

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

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MEETING

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Thursday,
April 26, 2001

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The Committee met at 8:00 a.m. in the Versailles Rooms of the Holiday Inn Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, Dr. L. Barth Reller, Chairman, presiding.

PRESENT:

L. Barth Reller, M.D. Chairman
Gordon L. Archer, M.D. Member
Dave Battinelli, M.D. Invited Guest
David Bell, M.D. Invited Guest
Joan P. Chesney, M.D. Member
Celia D.C. Christie-Samuels, M.D.,
M.P.H. Member
Alan S. Cross, M.D. Member
Barry Davis, Ph.D. Invited Guest
Steve Ebert, Pharm.D. Consumer Representative
Zachary D. Goodman, M.D. Invited Guest
Ralph Lazzara, M.D. Invited Guest
William M. Lee, M.D. Invited Guest
James E. Leggett, Jr., M.D. Member
Arthur Moss, M.D. Invited Guest
Barbara E. Murray, M.D. Member
Jeremy Ruskin, M.D. Invited Guest
David E. Soper, M.D. Member
Ciro Sumaya, M.D. Invited Guest
Ellen R. Wald, M.D. Member
Thomas H. Perez, M.P.H., R.Ph. Executive Secretary

S A G CORP.

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P-R-O-C-E-E-D-I-N-G-S

(8:00 a.m.)

1
2
3 DR. RELLER: Would everyone, please take
4 their seats so we can begin our meeting? Good
5 morning. I'm Dr. Barth Reller from Duke University
6 Medical Center. I'd like to open today's meeting of
7 the Anti-Infective Advisory Committee. We'll begin
8 with introductions going around the table. To my
9 right, Dr. Dianne Murphy.

10 DR. MURPHY: I'm Dr. Dianne Murphy. I'm
11 the office director for ODE IV which has the
12 antimicrobials.

13 DR. SORETH: Good morning, my name is
14 Janice Soreth. I'm the acting director for the
15 Division of Anti-Infectives with FDA.

16 DR. KORVICK: Joyce Korvick, acting team
17 leader Medical Group.

18 DR. ROSS: David Ross, Medical Team
19 Leader, Division of Anti-Infective Drug Products.

20 DR. SOPER: David Soper, Medical
21 University of South Carolina in Charleston.

22 DR. CHRISTIE: Celia Christie from
23 Pediatrics and Infectious Diseases University of the
24 West Indies, Kingston, Jamaica.

25 DR. WALD: Ellen Wald, University of

1 Pittsburgh, School of Medicine, Pediatric Infectious
2 Diseases.

3 DR. ARCHER: Gordon Archer, Virginia
4 Commonwealth University in Richmond, Virginia.

5 DR. CHESNEY: Joan Chesney, the University
6 of Tennessee in Memphis, Division of Infectious
7 Diseases and Pediatrics and St. Jude's Children's
8 Research Hospital.

9 DR. MURRAY: Barbara Murray, University of
10 Texas Medical School in Houston, Adult Infectious
11 Diseases.

12 MR. PEREZ: Tom Perez, Executive Secretary
13 for the Anti-Infective Drugs.

14 DR. EBERT: Steve Ebert, Professor of
15 Pharmacy, University of Wisconsin and Meriter
16 Hospital, Madison.

17 DR. LEGGETT: Jim Leggett, Providence
18 Portland Medical Center and the Oregon Health Sciences
19 University.

20 DR. DAVIS: Barry Davis, University of
21 Texas, School of Public Health in Houston.

22 DR. BELL: David Bell, assistant to the
23 director for Antimicrobial Resistance, the National
24 Center for Infectious Diseases at CDC.

25 DR. GOODMAN: Zachary Goodman,

1 Hepatopathology Division of the Armed Forces Institute
2 of Pathology.

3 DR. LAZZARA: Ralph Lazzara, University of
4 Oklahoma, Cardiology.

5 DR. RUSKIN: Jeremy Ruskin, Cardiology,
6 Massachusetts General Hospital, Boston.

7 DR. BATTINELLI: Dave Battinelli, General
8 Internal Medicine, Boston University School of
9 Medicine.

10 DR. LEE: Will Lee, UT Southwestern in
11 Dallas, Hepatology.

12 DR. SUMAYA: Ciro Sumaya, School of Rural
13 Public Health, Texas A & M University Health Science
14 Center.

15 DR. RELER: Thank you. We're delighted
16 to have not only our members but guest experts who
17 will be presenting at the meeting and participating in
18 the discussions today. We'll now have our opening
19 statement by Mr. Tom Perez, our Executive Secretary.

20 MR. PEREZ: Good morning. The following
21 announcement addresses conflict of interest with
22 regard to this meeting and is made a part of the
23 record to preclude even the appearance of such at this
24 meeting. Based on the submitted agenda for the
25 meeting and all financial interests reported by the

1 committee participants, it has been determined that
2 all interests and terms regulated by the Center for
3 Drug Evaluation and Research present no potential for
4 an appearance of a conflict of interest at this
5 meeting with the following exceptions.

6 In accordance with 18 U.S.C. 208(B) full
7 waivers have been granted to Drs. Gordon Archer,
8 Barbara Murray and Ellen Wald. A copy of these waiver
9 statements may be obtained by submitting a written
10 request to the agency's Freedom of Information Office,
11 Room 12A30, The Park Lawn Building. In addition we
12 would like to disclose for the record that Drs. Gordon
13 Archer, Steven Ebert and James Leggett have interests
14 which do not constitute a financial interest within
15 the meaning of 18 U.S.C. 208(A) but which could create
16 the appearance of a conflict.

17 The Agency has determined notwithstanding
18 these interests that the interests of the government
19 in their participation outweighs the concern that the
20 integrity of the agency's programs and operations may
21 be questioned.

22 With respect to FDA's invited guests,
23 there are reported interests which we believe should
24 be made public to allow the participants to
25 objectively evaluate their comments. Dr. Jeremy

1 Ruskin would like to disclose that he and his spouse
2 own stock in Pfizer and Merck. He also has received
3 consultant fees from Pfizer and Roche and has lectured
4 for Eli Lilly.

5 Dr. Barry Davis would like to disclose
6 that he is the PI on an unrelated grant from Bristol-
7 Myer Squibb and he is a consultant on unrelated
8 matters for the steering committee for Merck and Glaxo
9 Smith Kline. He is also consultant on unrelated
10 matters for Menarini Corp. Data and Safety Monitoring
11 Board and Pfizer's Data and Safety Monitoring Board
12 for Alliance.

13 Dr. William Lee would like to disclose
14 that he is a researcher for Glaxo Smith Kline, Bristol
15 Myer Squibb, Roche and Schering Plough. He also has
16 lectured for Roche.

17 Dr. Arthur Moss would like to report that
18 he has and will consult for Abbott Labs on unrelated
19 matters. He has also consulted on unrelated matters
20 for Eli Lilly.

21 Dr. Ciro Sumaya would like to disclose
22 that he owns stock in Glaxo Smith Kline and Pfizer.
23 Thank you.

24 One more thing, actually two more things.
25 In the event that the discussions involve any other

1 products or firms not already on the agenda for with
2 an FDA participant has a financial interest, the
3 participants are aware of the need to exclude
4 themselves from such involvement under exclusion will
5 be noted for the record. In addition, it has come to
6 our attention that some of the materials that FDA
7 typically puts up on the website were not made
8 available till late yesterday evening. They typically
9 go out the day before, hopefully, you know, as much as
10 24 hours before. We apologize for any inconvenience
11 this may have caused anyone.

12 We have brought several copies of the
13 background materials with us. They are available for
14 anyone wishing to review them at the FDA table out
15 front in the lobby. Again, our apologies for any
16 inconvenience this may have caused anyone. Thank you.

17 DR. RELLER: Thank you, Tom. We shall
18 next have opening remarks by Dr. Diane Murphy, who is
19 the Director of the Office of Drug Evaluation IV.

20 DR. MURPHY: I want to again thank our
21 committee members, our guests, sponsors and everybody
22 who is here to listen to these deliberations because
23 they -- the discussions today will involve topics that
24 this committee in particular has dealt with a number
25 of times. But, it always gets a little bit more

1 precise when we have a product instead of a general
2 topic. We have four issues that I think
3 you will hear themes brought up that, again, don't
4 just relate to this product. One has to do with the
5 development of drugs to treat infections that are
6 caused by resistant organisms and the need to make
7 sure we have a pipeline of products that are being
8 developed and yet at the same time that these products
9 developed are used in a way that does not undermine
10 our ongoing use of them and some people calls this
11 prudent use.

12 For us what it relates to or where it is
13 particularly important is because the patients who
14 have resistant organisms will be small in number
15 compared to the broad development plan that companies
16 will have, how do we deal with these issues of prudent
17 use of antibiotics when we have broad development
18 plans. And there's a benefit to a broad development
19 plan because it gives us a better picture of what the
20 adverse event profile may be. And that's a benefit to
21 everybody because as you know, the ability to detect
22 signals, a particularly rare signal, is limited by
23 sometimes our preclinical cause and certainly the size
24 of them.

