34:7; 37:8; 39:25; 53:6, 11, 24; 73:16; 80:1, 13, 25; 86:3, 5; 93:2; 102:25; 108:22; 112:20; 131:19; 132:16; 149:1; 150:17; 151:5; 154:6; 172:4; 189:10
significantly [17] 27:7; 32:6; 34:12; 36:7, 20; 37:2; 39:12, 16; 40:6; 66:18; 95:9; 104:18; 128:22; 129:25; 134:7; 136:11; 195:16
signs [7] 27:5; 33:2, 22; 73:13; 89:13; 167:5, 6
silicate [1] 33:4
simple [4] 98:7; 149:4; 178:9; 235:2
sina [1] 233:10
Single [1] 21:17
single [20] 16:8; 17:7; 18:12; 20:12; 21:1; 22:11; 27:24; 38:2; 43:12, 21; 46:13; 47:5; 97:20; 105:21; 108:16; 162:20, 24; 194:4; 208:11; 239:19
SIP [1] 227:23
sir [4] 72:10, 16; 73:7; 215:20
site [1] 220:12
sites [6] 16:9; 22:19; 26:25; 71:24; 72:1, 9
situation [5] 156:12; 215:12; 218:19; 222:15; 235:19
situations [5] 196:11; 207:1; 217:10; 218:3; 235:6
six [46] 10:14; 11:14, 22, 25; 17:12; 22:22; 24:9; 27:16; 28:15; 29:19, 25; 38:13; 39:25; 40:6; 44:14; 46:19; 53:17; 54:22; 57:21; 68:24; 77:19; 93:13, 19; 110:23; 116:11; 119:25; 121:23, 24; 122:10, 13; 131:8, 14; 145:2; 147:16, 21; 148:1;

154:23; 155:2, 10, 16; 159:21; 160:10; 168:10; 181:12; 186:10, 25
six-month [17] 23:4; 24:6; 28:22; 29:17; 31:3, 7, 19; 94:9, 10; 109:24; 116:6; 146:19; 147:17; 148:4; 155:24; 182:24; 187:6
six-months [1] 207:12
sixth [1] 157:15
Sixty-two [1] 121:23
size [3] 43:11, 21; 56:21
sizes [1] 43:24
skin [1] 73:23
Slide [9] 66:15, 21; 70:1, 5; 77:1; 84:4; 110:19; 111:15; 138:7
slides [10] 46:8; 67:9; 68:4; 88:22; 107:23; 116:21; 133:7, 24; 142:18; 144:11
Slight [1] 117:19
slight [8] 33:23; 34:16; 73:14; 95:15; 129:14; 140:21; 175:6; 205:18
slightly [14] 27:3; 33:19; 37:19; 66:22; 67:10, 11; 70:10; 92:14, 15; 102:17; 117:20; 126:14; 129:13; 177:24
slipping [1] 204:7
slow [2] 43:8; 167:4
slower [1] 54:19
slowly [1] 55:23
smaller [1] 93:8
smallest [1] 56:8
smear [1] 225:18
smears [4] 27:23; 33:3; 74:11, 20
Smith [1] 114:20
SNIDER [13] 4:20; 76:7; 77:22; 79:4; 80:2; 95:4, 18; 187:25; 209:6; 218:16; 222:5; 223:23; 242:14
Snider [11] 4:20; 6:24; 76:6; 78:10; 170:15; 187:24; 202:7; 209:5; 212:16; 218:15; 242:13
Society [2] 52:7; 154:21
society [1] 192:3
sole [2] 24:25; 32:10
solid [4] 41:21; 42:4, 17; 191:5
somebody [3] 89:4; 176:2, 16
somehow [5] 85:9; 139:16; 191:3; 215:5; 233:3
someone [9] 130:16; 147:2; 150:3; 158:22; 160:8; 174:25; 192:3; 236:4; 244:13
somewhat [11] 12:2, 6; 92:15; 100:17; 101:3; 114:2; 131:16; 153:9; 171:9; 207:3; 220:25
Somewhere [1] 94:24
somewhere [3] 86:2; 202:20; 238:5
sophisticated [1] 239:16
Sorry [1] 223:12
sorry [2] 138:17; 170:10
sort [19] 72:12, 25; 73:20, 21; 87:24; 140:11, 16; 141:17; 142:2; 157:20; 186:12; 187:7; 194:21; 199:9; 214:22; 240:25; 241:19, 22; 243:6
sorts [2] 216:3; 240:4

sounds [2] 22:9; 238:23
source [1] 18:6
South [16] 16:9; 22:19; 26:24;
 27:24; 72:21; 91:22; 92:7, 9,
 14, 17, 19, 23; 98:19, 25;
 99:10; 108:6
South [1] 93:1
speak [4] 165:21; 173:3;
 176:4; 198:6
speakers [1] 231:7
Speaking [1] 159:7
Special [2] 15:22; 168:2
special [1] 111:23
specific [16] 26:2; 74:8;
 90:14, 21; 144:16; 174:8;
 196:11; 204:19; 210:2, 9;
 220:12; 221:23; 228:2; 236:7;
 237:10; 242:1
Specifically [1] 145:18
specifically [15] 35:7; 71:24;
 72:21; 73:19; 74:2; 84:1;
 161:24; 191:20; 201:12; 206:8;
 209:2; 210:3, 5; 217:10;
 244:18
specified [2] 75:14, 15
specify [2] 75:24; 76:3
specifying [1] 76:1
speed [1] 216:24
split [1] 95:17
spoke [1] 210:16
spoken [1] 119:23
sponsor [22] 4:7; 13:1; 16:11;
 65:10; 76:7; 120:2; 134:19;
 138:9; 141:12; 142:14; 173:10;
 174:17, 25; 176:1; 203:17;
 206:20; 208:17, 23; 221:19;
 223:1; 227:1; 244:18
sponsored [3] 144:19;
 166:15; 170:16
sponsoring [1] 165:16
sponsors [2] 208:15, 18
sporadically [2] 56:10; 57:2
spot [2] 157:9, 17
spread [1] 112:7
spreading [1] 195:16
Sputum [1] 117:16
sputum [50] 23:10; 26:4, 6;
 27:19, 22, 23; 28:5, 7, 13, 18;
 30:5, 10; 38:25; 39:2, 10, 14,
 20, 23; 40:9, 12; 41:17; 44:21,
 25; 45:11; 56:19; 57:17;
 59:19; 89:20; 93:12; 104:17;
 118:7, 11, 21; 119:2; 120:17,
 25; 121:8; 123:22; 130:6, 9;
 136:14;
 142:14; 174:17; 176:15;
 196:25; 216:15, 24; 237:20;
 238:2
sputums [1] 118:17
SSRIs [1] 227:22
stacked [2] 41:14; 205:10
STALLARD [3] 99:4, 11, 14
Stallard [1] 99:4
standard [19] 45:19; 52:6;
 146:15; 147:6, 18, 25; 148:4;
 149:10; 155:1; 193:2, 16;
 194:12, 14; 195:8, 19; 196:3;
 200:3; 211:20; 220:17
standpoint [3] 188:9, 10;
 189:22
start [8] 4:12, 15; 7:18, 22;

93:7; 141:23; 176:8; 213:21
started [2] 162:5; 221:13
State [1] 64:15
state [6] 53:5; 55:10; 75:24;
 95:22; 99:24; 226:25
stated [6] 91:20; 93:15;
 106:18; 206:1, 10; 237:2
statement [6] 5:24; 6:16;
 83:7; 90:17; 202:11; 211:11
statements [1] 98:11
States [11] 14:3; 22:20; 91:24;
 94:8; 99:2, 12; 152:7; 158:18;
 165:18; 172:6, 8
states [1] 57:5
stating [1] 103:9
statistical [18] 29:22; 30:23;
 76:22, 24; 80:11, 17; 108:20,
 22; 115:5; 124:10; 141:18, 24;
 142:25; 146:25; 148:17; 149:1;
 194:12; 221:5
statistically [12] 32:5; 73:16;
 80:13; 112:15, 19; 128:22;
 129:25; 131:19; 132:16; 134:7;
 136:11; 150:8
statistics [1] 202:10
status [15] 17:17; 39:19;
 41:19; 65:20; 73:22; 74:2;
 77:6; 95:15; 99:20; 117:16;
 130:6, 10; 131:3; 136:14;
 204:21
stay [1] 71:16
steeply [1] 56:24
step [5] 186:18; 242:16;
 243:6, 7
Stephen [1] 64:10
stepped [1] 180:10
steps [2] 186:22, 23
sterilization [3] 163:11, 14;
 164:1
sterilizing [1] 57:5
Steve [3] 5:2; 69:22, 24
stiffening [1] 234:4
stockholders [1] 171:17
stone [1] 144:10
stop [4] 158:10; 191:11, 21;
 231:24
stopped [3] 149:22; 168:11,
 12
STOVER [2] 5:11, 25
Stover [2] 5:11, 23
strain [3] 123:18; 152:11, 13
strains [2] 53:2; 170:5
strange [1] 238:14
strata [1] 133:6
Strategic [1] 170:8
strategy [6] 14:17; 52:13, 15;
 63:14; 175:18, 20
stratified [1] 134:15
strength [1] 214:7
strep [1] 160:19
streptomycin [10] 54:11;
 55:20; 58:14, 18, 24; 109:7;
 159:19; 165:20; 236:10, 15
stretch [1] 10:15
strictly [2] 184:17; 185:9
striking [2] 44:12; 232:25
string [2] 118:17, 25
strong [2] 58:9; 195:11
strongest [1] 33:9
strongly [2] 51:20; 157:24
structure [1] 19:24