25 And we also know that our trials are

1 designed in such a way that we often exclude
2 populations because, again, they can only be so large,
3 you need to be able to clearly delineate what's going
4 on in a trial. However, once a product is approved,
5 then that product is used by a population that may not
6 have been included in the studies and appropriate use
7 meaning for the right indication. I'm not talking
8 about off-label prescribing. And that brings us to
9 the issue of enhanced risk as far as what are the --
10 what are the characteristics of the population that
11 may be taking products that are developed for a more
12 general use.

13 And I think all of us understand that many
14 of our older populations are on numerous products that
15 may have interactions. And this has been an
16 increasing issue for all the sponsors and for FDA and
17 that happens to be Cytochrome P450 and the interplay
18 between products that rely on these systems and their
19 interactions with other drugs.

20 Many of the sponsors have attempted to
21 address specific interactions and that's become an
22 increasing part of our drug development request.
23 However, again, populations that will be using this
24 and other products often take multiple products of
25 which it would be very difficult to ask a sponsor to

1 develop every possible combination that a patient may
2 be taking. So we have to look at the potential risks
3 when we're looking at our risk benefit ratio, which is
4 what we always do.

5 And the last thing that is another focus
6 of this discussion and many of you have heard these
7 discussions previously but we want to have some
8 background information presented to you this morning
9 and that's what we'll call the silent serious adverse
10 events particularly if they're rare but how do we deal
11 with adverse events such as QT and hepatic toxicity.
12 You don't break out in a rash. You know, you don't --
13 you may not know you're having that complication. How
14 do we deal with these in making our availability of
15 products appropriate and making sure that we have come
16 to the correct risk benefit assessment in our approval
17 and in our availability of these products.

18 These are complex issues and we really do
19 thank you for being here, for putting time and effort
20 into preparing for this discussion because many of the
21 things that we move forward on are evolving and your
22 discussions are important in helping us expand how we
23 think and how sponsors think about the development of
24 products in this area. Thank you.

25 DR. RELLER: Thank you, Dr. Murphy. Next

1 we'll have Dr. Janice Soreth, who is the acting
2 Director of the Division of Anti-Infective Drug
3 Products.

4 DR. SORETH: Good morning. Before I speak
5 a little bit to the organization of presentation for
6 our meeting today, I wanted to first make a quick
7 apology to members of the advisory committee who may
8 have experienced more than the usual difficulty in
9 making travel arrangements. I think recently some of
10 the rules may have changed, if not, in fact, then
11 contract and it came however late, that there was
12 well, let's just say glitches. We promise you in the
13 future we'll work very closely with you so that this
14 experience is improved upon.

15 I wanted to talk a little bit today about
16 the charge that is put before you as our Anti-
17 Infective Advisory Committee and that charge is
18 essentially to weigh in on the evidence that you'll
19 see presented to you today by both our colleagues at
20 Aventis as well as here at FDA on whether or not
21 substantial evidence has been submitted to speak to
22 both the efficacy of Ketek (Telithromycin) as well as
23 safety.

24 In order to strike that balance, we have
25 a couple of issues that you'll hear more about and

1 that this committee has heard quite a lot about in the
2 past decade or so for we have had no fewer than a half
3 a dozen meetings product specific for antimicrobial
4 agents that were requesting indications that included
5 resistant organisms as well as at least three or four
6 meetings in the past five years that have been non-
7 product specific, speaking to the appropriate
8 development scheme or schema for drugs seeking
9 resistant claims and in the same breath trying to
10 strike a balance with that, again, in the interest of
11 the public health for what the prudent uses of those
12 antimicrobials would be.

13 Next slide. In addition to hearing a
14 discussion of resistance previously as well as today,
15 we will also be focusing on safety. I think it a fair
16 statement that the independent FDA analyses that have
17 been conducted on Telithromycin data are in agreement
18 in general with those conducted by Aventis. We know
19 in general that with regard to safety, clinical trials
20 are not really powered to address those events which
21 are uncommon or rare.

22 Instead clinical trials are powered in the
23 realm of antimicrobial research to address efficacy
24 issues. Should safety concerns arise anywhere in a
25 development program, I think there are basically three

1 options; stop, and that's usually what happens if the
2 adverse events notes are of a very serious nature,
3 like death. Short of that, when we're not dealing
4 with a body count, but either clinical or laboratory
5 adverse events, there are additional options and those
6 include additional studies conducted premarketing that
7 would shed further light on the elucidation of risk
8 management to understand what the safety profile of a
9 product would be for its intended use.

10 At other times, given a particular
11 development program, one may choose to proceed given
12 the data that's been developed and try to put a drug
13 on the market and in the setting of post-marketing
14 have inquiry either in the setting of additional
15 trials or active surveillance so to speak, to
16 understand the use of the product, the safety of the
17 product in the setting of general use. We know that
18 our Phase III trials attempt to tell us that
19 information but at the end of the day we also know
20 that the experience with concomitant drug use and co-
21 morbidities is sometimes a small experience in Phase
22 III trials, even if the Phase III trial is relatively
23 large. The devil is in the details.

24 Exposure for a product that would target
25 respiratory infections such as you'll hear today is

1 one with potentially very, very broad use with
2 millions of prescriptions potentially written in a
3 single year. Next slide.

4 What are some of the lessons learned at
5 the agency with regard to safety? I would offer that
6 we have learned through experiences with Mibefradil or
7 Posicor, Terfenadine, Durac, et cetera, that once
8 prescribing patterns are established for a drug, it
9 becomes very, very difficult to change those patterns.
10 Next slide, please.

11 So to that end, we need to do it right and
12 we need to do it right the first time because again,
13 I think that is in the best interests of the public
14 health and it is also in the best interest of what I
15 think of as the marketing half-life of a product.
16 Next slide, please.

17 When in need, steal from a better writer.
18 Dr. Temple published a paper in JAMA in 1999 that
19 spoke to alternative means of looking at and gathering
20 safety information for new drug development and I
21 quote from that paper,

22 "The possibility of using more rigorous
23 methods, namely large, simple trials, to
24 detect such risks",
25 and by such it referred to a previous

1 point of modest risk, that which was not necessarily
2 common, somewhere between common -- certainly less
3 than common to rare,

4 "methods which would detect such risks
5 should be considered in some cases for
6 example, where very wide exposure is
7 expected".

8 And I would submit to you that for many
9 if not most of the antimicrobial products that have
10 come before this committee and come before us in the
11 agency, we typically are looking at broad use. Only
12 relatively recently in the setting of development of
13 drugs for resistant bacteria have we begun to talk a
14 lot about prudent use equalling less than very broad
15 use, again, in order to try to preserve those
16 products. Next slide.

17 And finally again from the paper in JAMA
18 authored by Dr. Temple, "If a question is important",
19 and I would add if a question is important
20 particularly with regard to safety, "answering it may
21 well be worth the cost and the effort".

22 We're going to hear this morning
23 presentations that are essentially a QT Primer 101 by
24 Dr. Jeremy Ruskin followed by an FDA presentation that
25 will take us through a tour of some of the post-

1 marketing data speaking to Torsades de Pointes and
2 finally wrapping up the morning will be presentations
3 on Ketek from Aventis. We'll break for lunch and then
4 come back and hear presentations from FDA underlining
5 where we, I think, see eye to eye on the efficacy data
6 in general but perhaps not clearly as much on safety
7 and finally wrap up with a discussion and a vote by
8 the committee.

9 I thank you for your attention and turn
10 the podium back to Dr. Reller.

11 DR. RELLER: We now look forward to the
12 presentation of Dr. Jeremy Ruskin.

13 PRESENTATION OF DR. JEREMY RUSKIN

14 DR. RUSKIN: Good morning. I was asked to
15 give a very basic introduction to this issue of QT
16 prolongation and Torsades and that's what I will
17 attempt to do but let me apologize in advance to the
18 many people in this room who are already well familiar
19 with these data. This is obviously a complex and
20 difficult subject from a regulatory perspective and I
21 certainly don't have any answers to it. What I can
22 hope to do perhaps is help frame some of the
23 discussion that will follow as we hear the data and
24 talk about these issues.

25 This is an example of the problem that

1 everyone is concerned about. This is a polymorphic
2 ventricular tachycardia occurring in the setting of a
3 long QT interval and in this particular situation it's
4 occurring in the setting of a bradycardia, which was
5 the circumstance under which Torsades was first
6 described. In fact, it was first reported in the
7 setting of complete heart block and we have learned
8 over the years that bradycardia is one of the most
9 potent predisposing conditions to the occurrence of
10 this form of tachycardia.