struggled [1] 101:18
stuck [3] 184:13; 185:1;
 203:25
studied [13] 8:10; 20:21;
 21:21; 53:1; 60:12; 94:17;
 197:11; 199:16; 212:5; 213:19;
 222:22; 223:21; 226:22
studies [52] 8:17; 21:11; 47:5;
 50:8; 53:21; 55:18; 57:6;
 60:17; 61:6, 22; 81:6, 7; 96:4;
 103:25; 104:11; 109:6; 111:24,
 25; 116:8; 137:20; 146:9;
 155:21; 158:4; 162:14; 163:10;
 170:18; 173:13, 25; 174:18;
 181:17; 184:9; 186:8; 196:19;
 197:17;
 200:6; 204:3, 19, 22; 213:17;
 221:14; 227:25; 229:11, 14;
 230:21; 231:2; 236:6; 238:7,
 21; 239:14; 243:25
Study [19] 47:2, 14; 48:22;
 49:4; 57:12; 115:15; 116:12;
 117:17; 148:12; 149:4; 155:25;
 156:9; 161:14; 165:16; 168:9,
 15, 19; 169:2
stuff [1] 216:4
sub-analyses [1] 87:6
sub-analyze [1] 198:18
subanalysis [1] 137:10
subcategorizing [1] 93:7
subdivide [1] 133:12
subgroup [10] 41:13, 18;
 42:13, 16; 43:3; 134:3; 135:7,
 9, 20; 182:6
subgroups [7] 40:23; 41:1;
 68:7; 80:18; 88:20; 133:12;
 134:8
subject [3] 108:24; 138:14;
 151:20
subjective [1] 225:16
subjects [46] 20:15, 17, 18;
 21:2; 46:15, 16; 47:5; 83:10,
 14, 20, 21; 110:2; 111:5, 23,
 24; 112:6, 14; 124:24; 127:19;
 129:3; 131:6, 25; 132:4, 6, 11,
 21, 25; 133:1, 2, 4; 134:3, 10,
 20, 23; 135:3, 13, 14, 19, 20;
 138:13, 16, 17, 18, 25;
 140:8
submit [1] 17:8
submitted [7] 6:5; 17:1, 11,
 16; 58:21; 115:9; 211:16
submitting [1] 6:17
subpopulations [2] 32:22;
 55:7
subsequent [6] 35:5; 61:22;
 67:9; 93:13; 131:22; 183:22
subsequently [2] 23:11; 54:4
subset [2] 195:10, 11
substantial [7] 9:17; 11:6;
 45:7; 52:21; 91:19; 122:12;
 211:16
substantially [2] 51:24; 94:20
substituted [1] 160:2
substituting [1] 223:15
substitutions [1] 157:13
subunit [2] 156:19, 20
Success [1] 29:15
success [24] 27:18; 28:12,
 20; 29:11, 24; 30:17, 19, 21,
 25; 45:22; 63:7; 85:19; 93:3;

113:2; 118:6; 146:8; 148:7;
 159:18; 185:15, 17; 195:3;
 216:21; 238:3; 243:20
successes [3] 30:16; 113:6, 9
successful [5] 58:16; 142:12;
 214:21, 24; 242:11
successive [1] 129:11
sudden [1] 235:23
suffer [1] 91:18
sufficient [13] 45:6; 63:6;
 78:18; 79:3; 93:18, 24; 103:4;
 105:11, 23, 25; 106:19, 22;
 148:17
sufficiently [3] 57:19; 66:6;
 75:23
suggest [12] 34:10; 45:3;
 59:17; 60:18; 62:4; 85:5;
 123:18; 185:10; 195:25;
 196:17; 224:23; 230:9
suggested [5] 78:4; 130:3;
 163:10; 168:15; 190:5
suggesting [4] 47:24; 169:13;
 227:12; 241:25
suggestion [3] 45:8; 105:16;
 204:20
suggestions [3] 213:14;
 221:23; 223:14
suggestive [1] 220:25
suggests [2] 34:14; 189:8
summaries [1] 115:6
summarize [5] 19:11; 20:10;
 46:8; 61:11; 157:20
summary [8] 19:15, 19; 44:4;
 46:4, 6; 49:14; 136:7; 181:20
superimposed [1] 37:17
superior [1] 85:4
supervise [2] 189:19; 243:18
supervised [2] 10:25; 222:20
supervision [2] 14:21; 241:24
supplies [1] 16:23
support [5] 16:23; 173:20;
 187:21; 223:21; 227:15
supported [2] 11:18; 16:21
supporting [1] 196:9
supportive [2] 55:24; 63:19
supports [1] 58:5
supposed [2] 99:6, 7
supposedly [1] 124:3
suppressed [1] 57:22
surely [2] 60:9; 174:21
surface [2] 34:9; 100:25
surplus [1] 59:10
surprising [2] 8:13; 50:1
surrogate [6] 10:7, 11; 11:12;
 182:23; 184:20; 207:11
surveillance [1] 221:4
susceptibility [2] 69:14;
 185:11
susceptible [12] 53:2; 115:13;
 145:18; 149:5, 8; 152:13;
 153:22; 154:12, 24; 155:19;
 156:18; 197:1
suspect [2] 171:8; 200:13
suspicion [2] 97:18; 98:2
suspicious [1] 99:7
sustain [1] 28:5
sustained [7] 27:20; 28:18;
 29:20; 118:11, 14, 22; 121:4
sweats [1] 27:6
switch [1] 218:23
symmetrical [1] 203:11

symptomatic [1] 176:21
symptoms [8] 27:5; 33:2, 22;
 48:2; 73:13; 89:13; 162:8;
 176:15
syndromes [1] 188:19
synopsis [1] 104:4
synthesis [3] 156:16, 21, 25
system [3] 23:23; 101:25;
 227:23
systematically [1] 72:7
systemic [1] 23:24
systems [1] 161:24

- T -

Table [3] 40:15; 100:19;
 102:18
table [8] 100:19; 103:6, 7, 17;
 133:16, 19; 135:8; 183:19
tablets [1] 19:25
talk [17] 7:25; 9:9; 100:22;
 124:12; 130:9; 139:10, 14;
 141:20; 177:2; 178:3, 16;
 181:21; 200:14, 19, 21; 206:6;
 214:12
talked [6] 11:23; 101:9;
 109:19; 205:7; 222:17; 243:13
talking [25] 9:12, 23; 96:7;
 104:22; 121:13; 157:21; 159:9;
 181:1; 192:22, 23; 193:14;
 201:12; 203:25; 204:1; 209:10,
 12; 219:1; 222:7, 8; 224:1;
 229:13; 230:13; 236:3
target [1] 177:7
targets [1] 170:2
task [1] 211:14
TB [80] 7:24; 8:24; 9:11; 11:3;
 13:23; 14:2, 9, 11; 16:4; 18:18;
 20:16; 23:22; 27:11; 33:3;
 51:21; 52:5, 13; 60:5; 61:16;
 90:6; 92:4; 94:5; 112:3, 6, 7,
 11, 13; 144:20, 22, 24; 146:7;
 149:7; 151:2, 12; 152:4, 6, 18,
 19, 25; 153:4, 11, 17;
 154:5, 10, 12, 16, 17; 156:12;
 157:23; 158:2, 5, 7; 159:4, 8,
 10, 11, 12; 160:10; 161:5;
 166:4, 12, 13; 170:13; 171:1,
 14, 18, 22; 172:7; 177:23;
 178:5; 186:23; 189:15; 197:1,
 23; 220:7; 232:10, 13; 242:25;
 243:11
team [1] 114:15
tease [1] 142:17
ten [13] 9:3; 31:1, 6; 42:1;
 128:20; 129:11; 140:20;
 147:23; 150:7; 155:22; 156:11;
 178:19; 179:16
tend [3] 83:12, 18; 190:4
tendency [2] 202:18; 203:4
tending [2] 189:9; 202:9
tension [3] 198:6, 14; 199:10
term [3] 209:17, 19; 238:3
termination [1] 93:19
terminology [1] 118:4
terms [48] 8:16; 10:20; 32:22;
 55:3; 59:13; 70:7; 81:5, 8;
 86:22; 87:2, 4, 20; 92:5; 95:10;
 111:3; 112:24, 25; 113:5;
 127:4, 6; 138:21; 141:13;
 156:9; 171:2; 178:3, 4; 191:22,

24; 192:17; 193:19; 198:4;
 200:17; 209:16, 24; 216:13;
 219:5; 220:4,
 7; 222:18; 228:13, 17; 229:3;
 230:12, 14, 17, 25; 240:21;
 242:24
terribly [4] 89:22; 199:2;
 219:12; 243:5
terrifically [1] 182:14
test [7] 24:2; 73:23; 119:23;
 130:1; 131:18; 141:14; 142:2
tested [1] 159:24
testing [1] 185:24
tests [2] 132:15; 141:18
text [1] 103:6
thalidomide [1] 145:22
Thank [63] 5:22; 7:13, 17;
 12:25; 51:8; 62:9; 65:8; 76:5;
 80:3; 83:3; 88:12; 91:8;
 100:14; 102:14; 109:1, 2, 17;
 110:10; 113:20; 114:8; 138:1;
 143:25; 144:1; 158:12; 161:8,
 9; 162:15; 164:3; 165:9, 12;
 172:25; 173:1; 174:3, 10;
 180:2, 8; 182:17,
 18; 183:10; 185:19; 187:23;
 191:12; 192:11; 194:25;
 196:20; 199:17; 201:23; 203:8,
 10; 205:24; 212:11; 218:14;
 223:3, 12; 228:5; 229:15;
 231:4; 234:13, 14, 16; 236:20;
 244:15, 20
thank [4] 236:19; 243:23;
 244:12, 16
thanking [1] 7:22
Thanks [6] 12:24; 76:4; 80:9;
 82:23; 144:8; 158:13
theme [1] 88:15
thence [1] 170:17
theoretical [5] 56:18; 184:22;
 185:12; 195:22; 230:23
therapeutic [16] 15:13; 31:12,
 18, 22, 24; 78:11; 81:1; 88:23;
 90:3; 115:24; 183:2; 189:14;
 207:21; 230:9; 232:4; 236:1
therapies [5] 145:21; 183:2;
 207:21; 219:13; 220:17
therapy [78] 10:5, 6, 14, 22,
 23; 11:9, 10, 15; 12:1; 14:15,
 20, 22; 15:16; 23:24; 51:24;
 52:4, 9, 12; 53:16; 54:8; 58:15;
 60:8, 22; 63:14; 70:3, 9, 11;
 76:10; 78:4, 8, 14, 18, 24;
 93:19; 109:9; 116:1, 11;
 117:25; 119:12; 120:24; 124:8;
 142:13;
 145:15; 149:20; 154:23; 159:6,
 11; 165:18; 177:18, 23; 179:4;
 186:4; 187:10; 189:23, 24;
 190:7, 11; 214:18; 215:3;
 216:1, 9; 217:13; 218:6, 20;
 221:12; 222:20; 224:15, 21;
 233:9; 234:5; 237:25; 241:2,
 10, 11, 14; 242:8, 25
thereby [1] 53:8
They'll [1] 175:19
They're [2] 93:2; 96:9
they're [10] 83:7; 84:23;
 101:1; 139:4; 157:12; 176:20;
 177:17; 190:24, 25; 227:22
they've [3] 143:7, 8; 185:22