11 Now, what I'd like to do in this slide is
12 make an analogy between the occurrence of drug induced
13 Torsades with non-antiarrhythmic drugs and a
14 lightning strike and the analogy is based on the fact
15 that -- it's not going to work. So much for my tricks
16 with PowerPoint. There was text. The text for this
17 slide basically said that this is a rare event, very
18 rare, potentially life threatening however and very
19 difficult to predict in any individual despite the
20 fact that we are aware of risk factors and can define
21 some of those risk factors.

22 There it is. The issue of QT prolongation
23 and Torsades spans many disciplines and that -- I
24 think that is familiar to everyone who has looked at
25 these data and these include cardiac

1 electrophysiology, pharmacology, genetics, and both
2 clinical practice and regulatory medicine and we'll,
3 obviously, be confronting all of these areas as we
4 talk about the data. What I'd like to do in the next
5 several minutes then is say a few words about the
6 mechanisms of QT prolongation and Torsades, talk a
7 little bit about how drugs effect that QT interval,
8 say a few words about some specific agents that serve
9 as illustrative examples of the problem that we're
10 grappling with, emphasize some of the risk factors
11 associated with drug induced Torsades and also then
12 mention at least a few comments about the clinical and
13 regulatory implications.

14 This is a partial list of drugs that have
15 been shown to prolong the QT interval. Many of these
16 have been associated with rare instances of Torsades.
17 The list is actually incomplete and I show it just to
18 emphasize one, the very large number of agents that do
19 effect cardiac repolarization and two, the fact that
20 these agents span almost every therapeutic discipline
21 in medicine, or at least certainly many of the major
22 ones including neurology, allergy, cardiology,
23 infectious disease and psychiatry.

24 There are two major syndromes, if you
25 will, of long QT, the first being congenital which we

1 are not going talk about today except in passing and
2 second the acquired long QT syndromes which is clearly
3 the topic of interest today, the major cause of which
4 at least for the purposes of today's discussion are
5 drugs. But it's important to emphasize that drugs are
6 not the only cause of acquired long QT and this has
7 implications when one talks about multiple risk
8 factors and these include bradycardia, electrolyte
9 abnormalities and certain forms of heart disease
10 including hypertrophy and congestive heart failure in
11 which repolarization is intrinsically abnormal.

12 This slide is shown just to illustrate the
13 fact that cardiac electrical activity is comprised of
14 a fairly heterogenous group of action potential
15 configurations and durations. But in the normal
16 situation, the heterogeneity exists within fairly
17 tight boundaries and when that heterogeneity is
18 exceeded either as a result of a drug or some
19 pathologic state, we have an environment in which
20 arrhythmias can occur and one form of these
21 arrhythmias is Torsades de Pointes which we'll focus
22 on today. The major interest with regard to today's
23 discussion focuses not on depolarization but rather on
24 repolarization which results from a complex series of
25 events that involves many ion channels. But for the

1 purposes of today's discussion and particularly with
2 reference to drugs that cause Torsades, one can
3 simplify this and this is a gross over-simplification
4 to a discussion primarily of three channels, the
5 sodium channel which is responsible for
6 depolarization, and then the calcium channel which is
7 responsible for the plateau phase of the action
8 potential and then repolarizing potassium currents, in
9 particular the rapid and slow components of the
10 delayed rectifier current.

11 It turns out, and this will come up
12 repeatedly, that almost all of the drugs that are
13 known to cause Torsades in fact, effect this channel.
14 And it's also important to emphasize that the duration
15 of the action potential, which is what determines the
16 duration of the QT interval, is a complex inter-play
17 of all of these channels and it is possible to prolong
18 the action potential duration by interfering or
19 inhibiting the outward movement of potassium from the
20 cell.

21 One could also enhance inward movement of
22 calcium thereby prolonging the plateau phase and if
23 the sodium channels fail to inactivate when they
24 normally should, it's also possible to prolong action
25 potential duration. But the primary mechanism by

1 which this occurs in clinical practice with the drugs
2 that we use, is a result of block of the IKr current.

3 The question of why IKr is so sensitive to
4 a drug inhibition is not completely understood but
5 there are some fascinating data from Dr. Sanguinetti's
6 lab in Utah which are based primarily on structural
7 analyses of the -- of IKr, of HERG and suggest that
8 this channel has a particularly large vestibule in the
9 pore region, that's an intra-cellular receptor
10 obviously in which potassium is pumped from inside
11 the cell to the outside of the cell.

12 This pore region and, particularly the
13 vestibule of this pore region, is unusually large
14 compared with other channels and for that reason
15 appears to have a certain degree of non-specificity to
16 it with regard to its capacity for drug trapping. So
17 many, many drugs in fact will effect IKr and this is
18 largely a concentration dependent phenomenon. If you
19 give enough of many, many drugs, you will get an
20 effect on IKr. The question really is what is the
21 potency of that effect and how does it translate at
22 therapeutic concentrations into an effect on the QT
23 interval in humans.

24 The mechanism of Torsades de Pointes is
25 not completely understood but there are important

1 observations that have come to light in the last five
2 to seven years that suggest that while early after
3 depolarizations which is a focal mechanism and was
4 previously thought to be the primary mechanism, is
5 probably not responsible for the arrhythmia itself,
6 that is the sustained arrhythmia, but rather it is
7 likely due to a form of reentry within the wall of the
8 ventricle muscle. And this is a copy of a figure from
9 a manuscript by Charles Antzelevitch, who has done
10 some seminal work on examining different layers within
11 the left ventricular myocardium and demonstrating that
12 in fact, action potential characteristics in the
13 epicardium, mid-myocardium and endocardium are quite
14 different and that this heterogeneity within the wall
15 of the muscle may be in part responsible for
16 susceptibility to drug induced effects and the
17 occurrence of Torsades.

18 These are recordings also from a paper
19 from Antzelevitch's lab demonstrating that the mid-
20 myocardia layer, the so-called M cells generally have
21 significantly longer action potential durations than
22 cells within the sub-epicardium and in the endocardium
23 and in addition, these M cells appear to be more
24 sensitive to rate effects particularly slowing of the
25 rate, and to drugs which inhibit IKr than either the

1 endocardium or the epicardium. And remember we talked
2 earlier about the issue of heterogeneity. When one
3 has heterogeneity within the wall of the muscle or any
4 other place in the heart, one has a potential
5 substrate for a re-entrant arrhythmia and this is just
6 a cartoon that created by lifting these action
7 potential figures from one of Antzelevitch's papers,
8 lining them up with the epicardium, mid-myocardium and
9 endocardium and if one gets significantly long enough
10 prolongation within the mid-myocardial layer, such
11 that this area is unresponsive for a longer period of
12 time than either the epicardium or the endocardium,
13 the potential for re-entry exists.

14 And one of the proposed mechanisms of
15 Torsades is as follows. A ventricular premature beat
16 perhaps due to an early after depolarization may arise
17 anywhere within the heart and I've just placed it in
18 the endocardium. These can arise from the mid-
19 myocardium or from the His-Purkinje system and this
20 ventricular premature beat occurs with timing such
21 that when it conducts into the mid-myocardial layer,
22 it encounters refractoriness because of the long
23 action potential duration in this portion of the
24 ventricular wall, and therefore, it blocks.

25 It then travels around this zone of block

1 for a sufficient period of time to reach some portion
2 of the mid-myocardium that has recovered and once it
3 does that, it can excite the mid-myocardial layer,
4 reach the epicardium and then descend again through
5 the wall of the heart, resulting in a re-entrant
6 arrhythmia. And there are very good animal models
7 demonstrating that this is capable of producing what
8 we see in clinical Torsades, that is a polymorphic VT
9 varying configuration.

10 In fact, if one thinks of these as rotors,
11 three dimensional rotors, that may migrate through the
12 wall of the heart, it's not hard to imagine how the
13 kind of polymorphic VT that we see in drug induced
14 Torsades could be produced by this form or re-entry.

15 Now what about the QT interval? The QT
16 interval, as you all know, is an electrocardiographic
17 measurement. It's made from the onset of the Q wave
18 to the end of the T wave and is taken to represent
19 repolarization. In fact, it represents both a
20 combination of depolarization because it includes the
21 QRS complex and repolarization. And it's important to
22 emphasize that drugs or pathologic states that prolong
23 the QRS duration may, in fact, effect the QT interval
24 and if we were going to be purists about it, we would
25 probably measure the JT interval but in clinical

1 practice and drug development, that is not done.

2 It's also important to emphasize that this
3 is not an easy measurement to make with a high degree
4 of accuracy. The little boxes on those EKG's are 40
5 milliseconds. The calipers are about 20 milliseconds
6 wide, half a box or a little less than that and there
7 is tremendous variability both in the way that it's
8 measured and also in the measurement itself within any
9 individual over the course of 24 hours. So the
10 techniques that are used to measure QT intervals and
11 to assess the effects of drugs need to be extremely
12 precise and this is not an easy undertaking.