thinking [8] 98:7; 169:19;
 174:5; 191:22; 198:4; 203:19;
 216:13; 238:25
Third [4] 46:17; 53:4; 124:18;
 136:13
third [11] 30:7; 99:1, 17;
 125:5; 130:24; 135:1; 139:5;
 152:14; 159:25; 207:6; 243:16
Thirdly [1] 54:13
Thirty [1] 48:9
Thirty-eight [1] 120:9
Thomas [1] 5:13
Thoracic [2] 52:7; 154:21
thorough [1] 244:12
thoughts [2] 182:12; 183:20
threat [1] 78:10
threatening [3] 10:4; 17:4;
 236:4
Three [1] 157:12
three [56] 21:6; 23:15; 24:9;
 30:3; 33:13; 40:23; 53:19;
 55:5; 60:2; 65:13; 67:6; 89:1,
 7, 9; 97:13; 104:12; 106:14;
 108:21, 23; 110:24; 116:10;
 119:25; 124:7, 12; 125:15;
 129:7; 130:10; 132:12; 133:7,
 16; 134:2, 5; 141:22; 147:11,
 13; 150:5,
 12; 155:22; 159:7; 177:20;
 180:24; 181:21; 204:25; 205:1;
 211:7, 12; 218:21, 23, 24;
 219:2, 17; 221:17; 223:8;
 234:21; 243:14, 15
three-quarters [1] 70:23
thrice [2] 15:11; 217:13
thrombocytopenia [1] 188:19
throw [1] 190:19
tie [1] 166:5
tied [1] 224:16
timed [1] 113:22
timely [1] 16:12
times [15] 23:15; 53:19;
 127:14; 129:2; 136:8; 141:11;
 194:5; 205:1; 218:21, 23, 24;
 219:3; 227:6; 243:14, 15
timing [2] 110:14; 124:16
tiny [1] 243:7
tissue [3] 34:12; 55:9; 56:2
toe [1] 190:13
tolerable [2] 193:9, 11
tolerate [2] 194:18; 228:24
Tom [1] 5:18
tools [3] 14:14; 52:14; 179:23
total [8] 31:4, 5; 100:24;
 103:8; 120:11; 171:14; 186:19;
 197:6
Toursade [1] 235:22
towards [8] 73:15; 151:8;
 159:12, 14; 177:14; 202:9, 19;
 203:4
toxicology [1] 114:20
track [1] 9:4
traditional [2] 208:25; 221:22
traditionally [1] 15:9
transcript [2] 4:13; 95:23
transmission [2] 53:8; 206:16
transmittable [1] 52:2
treat [31] 11:5; 25:25; 28:23;
 50:24; 84:22, 25; 86:9, 21, 22;
 90:16; 91:2; 96:3, 21; 120:5;
 128:5, 8; 141:1; 143:23; 146:3;

159:2, 10; 160:10; 169:11;
 172:12; 176:22; 178:8, 22;
 186:14; 234:25; 241:14; 242:5
treated [17] 24:22; 29:8;
 41:10; 46:18, 23; 109:7; 123:5;
 127:22; 128:3; 139:16; 146:14;
 148:3; 149:2; 155:10; 158:8,
 23; 161:6
treating [4] 14:23; 163:6;
 231:9; 234:25
Treatment [3] 28:1, 20; 32:2
treatments [10] 29:23; 32:15,
 18; 71:11; 83:8; 85:15; 92:24;
 127:9; 139:13; 178:1
tremendous [2] 216:8; 242:24
tremendously [1] 243:2
trend [7] 27:9; 33:23; 42:4;
 43:4; 73:15; 151:8; 172:9
trends [2] 176:9; 228:17
Trial [4] 46:7; 49:25; 58:11;
 94:8
trials [51] 9:15; 10:13; 11:17;
 18:4; 19:21; 30:18; 46:5; 47:1,
 8; 49:14, 22; 50:5, 10; 57:6;
 58:21; 59:4; 61:1; 87:13, 21;
 94:6; 96:14; 139:11, 14;
 142:22; 145:9; 146:3, 6; 148:7;
 156:2; 163:5, 9; 165:18;
 166:23, 25; 167:3, 18; 168:16,
 22;
 170:20, 22; 171:2; 174:6, 24;
 182:10; 185:14, 22; 211:8;
 222:22; 234:3; 237:12; 240:12
trivial [1] 205:3
trouble [2] 179:5; 225:10
troubling [2] 54:2; 237:17
trough [2] 227:14; 232:1
true [2] 69:17; 227:17
tubercle [1] 55:7
tuberculin [1] 73:22
Tuberculosis [4] 13:21; 65:1;
 165:15; 172:16
tuberculous [1] 49:1
Twenty-five [1] 144:24
twenty-four [1] 25:15
Twenty-one [1] 153:19
twenty-three [1] 120:18
twice [43] 15:6, 11; 23:13;
 25:4, 11; 35:20; 48:19; 50:15;
 53:19; 59:14; 60:8, 18, 21;
 71:8; 78:3, 21; 117:2; 149:13;
 179:5; 189:2, 4, 24; 190:6, 11;
 193:11; 204:14, 24; 215:3;
 217:11, 25; 218:24; 219:3, 19;
 226:8; 231:13; 238:11; 239:5,
 20;
 241:1, 10; 242:6; 243:14, 15
two-month [4] 41:19; 45:12;
 69:20; 149:10
two-year [4] 17:10; 173:17;
 182:25; 207:13
type [6] 156:11, 18; 188:19;
 194:5; 196:10; 224:8
types [1] 173:13
typical [1] 153:5
typically [2] 55:15; 176:23
typified [1] 169:1

- U -

U.S. [8] 9:20; 16:2; 92:1, 4,

11; 94:8; 148:11
ultimate [8] 10:8; 131:6, 24;
 132:20; 133:9, 15; 135:5;
 221:22
Ultimately [1] 12:12
ultimately [7] 194:6; 198:23;
 207:1; 211:25; 231:15; 232:7,
 11
Un-huh [1] 163:20
unanswered [1] 116:17
unbalanced [1] 78:13
unblinded [1] 88:17
unbroken [1] 130:13
unchanged [1] 39:9
unclarified [1] 201:10
unclassified [1] 154:2
uncontrolled [3] 47:8; 49:22;
 50:5
underlying [1] 163:22
understand [21] 32:21; 42:10;
 63:5; 69:5; 70:13, 16; 83:23;
 85:13; 87:3; 100:18; 101:4, 20;
 102:7, 21; 107:7; 140:15;
 141:15; 169:5; 171:16; 174:16;
 188:10
understanding [5] 11:19;
 99:11, 14; 169:25; 186:14
understood [1] 89:10
unease [2] 186:20, 21
unemployment [1] 27:12
unexpected [1] 204:15
Unfortunately [2] 139:13;
 200:8
unfortunately [2] 98:8; 242:19
unilateral [4] 103:2, 10;
 133:17; 134:12
unintentional [1] 48:10
Union [1] 172:16
unique [2] 57:3, 7
United [11] 14:2; 22:20;
 91:24; 94:8; 99:2, 12; 152:6;
 158:18; 165:17; 172:6, 8
units [1] 104:16
univariate [3] 76:13; 151:13;
 154:6
University [11] 4:19; 5:1, 3, 4,
 7, 14; 18:23; 64:15, 21; 65:5;
 178:15
unjustified [1] 217:4
unknown [1] 121:5
unlikely [2] 8:12; 170:11
unmet [1] 115:22
unnecessarily [1] 172:13
unreasonable [1] 205:22
unresolved [1] 234:8
unsuccessful [1] 59:9
untreated [2] 23:9; 196:25
upper [3] 23:13, 15; 30:24
upset [1] 162:12
ureates [1] 79:24
uric [1] 48:1
urinalysis [1] 72:14
urine [1] 47:16
urines [1] 72:7
usage [1] 61:19
USDHS [1] 211:14
useful [15] 12:8; 34:22; 81:16;
 96:6; 116:25; 148:22; 199:13;
 200:8; 216:1; 218:7, 18;
 228:23; 230:20; 231:3; 236:14
uses [1] 203:6

USPHS [2] 16:17; 186:8
usual [4] 56:25; 74:3; 98:11;
 209:20
ut [1] 81:18
utility [2] 102:13; 191:3
utilize [2] 189:18; 217:1
utilized [1] 115:15