13 Automated QT analysis has been used in a
14 number of programs. I don't think it's used much any
15 more. We all look at EKG's that show us QT interval
16 measurements and while they are often quite reliable
17 in the setting of normal T waves at physiologic heart
18 rates, they are unreliable at extreme of heart rate
19 and certainly in the presence of abnormal T waves or
20 prominent U waves. In addition, the automated
21 analyses tell us nothing about the TU wave complex
22 morphology, a feature of these EKG's that is extremely
23 important to pay attention to because drugs, in fact,
24 may alter the QT -- excuse me, the TU morphology as
25 their only sign of an effect on IKr and I've seen

1 situations in which a significant QT effect has been
2 missed entirely because of failure to pay attention to
3 morphological changes.

4 So these EKG's have to be analyzed by
5 people who are expert at doing it and if they're done
6 by technicians, they need to be over-read carefully by
7 cardiologists. This is an electrocardiogram from an
8 entirely asymptomatic young individual who turns out
9 to have a genetic abnormality that is a polymorphism
10 of an HERG, an IKr abnormality, and the evidence of
11 that is in lead two, in which there is a splayed,
12 notched T wave with a fairly large U wave. This
13 morphological change is fairly typical of one form of
14 the congenital long QT syndrome, the one that effects
15 IKr and it's also not uncommon with drugs that have
16 very significant effects on IKr.

17 This QT-U complex -- this pointer is on
18 way out. If you have a backup, I'd be very grateful.
19 This QT-U complex is distinctly abnormal but if you
20 didn't notice this, and simply looked at the automated
21 analysis, you'd see a QT of 400 and a QTc of 401. In
22 fact, those numbers are wrong and in addition, there
23 is no comment at all -- thank you -- about the
24 morphologic abnormality which is really the only way
25 to detect this problem.

1 Sorry about that. Thanks. The QT
2 interval is a variable phenomenon. It is highly
3 labile and one of the most important influences on the
4 QT is heart rate. You can see that the QT interval
5 prolongs at slow heart rates and shortens at high
6 heart rates. There's a direct relationship between
7 cardiac cycle length and QT; the slower the cycle
8 length, the longer the QT, the shorter the cycle
9 length, the shorter the QT and in order to make
10 comparisons at different times of day or under
11 different circumstances, one has to use correction
12 formulae that take into account the effective rate on
13 the QT interval in any one individual.

14 In the vast majority of development
15 programs, and certainly in clinical medicine, the
16 formula that's used is the Bazett Formula which is the
17 QT interval, the absolute QT divided by the square
18 root of the RR interval that precedes that measured
19 QT. And in the general population, this averages
20 somewhere around 380 to 400 milliseconds, probably
21 closer to about 380 milliseconds. The problem is that
22 the Bazett formula is extremely limited. It falls
23 apart at high heart rates and at very low heart rates
24 and it is, in fact, probably the least accurate of all
25 the formulae that are available. It was kind of

1 defined into existence about 70 or 80 years ago based
2 on 39 patients who were reported by Bazett and because
3 it was the first description of this correction, it
4 has stuck, but it is clearly a problem and one that I
5 would at least argue should be abandoned.

6 There are many other formulae, including
7 Fridericia, which uses the cube root baseline
8 correction formula and a host of linear and non-linear
9 regression formulae that can be used to correct for
10 heart rate. I'm not aware of a perfect way of doing
11 this. This is an area where the state of the art has
12 not yet been defined and it is certain influx. I
13 think the only important point I would emphasize is
14 that the Bazett formula has very major limitations and
15 particularly in the setting of drugs that increase
16 heart rate may result in very misleading QTc
17 intervals, that is over-estimates of the QTc interval.

18 The formula tends to over-correct, that is
19 give you a longer corrected QT when the heart rate
20 goes up. The normal range for intervals is listed
21 here and for males it's somewhere under 430, females
22 under 450. Clearly prolonged is greater than 450 in
23 males and greater than 470 in females and this gender
24 difference is important, not terribly well understood,
25 but what is clear is that females tend to have longer

1 QTc intervals at baseline and are also generally more
2 susceptible to the effects of IKr blocking drugs and
3 in fact, much if not most of the drug induced Torsades
4 that occurs tends to occur in women and I'll show you
5 some data on that in just a minute. In fact, I'll
6 show it to you here.

7 These are data from two separate series.
8 This series was reported by Makkar in 1993 in which he
9 analyzed 332 cases of anti-arrhythmic drug induced
10 Torsades de Pointes in which either a QT or a QTc
11 interval was measured around the time of the event.
12 And what he found was that about 90 percent of the
13 patients who were described in these series had
14 corrected QT intervals of greater than 500
15 milliseconds and of those in whom the QT but not the
16 QTc was reported, about 80 percent had a QT greater
17 than 500, suggesting that the degree of QT
18 prolongation particularly when it exceeded 500
19 milliseconds, may be important in defining a subset of
20 patients at increased risk for Torsades.

21 A similar analysis in 189 cases of
22 Torsades with non-anti-arrhythmic drugs turned up
23 virtually the same numbers. That is the vast majority
24 of reported cases had QTc's or QT's greater than 500
25 milliseconds at the time of the event. There is,

1 however, a potential reporting bias here and one has
2 to be very careful about interpreting these data
3 because we don't know what the denominator is in fact,
4 investigators may be somewhat biased away from
5 reporting cases in which the QT is not markedly
6 prolonged. There's no way to know that with certainty
7 but these are the best data we have.

8 These are the gender distributions in both
9 series with anti-arrhythmic drugs. Seventy percent of
10 the events occurred in women, 30 percent in men and
11 with non-anti-arrhythmics it looks essentially exactly
12 the same and this is obviously important in a drug
13 development program wherein assessing the potential
14 risks of a drug you have to have data on sufficient
15 numbers of women to determine whether there is a
16 gender difference because clearly this is a risk
17 factor for drug induced Torsades.

18 Now, what about some specific agents or at
19 least classes of agents? I've divided them into two
20 categories and I think about drugs in terms of two
21 categories; those in which the therapeutic effect of
22 the drug is directly tied to its IKr blocking
23 properties and if you don't have the IKr effect you
24 don't have the therapeutic effect and these are the
25 anti-arrhythmic drugs, a least a partial list of the

1 anti-arrhythmic drugs that exert this effect and we
2 understand and accept the fact that Torsades de
3 Pointes is part and parcel of using these agents.
4 Most of them have an incidence of Torsades that is in
5 the range of one percent and sometimes a little
6 higher.

7 What's more important for the purposes of
8 today's discussion and what creates the regulatory
9 conundrum that everybody is facing these days are the
10 low risk drugs, that is drugs in which the therapeutic
11 effect is entirely independent of the IKr blocking
12 properties of the drug, where in situations in which
13 the IKr blocking effect is an undesirable side effect
14 of the drug and in which the risk of Torsades is very
15 low, that is less than .1 percent and often two orders
16 of magnitude less frequent than that. And these
17 include drugs that you're familiar with,
18 antihistamines, antibiotics, antiviral agents,
19 psychotropics and many, many other agents.

20 The occurrence of drug induced Torsades de
21 Pointes generally with the latter class of drugs and
22 that's all I'm going to focus on for the rest of this
23 discussion, that is the drugs in which Torsades is an
24 extremely rare occurrence, the occurrence of TdP in
25 that situation is rarely a result of the use of the

1 single agent by itself in a perfectly normal patient.
2 It is more commonly due to the combination of a mild
3 but modest drug effect on IKr in the setting of an
4 effect amplifier. And this is a challenge because
5 it's very hard to study all of these and two, it's
6 extremely difficult to predict them in any population
7 or any one individual over the course of time and
8 these include bradycardia, electrolyte abnormalities,
9 heart disease, particularly hypertrophy or congestive
10 heart failure in which we know IKr is down regulated
11 and action potential durations are long to start with,
12 atrial fibrillation in which irregular cycle lengths
13 predispose to the occurrence of Torsades particularly
14 in the setting of anti-arrhythmic drugs, female
15 gender, undetected mutations in the HERG gene, which
16 codes for IKr. We know now that there are individuals
17 out there who have phenotypically normal EKG's and who
18 are asymptomatic yet who carry mutations in the HERG
19 gene and are susceptible to polymorphic ventricular
20 tachycardia and sudden death and these patients, while
21 probably not numerous, are probably when exposed to
22 IKr blocking drugs, significantly more sensitive than
23 those who don't have these mutations.

24 High doses of drugs, metabolic inhibitors
25 that result in pharmacokinetic interactions and

1 pharmacodynamic interactions with other drugs that
2 cause IKr blockade. This is just an example of the
3 impact of hypokalemia on potency of IKr blockade.
4 This is from Dan Roden's lab, showing you ~~some~~
5 examples of -- excuse me, these are concentration
6 effect curves on IKr and let's just look at quinidine
7 for a moment. This would be the IC50, the
8 concentration of quinidine ~~required~~ to produce 50
9 percent block of the channel and you can see that at
10 eight millimolar potassium, the IC50 is 3.8. This
11 falls to 0.4. That is an order of magnitude change in
12 potency at a potassium concentration of one
13 millimolar. So electrolyte abnormalities can unmask
14 a potentially very serious effect that would not be
15 seen in the setting of normokalemia.

16 Metabolic interactions are obviously
17 critically important. These were eluded to by -- in
18 the introductory comments by previous speakers. In
19 particular many IKr blockers are either CYP450
20 substrates and some of them are CYP450 inhibitors and
21 that creates the potential for interaction both in the
22 gut wall and in the liver and terfenadine is a good
23 example of that and I'll come back to that in just a
24 moment. In addition, elimination may also be an
25 important issue particular in the setting of drugs

1 that are renally excreted like Sotalol and Dofetilide.
2 Renal dysfunction may predispose patients to markedly
3 elevated plasma concentrations and increased risk of
4 QT prolongation and Torsades.

5 This is just a partial list of 3A4
6 inhibitors to emphasize that they span a fairly broad
7 spectrum of therapeutic classes and with many of these
8 drugs and in particular grapefruit juice, which
9 effects gut 3A4, the effect of these agents on the
10 enzyme systems may long outlast the presence of the
11 drug in the body. This is just a partial list of
12 drugs that cause Torsades. All of them are IKr
13 blockers and I show it just to emphasize that most of
14 them are also either 3A4 substrates or inhibitors.
15 It's an unfortunate combination of properties.

16 Here's an example of this kind of
17 interaction, Terfenadine, well-known to everybody in
18 this room, a drug with rather modest effects by itself
19 when used at indicated -- at recommended doses of 60
20 milligrams BID, the effect trough on the QT interval
21 was about 6 milliseconds, at peak about 18
22 milliseconds when given alone, but in the setting of
23 a potent CYP3A4 inhibitor, there were marked increases
24 in plasma Terfenadine concentrations and profound
25 effects on the QTc in the range of 80 milliseconds.

1 This is a drug that is subject to very significant
2 first pass metabolism. Terfenadine largely disappears
3 by the time its passed the liver and the active
4 metabolite effects of Fenadine is, in fact, the drug
5 with the antihistaminic effect but the QTc liability
6 is related to the parent compound.

7 And if the parent compound is not
8 metabolized in the gut or the liver effectively and
9 the body sees large concentrations of it, this is the
10 impact. This just emphasizes the difficulty in
11 detecting this kind of risk. Trefenadine was
12 prescribed more than 100 million times during the time
13 that it was on the market. During the course of its
14 development, it appeared to have relatively modest
15 effects on the QTc interval by itself, but in the
16 presence of Ketoconazole, marked increases in QTc, a
17 clear-cut risk of Torsades and an increased risk of
18 sudden death which led ultimately to the withdrawal of
19 this agent.

20 Another example is Cisapride, which was
21 also recently withdrawn. This is a modest IKr blocker
22 with an effect on QTc, that's under 10 milliseconds.
23 It is a CYP3A4 substrate and in the setting of CYP3A4
24 inhibitors, patients were exposed to markedly
25 increased concentrations of the drug. Again, very

1 difficult to detect any risk in the development
2 program, more than 30 million prescriptions written
3 for the drug, no arrhythmia signal and a very large
4 data base review or in the NDA, yet between '93 and
5 '99 there were 270 cases of serious arrhythmias of
6 which 70 were fatal reported to FDA and ultimately the
7 drug was withdrawn.

8 If one simply looks at these numbers,
9 there's an adverse event rate here of less than one in
10 100,000, obviously impossible to detect in any drug
11 development program and very difficult to detect even
12 with post-marketing surveillance. Let me just come
13 back then to this so-called multiple-hit hypothesis
14 with drugs that have mild to modest effects on the
15 QTc. It requires more than the drug alone to produce
16 problems and we've listed those and discussed them
17 earlier. This is a list of drugs withdrawn because of
18 Torsades de Pointes and again, most of these drugs had
19 relatively modest effects on the QTc when used alone
20 but had some sort of metabolic liability associated
21 with them and they include Trefenadine, Sertindole,
22 Astemizole, Grepafloxacin and Cisapride.

23 QT prolongation is a significant issue in
24 the overall scheme of drug monitoring. This is a
25 table extracted from a Government Accounting Office

1 report in January of this year which listed 10 drugs
2 that were withdrawn from the market between January
3 1997 and December of 2000 specifically focusing on
4 evidence of greater health risk in women and, in fact,
5 eight of these 10 drugs had ~~were~~ associated with
6 greater risk in women than in men, but I show it just
7 to emphasize that of the 10, the most frequent cause
8 for withdrawal was Torsades which was the cause in
9 four of these 10 agents. So this is not a minor issue
10 from a regulatory perspective.

11 With regard to screening drugs in a
12 development program, and I'm going to skip through
13 this very quickly because you will see and hear this
14 data and I think everybody in the room is familiar
15 with them, it is important to understand the effects
16 of all new agents on IKr probably as well as on the
17 calcium and sodium currents and also to assess in
18 vitro action potential duration effects and this can
19 be done in a number of systems. What's critical is
20 that all of these parameters be evaluated over a very
21 wide range of concentrations, preferably around 1000
22 fold. One can't always do that for technical reasons
23 but that should be the target. These things should be
24 assessed over a very wide range of heart rates and
25 wherever possible, it's important to characterize the

1 effects of metabolites on these parameters as well.
2 A number of other in vitro models have been used
3 including the left ventricular wedge preparation which
4 I described to you, the perfused rabbit heart and a
5 host of in vivo models ~~offersades~~ including conscious
6 and anesthetized ~~rabbit~~ models and a canine AV block
7 model.

8 It's important to emphasize, however, that
9 none of the pre-clinical approaches can exclude with
10 certainty some risk of QT prolongation and Torsades
11 and the bottom line is always the QT effect in humans.
12 When one looks at the QT effect in patients or
13 volunteers, we examine and the committee will be
14 looking at these data today, both mean and mean max
15 changes compared with placebo. This is effect on QT
16 and QTc in particular, categorical analyses, that is
17 percentage of patients who have prolongations of 30 to
18 60 milliseconds or greater than 60 milliseconds and
19 outliers with QTc's of greater than 450, 470 and 500
20 milliseconds.

21 What's particularly important and often
22 very difficult and I think this is a major challenge
23 to sponsors, is to focus as much as possible on
24 special populations, particularly patients with
25 various forms of heart disease, hypertension,

1 congestive heart failure and hypertrophy and coronary
2 artery disease. In addition, it's very important that
3 development programs have sufficient number of females
4 in their studies to evaluate the differential effects
5 of these agents on QTc with regard to gender.

6 Other aspects that one looks at in a
7 development program include the occurrence of Torsades
8 de Pointes which you almost never see in the kinds of
9 drugs that we're talking about, the incidents of other
10 ventricular arrhythmias, the incidents of syncope and
11 the incidents of sudden death. Dizziness is often
12 listed as well. I think that's a highly nonspecific
13 symptom and one that can't be used with any degree of
14 comfort to point to the occurrence of a cardiac
15 arrhythmia.

16 Finally, let me just re-emphasize then the
17 critical importance of pharmacokinetic and
18 pharmacodynamic interactions which can be assessed and
19 then the potential for drug gene interactions which at
20 the moment we are unable to assess. I think we've
21 covered and let me just conclude with this slide which
22 emphasizes that when one examines the potential
23 liability of an agent with a modest effect on QT, a
24 whole host of issues need to be considered, including
25 the pre-clinical finding but most important the QT

1 effects in humans, the adverse event profile, which
2 we've discussed, and all of these have to be evaluated
3 in the setting of the therapeutic target. One's
4 tolerance for some risk is likely to be higher in the
5 setting of a life-threatening problem than it is in
6 the setting of a non-life threatening problem.

7 The relative efficacy of the drug, as well
8 as unique advantages need to be considered as do
9 alternative options that may have a different and
10 perhaps a somewhat better safety profile. And
11 finally, when these are then evaluated a risk/benefit
12 assessment has to be constructed and the challenge,
13 obviously here is we're reasonably good at assessing
14 benefit, but in this particular situation not terribly
15 good at assessing risk because we have a measurement,
16 the QTc, which is a long way from the issue at hand,
17 that is the occurrence of Torsades de Pointes and
18 sudden cardiac death.

19 Let me just conclude by saying that there
20 is no way to exclude risk with agents that have modest
21 effects on the QTc interval. The other side of that
22 coin, however, is that if we eliminated all drugs with
23 some effect on the QTc interval, we would profoundly
24 reduce our therapeutic armamentariums in many areas of
25 medicine, in particular cardiology, infectious

1 disease, psychiatry and oncology.

2 Thank you.

3 DR. RELLER: Thank you, Dr. Ruskin, for
4 that telling tutorial. Our next speaker will be Dr.
5 Douglas Shaffer, who will present the FDA post-
6 marketing review of Torsades.