- V -

valid [1] 143:9
validated [1] 101:13
validity [1] 57:9
valuable [1] 242:10
value [5] 100:20; 102:22;
 103:4, 8; 225:7
values [21] 20:5, 8; 30:4, 7,
 10, 14; 80:18; 84:2, 14, 21;
 85:16; 102:18; 103:15; 111:4,
 22; 113:1, 6, 9, 10
variable [2] 63:1; 117:17
Variables [2] 32:24; 55:7
variables [9] 26:21; 32:16;
 33:7; 61:21; 77:4, 17, 18;
 100:1; 225:11
variations [2] 95:16; 117:19
varied [1] 30:16
varies [1] 134:1
variety [5] 12:19; 27:11; 90:8;
 97:14; 200:6
vary [1] 225:13
varying [1] 40:20
vectors [1] 94:1
verify [1] 244:9
version [1] 55:3
versus [31] 54:20, 24; 58:14;
 93:1, 12; 103:2, 3; 112:3, 4;
 113:2, 5; 125:23, 25; 131:12,
 13, 17; 132:1, 2, 5, 7, 22, 23;
 133:2, 3; 154:23; 193:8, 10,
 18; 194:6; 198:24; 239:20
Veterans [1] 7:1
viable [1] 196:16
Vice [4] 13:6; 18:10; 64:6, 10
view [2] 228:1; 234:10
viewed [1] 73:24
viral [2] 99:24; 227:18
virologist [2] 5:13; 202:2
virology [1] 159:13
virtually [2] 37:17; 199:21
virus [1] 160:11
visit [7] 22:25; 31:8; 35:6;
 121:1, 8, 9; 130:25
visiting [1] 225:3
visits [10] 24:9; 97:17; 116:3;
 121:1; 131:21, 23, 25; 138:13;
 142:12; 219:10
vitality [1] 209:8
vitro [8] 53:21; 57:5; 61:6;
 184:18; 185:11; 195:24;
 208:11; 238:16
voice [1] 184:4
voiced [2] 185:8; 207:16
volunteer [1] 21:24
vote [14] 6:22; 183:21, 22;
 184:2, 5; 194:23; 208:20;
 209:6, 8; 212:14, 18, 24;
 229:17
voted [1] 244:6
votes [1] 213:1
voting [2] 183:16; 212:22

vulnerability [1] 56:11

- W -

wage [2] 178:23; 192:1
wait [1] 114:9
waiver [2] 6:15, 16
wall [2] 55:16; 56:3
WALLER [5] 13:4; 62:11;
 173:15; 174:8; 183:10
Waller [3] 13:3, 6; 62:10
wanted [12] 70:6; 84:16; 85:3;
 90:7; 101:1; 103:19; 107:17;
 156:4; 166:1; 224:9; 240:18;
 243:23
warrant [1] 182:5
Washington [1] 5:3
water [1] 190:13
wave [1] 177:25
ways [9] 83:17; 130:11;
 180:24; 191:16; 217:19; 226:5,
 6; 242:2, 9
We'd [1] 181:13
we'd [1] 213:5
We'll [6] 65:15; 86:12, 17;
 90:21; 113:22; 183:11
we'll [5] 19:6; 114:3; 173:20;
 180:3; 183:22
We're [14] 4:9; 83:25; 84:1;
 96:7; 109:24; 113:21; 114:2;
 123:11; 138:3; 141:3; 181:1;
 184:13; 230:13; 235:23
we're [53] 68:16; 82:11;
 87:15; 105:9; 106:25; 107:21;
 109:25; 119:21; 121:13; 141:5;
 146:3; 172:8; 178:24; 182:21;
 183:12; 185:1; 189:7; 191:5;
 193:14; 194:2, 15, 18; 195:20;
 200:19, 20; 201:14; 204:1;
 207:11, 12, 14; 208:9; 209:7,
 10, 12;
 210:5, 8; 212:6; 213:3; 215:15;
 219:1; 221:3; 222:7, 22;
 223:25; 228:17; 229:6; 234:25;
 235:2, 17, 21; 236:3, 24;
 241:19
We've [3] 173:22; 204:1;
 238:10
we've [23] 19:4; 53:16; 85:18;
 105:4; 110:17; 153:15; 172:10;
 179:16; 187:12; 188:17; 196:2,
 8; 200:4; 205:7; 210:24;
 220:8; 222:17; 224:6; 225:7;
 235:5; 239:3; 242:6; 244:4
weak [1] 109:11
week [57] 53:20; 71:8; 77:23;
 78:3, 8; 105:13, 24; 106:4, 21;
 117:2, 10, 13; 149:13, 14;
 153:13; 154:20; 179:5, 9, 14;
 189:2, 3, 4, 20, 23, 24; 190:4,
 7, 11, 20; 194:5; 197:21;
 200:25; 204:17, 24; 215:3;
 218:21, 24, 25; 219:3; 220:24;
 221:1,
 12; 222:18; 223:25; 224:6, 25;
 226:2, 8; 227:6; 231:13; 242:7;
 243:14, 16
weekends [1] 35:15
weekly [55] 15:7, 8, 11; 25:4,
 10, 11; 35:20; 45:5; 48:19;
 50:15; 57:18; 59:14; 60:3, 9,
 18, 21; 78:18, 21; 79:1, 2;
 93:23; 103:23; 105:5; 109:10,
 16; 148:13; 163:5, 9, 15;
 183:4; 204:13; 205:17, 20;
 217:11, 13, 16, 21, 25; 218:3,
 8, 12; 219:19;
 237:25; 238:11, 12; 239:5, 18,
 20; 241:2, 3, 10, 14; 242:6
weeks [4] 50:16; 60:24;
 214:18; 241:1
weighed [1] 92:19
weight [6] 24:16; 25:6, 14;
 26:21; 27:6; 33:2
weird [1] 79:13
welcome [2] 4:5; 9:18
welcoming [1] 7:18
weren't [2] 72:8; 189:1
Western [1] 99:8
whack [1] 193:2
whereas [2] 172:3; 219:7
Whereupon [3] 113:24;
 164:13; 244:21
white [2] 58:20; 60:16
wholly [1] 60:14
wide [3] 12:19; 88:9; 140:11
widely [1] 235:25
wider [1] 12:2
width [1] 85:1
wild [2] 156:11, 18
wilds [1] 176:23
willing [3] 192:23; 194:18;
 226:3
WINTERS [1] 213:3
wisely [2] 179:22; 189:19
wish [2] 7:12; 174:13
wishes [1] 173:4
withdrawals [2] 28:2; 136:24
withdrew [1] 122:17
witnessed [1] 53:16
women [8] 14:4; 20:14;
 111:10, 22, 25; 112:10; 233:1,
 4
won't [5] 175:7, 24; 199:1;
 203:6; 233:17
wonder [4] 89:4; 107:10, 18;
 192:2
wonderful [1] 182:14
wondering [3] 82:8; 95:1;
 174:24
word [1] 141:10
wording [4] 115:14; 209:23;
 231:21, 22
work [9] 100:3; 168:24;
 173:19; 175:7, 9; 206:9; 218:9,
 10; 230:23
worked [2] 16:11, 14
working [5] 16:13; 162:19;
 166:4; 172:15; 196:1
workshop [1] 11:16
World [7] 14:9; 52:10; 65:7;
 145:1; 169:14; 178:16, 18
world [18] 94:5, 18; 172:6;
 176:13, 22; 177:11, 18; 179:2,
 25; 202:15; 205:21; 218:18;
 219:12, 13; 222:14; 232:4, 21;
 237:3
worldwide [1] 216:8
worried [1] 224:20
worry [2] 87:13; 202:21
worrying [2] 88:21; 228:10
worse [7] 85:18, 19; 125:22;