7 PRESENTATION OF DR. DOUGLAS SHAFFER

8 DR. SHAFFER: Good morning. It is my
9 pleasure to present results of a post-marketing
10 analysis regarding macrolide antibiotics and Torsades
11 de Pointes completed by Sarah Singer and myself. We
12 used the following outline. First, I will identify
13 the goal and rationale for the presentation this
14 morning.

15 Second, I will focus on the post-marketing
16 analysis. The majority of the time will be dedicated
17 to a descriptive analysis of the adverse event
18 reporting system or AERS data base. I will present
19 data from IMS Health in an attempt to describe
20 macrolide utilization and finally I will briefly
21 present reporting rate comparisons among the macrolide
22 antibiotics incorporating a negative control.
23 Finally, I will conclude with summary and conclusions.

24 The goal of this analysis is to
25 systematically evaluate post-marketing data and

1 attempt to provide the advisory committee with a
2 descriptive overview of Torsades de Pointes and
3 association with macrolide antibiotics. Two
4 properties identified in the KETEK advisory committee
5 packet and shared by the macrolide and microbials,
6 specifically Clarithromycin and Erythromycin will be
7 incorporated into results presented today.

8 First, the pharmacokinetic property,
9 cytochrome P450 3A4 metabolism and second, the
10 pharmacodynamic property of concentration related
11 lengthening of the QTc or corrected QT interval.

12 While Telithromycin has not been marketed
13 in the United States a post-marketing analysis now is
14 warranted. This is recognized by the following quote
15 for the European Society of Cardiology Policy
16 Conference addressing iatrogenic QT prolongation and
17 Torsades de Pointes. "Of concern is the interval
18 usually measured in years from the marketing of these
19 drugs to initial recognition of their association with
20 QT interval prolongation and/or Torsades de Pointes.
21 It is in the public's best interest to begin
22 considering any potential for Torsades de Pointes
23 sooner rather than later.

24 Considerable time and attention is
25 warranted to randomize control trial data and drug

1 development. However, we are well aware in the
2 practice of medicine that adverse events often ignore
3 the randomized control trial. It is important to keep
4 in mind this presentation is in the context of the
5 post-marketing setting. I would like to propose the
6 following hypothetical scenario.

7 Consider a 61-year old female receives a
8 broad spectrum antibiotic for acute sinusitis. This
9 antibiotic undergoes hepatic metabolism and also has
10 the potential to prolong the QT interval. After one
11 drug, one patient, the controlled environment of the
12 clinical trial abates and confounding variables become
13 significant. This hypothetical situation may result
14 in QT prolongation and ultimately a pro-arrhythmic
15 milieu. From here we can postulate three outcomes.

16 By far and most common, there is not
17 pathophysiologic event, that is the patient takes the
18 antibiotic without adversity rarely and as we just
19 heard approximately less than one percent, the patient
20 may experience a non-sustained arrhythmia. Even more
21 rarely, the patient may experience cardiac sudden
22 death. Our analysis today will be focusing on these
23 confounding variables and presenting the patients that
24 fall into the non-sustained arrhythmia and cardiac
25 death categories.

1 Finally, as introduction to our AERS
2 analysis, I would like to present a representative
3 AERS report. Approximately one-third of our cases
4 presented with a syncopal episode or near syncope.
5 From there, the patient is seen in the emergency room
6 where an ECG is obtained and QT prolongation is
7 documented and ultimately Torsades. We commonly
8 observe three outcomes; first, drug discontinuation
9 and resolution; second, rapid debridement and
10 treatment, for example, with magnesium or other NCCLS
11 protocol and rarely we do observe death.

12 I will now present results of our
13 descriptive analysis of the AERS data base. We
14 queried the AERS data base using four individual
15 macrolide drugs as the exposure; Azithromycin,
16 Clarithromycin, Dirithromycin and Erythromycin. We
17 used the preferred term, Torsades de Pointes as the
18 outcome of interest and since Torsades was not coded
19 prior to 1995, we used the ventricular tachycardia for
20 this time period. We included all reports regardless
21 of nationality or routed administration.

22 In our description analysis our aim was to
23 capture as much data and as many reports as possible.
24 We excluded duplicate reports or reports prior to 1995
25 without Torsades de Pointes in the text. We

1 systematically extracted pharmacoepidemiological data
2 from each case report. PC SAS was used for analyses.

3 Our search query resulted in 268 reports
4 being reviewed, 112 were excluded and 156 were
5 analyzed and I will be presenting the details of this
6 156. Overall Erythromycin accounted for the majority
7 of Torsades de Pointes reports, 53 percent. This was
8 followed by Clarithromycin, 36 percent, Azithromycin,
9 11 percent. There were no reports of Torsades de
10 Pointes associated with Dirithromycin which may be
11 reflective of its relatively little utilization as I
12 will show later. Twenty-eight percent of reports
13 included an intravenous route of administration and 25
14 percent of the reports were of foreign nationality, a
15 statistic that is not on this slide.

16 This is the first in a series of four
17 slides where I will present pharmacoepidemiological
18 data extracted from the AERS reports. For
19 orientation, the variable of interest will be
20 presented in the first column and the corresponding
21 statistic, mean and standard deviation or frequency
22 will be in the second column. Where indicated and
23 appropriated at the bottom of the screen, I will
24 provide the proportion of AERS reports providing
25 information for the variable interest. For example,

1 93 percent of our cases reported information regarding
2 age, 94 percent regarding gender, far less regarding
3 race, 16 percent and weight was available in 26
4 percent of the reports.

5 Given this, the majority of Torsades de
6 Pointes reports were primarily from older female
7 patients. The mean age was 61 years and 70 percent of
8 the reports providing gender were female. While very
9 limited reports provided this data, those providing
10 information, 60 percent were Caucasian and the mean
11 weight was 152 pounds.

12 Approximately one-third of the AERS cases
13 provided ECG data. Of this, 59 percent identified the
14 QTc. The mean baseline QT in our AERS' analysis was
15 432 milliseconds. This is within normal limits for
16 females and at the border upper limit of normal for
17 males. The mean event QT were the QT Antecedent two
18 or associated with the Torsades de Pointes report was
19 594 milliseconds and the mean change was 172
20 milliseconds. The interval between the initiation of
21 the macrolide drug and the reported event was a mean
22 of four days with three outliers greater than 120 days
23 being excluded.

24 While we cannot assign causation and our
25 aim is not to assign causation. Fatalities were

1 reported. Fourteen outcomes of the 156 reports ended
2 in a fatality. We also extracted data regarding co-
3 morbid risk and co-morbid disease states. Forty-two
4 percent of the AERS reports included any evidence of
5 cardiac disease the most frequent cardiac disease
6 reported was congestive heart failure, 23 percent.
7 Renal disease and hepatic disease were both less
8 frequent, 11 and 6 percent respectively. Hypokalemia
9 or hypomagnesemia was present on 17 percent of the
10 reports and hypokalemia alone on 15 percent.

11 Finally, we extracted data regarding
12 concomitantly administered or concomitantly reported
13 drugs and the mean number of drugs concomitantly
14 administered or reported on our case series was four
15 with a standard deviation of three and a range of zero
16 to 15. We also evaluated two mutually exclusive
17 classes of drugs or drug combinations. First, we
18 looked for evidence of a drug interaction focusing on
19 contra-indicated drug interactions using the product
20 labels as guides.

21 In preview, this in general involves
22 Erythromycin or Clarithromycin and a combination of
23 Astemizole, Cisapride, Penazide or terfenadine.
24 Thirty-one percent of the AERS reports had evidence of
25 this contra-indicated drug interaction. In addition,

1 after this, we further evaluated the reports to see if
2 there was evidence of drugs or drug classes known to
3 prolong the QT interval in uses less similar to that
4 seen in the introduction. An additional 22 percent of
5 the reports included drugs known to prolong the QT
6 interval. This pie chart demonstrates the three
7 resulting categories of AERS reports. In maroon, as
8 I've just indicated, 31 percent of reports met the
9 criteria for a drug interaction or contra-indicated
10 drug interaction. In addition, 22 percent of the
11 reports had evidence of drugs or drug classes known to
12 prolong the QT interval. This leaves basically half,
13 47 percent, of the reports listing the macrolide drug
14 as the sole suspect.

15 I would like to further describe the
16 maroon section of the pie chart or the contra-
17 indicated drug interaction section. As I mentioned,
18 we defined this as Clarithromycin and Erythromycin and
19 a combination of four drugs. As you can see,
20 Cisapride accounted for the vast majority of drug
21 interactions noted in our analysis. This was followed
22 by Terfenadine and Astemizole. Two points should be
23 noted.

24 First, Astemizole specifically is not a
25 drug interaction with Clarithromycin but is with

1 Erythromycin. Second, as just pointed out, these
2 three drugs have been removed from the market. The
3 second portion of our analysis involves data from IMS
4 Health. We queried IMS Health's National Prescription
5 Audit Plus to estimate macrolide drug utilization. We
6 evaluated retail outpatient prescriptions dispensed
7 focusing on oral formulations only since the
8 formulation being considered today as oral.

9 I will present the data in two manners.
10 First, I will use a figure to describe the
11 representation of annual drug use and second, we will
12 use this data in comparison of relative estimated
13 reporting rate ratios. For this ratio, we consider
14 the reports or numerator and we consider only domestic
15 oral formulation or outpatient reports. Drug
16 utilization will serve as a surrogate analytic
17 population or denominator and we will use cefuroxime
18 as a negative control.

19 This figure depicts annual macrolide
20 antibiotic utilization with total prescriptions from
21 zero to 35 million on a Y axis and years from 1993 to
22 2000 on the X axis. As you can see in the light blue
23 line, Erythromycin use has steadily declined since the
24 introduction of the newer macrolides. Clarithromycin,
25 in a dark red or maroon appeared to plateau in 1996

1 and has a gradual decline since then. In contrast
2 Azithromycin, a drug with five-day dosings, similar to
3 a dosing we may see today has benefited from a marked
4 positive trajectory and has only experienced a
5 potential plateau in the last year.

6 Dirithromycin is not on the graph and this
7 is due to its relatively low utilization averaging
8 less than 500 prescriptions dispensed yearly.
9 Finally, we presented to compare report utilization
10 ratios within the macrolide drugs using Cefuroxime as
11 a negative control. To do this we considered reports
12 only of domestic oral formulation, outpatient origin
13 and used 1993 to 2000 utilization after the drug
14 listed in the first column reports follow in the
15 second column, utilization in the third column and
16 finally the report utilization ratio in the last
17 column. I will focus on the last column.

18 Clarithromycin has the largest report
19 utilization ratio among the macrolide antibiotics when
20 considering domestic oral-formulation and outpatient
21 reports only. This was followed by Erythromycin and
22 then Azithromycin and Cefuroxime was used as our
23 negative control. We are limited in the degree of
24 certainty that can be placed upon these estimates due
25 to the use of a surrogate analytic population and

1 reporting biases known in the spontaneous system.
2 From this slide, we propose to conclude that
3 Clarithromycin had the greatest reporting ratio among
4 the macrolide antibiotics and this was approximately
5 nine times that of the negative control.

6 In summary, macrolide associated Torsades
7 de Pointes reports are from primarily older female
8 patients. Concomitant diseases and drugs are
9 prevalent in potentially modifiable risks.
10 Erythromycin overall accounts for most reports.
11 Clarithromycin has the greatest reporting rate when
12 considering domestic outpatient oral cases and
13 accounting for drug utilization and finally
14 Clarithromycin and Erythromycin Torsades de Pointes
15 reporting rates are nine and three times that of
16 Cefuroxime respectively.

17 Limitations must be addressed in
18 considering results presented. First are those
19 limitations germane to the spontaneous reporting
20 system. These include adverse event recognition and
21 report data quality. Torsades de Pointes is a
22 difficult adverse event to capture. We evaluated each
23 report individually in an attempt to assure reporting
24 accuracy. However, without an ECG rhythm strip or
25 data from telemetry we cannot have 100 percent

1 certainty.

2 We must also consider the influence of
3 biases. Market time and market environment are biases
4 that should be considered. We did not adjust for
5 secular trends. Rather we propose to let the data
6 speak freely and consider these results in light of
7 biases and the implication they may hold. Under-
8 reporting has a well-known bias with spontaneous
9 reports ranging anywhere from one to 10 percent of
10 adverse events making it to the FDA depending on the
11 severity.

12 I propose that we should consider a
13 competing bias as well. We cannot overlook the
14 potential bias in Clarithromycin reports due to the
15 Cisapride received. As I showed, Cisapride was the
16 most common drug interaction and overall in our data
17 base accounted for approximately one-fifth of the
18 reports. It is possible among the macrolide drugs
19 that Clarithromycin received relatively more reports.

20 We cannot make inferences regarding
21 missing data and this addresses the specificity of
22 spontaneous reports. An example is Telithromycin. We
23 do not see reports of Torsades de Pointes with
24 Telithromycin. However, it would be inappropriate to
25 conclude that there is no association.

1 And finally, we are unable to establish
2 causation in this type of analysis. Our goal was to
3 present a descriptive overview. And last, reporting
4 rate estimates are not synonymous with incidents
5 rates. I propose, however, there are several
6 advantages to consider. We systematically proceeded
7 with pharmacokinetic data extraction within
8 this class to an extent not previously seen before.
9 This is a cost efficient analysis. In clinical
10 research today we must recognize the need for cost
11 efficiency. Spontaneous reports are a relatively cost
12 efficient means for this type of analysis.

13 Regarding best available evidence, it is
14 not always possible to turn to the randomized control
15 trial or large cohort study particularly when
16 evaluating rare potentially fatal outcomes. The AERS
17 data base is arguably among the best available for not
18 only single generation but descriptive and qualitative
19 analyses as well.

20 Finally, we provided a detail analysis of
21 individual drugs in the post-marketing setting. This
22 series of case reports offers a descriptive overview
23 of tangible data unavailable in the clinical trial.
24 In conclusion, Telithromycin, the first of a new class
25 of antimicrobials related to macrolides interacts with

1 cytochrome P450 metabolism and prolongs the QT
2 interval.

3 Recognition of the potential for Torsades
4 de Pointes should clearly be acknowledged. And
5 monitoring of post-marketing data and development of
6 risk management strategies would be critical if the
7 drug was marketed in the United States.

8 Thank you. And I would certainly like to
9 take the opportunity to state that our AERS data base
10 is in part dependent on the quantity and quality of
11 reports submitted and we certainly encourage use of
12 this valuable asset. Thanks.

13 DR. RELLER: Thank you, Dr. Shaffer, for
14 that balanced review. We will now take a short break
15 but please reconvene at 9:35 promptly to begin the
16 sponsors' presentations.

17 (Whereupon, the meeting went off the
18 record at 9:21 a.m. and went back on the record at
19 9:38 a.m.)

20 DR. RELLER: I should like to introduce
21 Dr. Mindell Seidlin, Vice President for Clinical
22 Development of Anti-Infectives Aventis. Dr. Seidlin.

23 INTRODUCTION OF DR. MINDELL SEIDLIN

24 DR. SEIDLIN: Thank you, Dr. Reller. Good
25 morning, ladies and gentlemen. It is my privilege to

1 introduce the Aventis presentation on Telithromycin,
2 the first Ketolide. This is the agenda for the
3 Aventis presentation. This introduction will focus on
4 the need for new antimicrobials in this era of increasing
5 resistance. Subsequent presentations will detail the
6 mechanism of action and in vitro microbial profile and
7 human pharmacology of the drugs. The clinical
8 efficacy and safety with special discussion on the ECG
9 findings will follow. I will then summarize the
10 unique features of Telithromycin which represent a
11 advance in antimicrobial chemotherapy and address
12 current therapeutic needs in this area.

13 Clearly, the emergence of multi-resistant
14 respiratory pathogen, particular *streptococcus*
15 *pneumoniae* have driven the need for new drugs in this
16 area. Currently, physicians who perceive their
17 patients to be at risk for drug resistant respiratory
18 infections have only one or two classes of drugs to
19 choose from. Availability of new drugs with novel
20 mechanisms of action will reduce the resistance
21 pressure on existing classes. While the emergence of
22 multi-resistant strains is a key driver of medical
23 needs in this area, we must not lose sight of the
24 other elements for successful therapy of respiratory
25 infections. Out-patient therapy is moni-therapy. New

1 respiratory antibiotics must be effective against the
2 full range of pathogens responsible for these
3 infections; common, atypical and intra-cellular.

4 Ideally, they should be effective when
5 administered with a brief simple regimen that can
6 facilitate patient compliance and minimize drug
7 exposure. Brief regimens which do not lead to
8 misdoses in sub-therapeutic levels may limit further
9 resistance. Recent policy statements by both the
10 World Health Organization and the United States
11 Department of Health and Human Services have included
12 recommendations on development of new antibiotics in
13 addition to judicious use of existing agents.

14 New drugs for community respiratory tract
15 infections must be effective against the full range of
16 relevant pathogens and must reach sufficient
17 concentrations at the site of infection. *Streptococcus*
18 *pneumoniae* is key because it is the most common
19 pathogen but also the one most associated with serious
20 sequelae and bacteremia. Rapid and cidal activity
21 against sensitive strains of the pneumococcus may
22 reduce the likelihood of emergence of resistant
23 strains.