127:4, 6; 133:17; 199:2
 worst [2] 29:10; 44:4
 worth [3] 132:8; 143:7, 24
 worthwhile [1] 232:17
 Wouldn't [1] 101:16
 wouldn't [9] 79:7; 98:7;
 163:2; 216:10; 218:11; 220:20;
 224:10; 225:23; 243:20
 wrapped [1] 208:21
 wrestle [1] 207:19
 write [1] 198:11
 written [2] 6:17; 100:19
 wrong [1] 169:20
 wrote [1] 202:8

- X -

X-ray [6] 124:7; 130:6; 133:15,
 21; 136:15; 175:14
 X-rays [9] 33:25; 34:3, 5;
 73:18; 74:21; 75:4; 102:11;
 133:17; 199:2

- Y -

Yeah [18] 68:10; 69:5; 70:13;
 82:6; 85:13, 17; 86:19; 99:9;
 107:13, 15; 139:7; 160:7;
 161:16; 162:2; 163:8; 201:25;
 223:23; 241:17
 yeah [4] 66:22; 106:15;
 138:11; 214:12
 year [8] 13:22; 149:22;
 160:10, 15; 169:13; 171:12;
 172:7; 211:18
 years [33] 9:4; 10:14, 16;
 11:16, 21, 22; 12:1; 13:15;
 14:2; 23:8; 53:15; 61:18;
 149:16; 153:18; 157:2; 159:21;
 166:3, 20; 167:7, 22; 168:5,
 10; 170:19; 171:6, 13; 178:19;
 179:17; 181:16; 184:9; 185:22;
 211:2; 220:8
 yellow [1] 113:6
 York [11] 4:24; 60:18; 144:23;
 151:22, 24, 25; 152:4, 8;
 153:2, 5, 11
 you'd [6] 85:5; 107:10;
 175:20; 181:14; 221:24;
 226:14
 You've [4] 10:1; 165:22;
 181:3; 182:10
 you've [12] 51:16; 53:22;
 71:22; 85:17; 94:5; 98:10;
 107:19; 109:19; 159:11;
 180:13; 214:18; 223:20
 young [1] 153:6
 younger [1] 150:25
 yourself [1] 141:16

- Z -

Zero [1] 150:11
 zero [4] 42:24; 126:13;
 128:23; 129:7
 zone [1] 101:25