24 The other typical bacterial species which
25 are associated with these infections include

1 *Hemophilus influenza* and *moraxella catarrhalis*, both
2 of which now include many beta lactamase positive
3 strains. Achievement of adequate levels in plasma and
4 particularly for pneumonia an extracellular fluid are
5 important when treating these infections. The
6 importance of atypical and intracellular pathogens is
7 increasingly being recognized. In these infections,
8 intracellular levels of drug are key.

9 Let us now turn to the clinical relevance
10 and impact of resistance. Demonstration of the
11 clinical impact of penicillin resistance was first
12 observed in patients with pneumococcal meningitis.
13 Due to relatively poor penetration of many beta
14 lactams across the blood/brain barrier, even strains
15 with intermediate levels of resistance to penicillin
16 failed therapy in this indication. As the prevalence
17 of high level resistance increased in the late '90's,
18 outcome studies began to demonstrate impact of
19 penicillin resistance on mortality, suppurative
20 complications and other clinical adverse outcomes.
21 It's important to remember in this context that some
22 60 percent of penicillin resistant pneumococci are
23 also resistant to other classes of drugs.

24 The first cases of clinical failure of
25 patients with Erythromycin resistance *streptococcus*

1 pneumonia who were treated with macrolides were
2 reported in the early '90's. At that time, there were
3 few isolates with MICs greater than or equal to 4.
4 Recently there have been an increasing number of
5 reports. ~~MIC~~ of the reports in the latter part of the
6 '90's have occurred in patients whose organisms have
7 MICs of 8 or more. In contrast to the situation with
8 penicillin and beta lactams, where high plasma levels
9 can be achieved with increasing doses of the drug,
10 increasing doses of macrolides to achieve plasma
11 levels that will cover MICs of 8 or more is simply not
12 feasible.

13 This slide shows data that was kindly
14 shared with us by Dr. Cynthia Whitney at the CDC. In
15 the left-hand panel, you can see the increasing
16 frequency of Erythromycin A resistance among sterile
17 sites of pneumococcus. In 1999, 20.3 percent of these
18 isolates were Erythromycin A resistant. In the same
19 year 16 percent were penicillin G resistant. The
20 panel on your right shows the frequency of MICs of 8
21 or more in these same isolates. This demonstrates
22 that not only has the frequency of Erythromycin
23 resistance increased but the level of resistance has
24 increased as well.

25 Here is the dilemma faced by physicians

1 who must prescribe for out-patients with bacterial
2 respiratory tract infections. Let's take community-
3 acquired pneumonia as an example. Current Infectious
4 Disease Society of America guidelines suggest that if
5 a patient is not at risk for drug resistant
6 *streptococcus pneumonia*, there are three options;
7 macrolides, tetracyclines or flouroquinolones. If,
8 however, the physician judges that the patient is at
9 risk for drug resistance *streptococcus pneumonia*, the
10 options reduced to one, flouroquinolones. The lack of
11 options will further increase resistance pressure on
12 this class. Further, there are no options for
13 patients intolerant to that class.

14 Telithromycin is the first key light. It
15 has excellent pneumococcal activity. This is crucial
16 because in addition to being the most common bacterial
17 respiratory pathogen, it is the one most associated
18 with serious consequences. Telithromycin retains
19 activity against Erythromycin A and Penicillin G
20 resistant strains of the pneumococcus and is effective
21 against all of the key community respiratory
22 pathogens. The pharmacokinetic profile support a
23 brief simple therapeutic regiment which will
24 facilitate patient compliance.

25 This slides lists the indications that

1 were proposed for Telithromycin. The mechanism of
2 action and in vitro anti-microbial profile will now be
3 presented by my colleague, Dr. Bryskier.

4 PRESENTATION OF DR. ANDRE BRYSKIER

5 DR. BRYSKIER: Good morning. It will be
6 a pleasure for me now to share with you our current
7 knowledge on the anti-bacterial activity and the mode
8 of action of Telithromycin new Ketolide. Ketolide
9 will synthesize and design to overcome Erythromycin A
10 resistance within gram-positive cocci. This figure
11 illustrates the structure of a Ketolide. The Ketolide
12 are composed of three parts; the lactone ring, a 3-
13 keto function and a C11-C12 carbamate residue
14 substituted by a long side chain.

15 Now, I want to share with you the property
16 issue for this chemical structure. Here you have the
17 cladinose, a natural sugar. If you remove the
18 cladinose and by chemical modification you obtain the
19 3-keto function. The name came from the 3-keto
20 function the Ketolide. Most important, the property
21 you obtain with the 3-keto function as a following,
22 first, high stability in acidic environment. After
23 six hours of contact of pH1 95 percent of the
24 Telithromycin activity remain.

25 Second, the anti-bacterial activity

1 against erm-containing strains remain. Inability to
2 induce macrolide lincosamine streptogramin-B
3 resistance. Now, the second part of the structure.
4 The C11-C12 carbamate residue substituted by a long
5 side chain, you obtain the innovation of this
6 compound. The C11-C12 gives you the following:
7 reduced impact of efflux mechanism of resistance;
8 second, enhanced antibacterial activity against gram-
9 positive bacteria; third, proven intracellular
10 accumulation and efflux in phagocytes and most
11 important the mode of action.

12 I will call your attention of the mode of
13 action. The first to know we are really on the front
14 of the knowledge and the science with the mechanics of
15 action and resistance to macrolide and Ketolide today.
16 Telithromycin inhibits protein synthesis. Second,
17 Telithromycin deplete ribosomes contained in bacterial
18 cells. Let's have a look on protein synthesis.

19 Protein synthesis is the protein produced
20 in bacterial ribosome. Ribosome are constituted by
21 two subunits, small one 30S and a big one 50S subunit.
22 The target for Telithromycin is located on the 50S
23 subunit. One side is the peptidyl transferase site
24 and especially in rRNA place, a subunit of ribosome
25 constituted by protein and rRNA.

1 As molecular, the peptidyl transferase is
2 constituted by three parts. In 23S rRNA you so-called
3 six domains. Two domains constitute the peptidyl
4 transferase site, Domain V, Domain II and the link
5 with another rRNA, the fifth rRNA. The difference
6 between Erythromycin, Clarithromycin and Telithromycin
7 is where the drug is fixed. When the drug enters in
8 the pocket, here you have a fixation on Domain V
9 through the desosamine, an amino sugar, Erythromycin,
10 Clarithromycin, Azithromycin. Telithromycin also
11 entered the desosamine so Telithromycin is also fixed
12 on Domain V but the difference, there is a very long
13 side chain, a carbamate side chain. This carbamate
14 side chain allows you to be fixed on Domain II.

15 So the difference, you have a double
16 fixation on the peptidyl transferase sites. Now, the
17 depletion of the ribosomal contained. Inhibition of
18 ribosomal subunit formation, 30S subunit, 50S subunit
19 gives you this big ribosome system. With Erythromycin
20 A, you have inhibition and abnormal protein form
21 within 50S subunit. These proteins are destroyed and
22 you have a depletion of ribosome. Telithromycin also
23 acts on the 50S subunit but the difference, you have
24 a double blockage, 30S subunit is also blocked. And
25 I remind you that the 30S subunit is also the place

1 where the protein synthesis is processed, so that
2 means that you have a deep depletion and a total
3 blockage of your synthesis and the consequence is that
4 the drug is bactericidal. What is a consequence of a
5 double binding?

6 So first, we explain that the mode of
7 action is due to the C11-C12 side chain. Also
8 overcoming mechanisms of resistance is partly due to
9 this chain. If you have methylation for instance on
10 the Domain V, Erythromycin is unable to be fixed and
11 the drug is more active. So you have a resistance
12 to Erythromycin and a cross-resistance with other like
13 Erythromycin and Clarithromycin. Telithromycin could
14 be also blocked in Domain V but a second arm on Domain
15 II and Telithromycin retain activity against
16 Erythromycin air resistance organisms.

17 Telithromycin is also active against
18 another mechanics of resistance to Erythromycin efflux
19 by another way. The drug is pumped out, when you have
20 a poison in the cells, the cells wants to pump out the
21 drug to survive. The blood is able to pump out
22 Erythromycin A due to a high affinity to the pump, but
23 the low affinity is for Telithromycin and you don't
24 have this problem, so activity retained for
25 Telithromycin. And that's a type of mechanism of

1 mutation on protein, ribosome protein and
2 Telithromycin retained activity for exactly the same
3 problem with the C11 - C12 side chain.

4 Telithromycin is today the most active
5 drug against pneumococci. On this shot, this work was
6 done by NCCLS methodology and it was done by Gary
7 Doern. And here you have Telithromycin.
8 Telithromycin is more active than Clarithromycin,
9 Azithromycin, Levofloxacin, as seen here, and
10 Linezolid.

11 There's an anti activity that is a third
12 property of this C11-C12 side chain is not only an
13 anti-activity but also the drug is active against
14 strep pneumonia resistance to other compounds which
15 act on *S. pneumoniae*. Here you have comparison
16 between Telithromycin and Clarithromycin. It's very
17 evident that even if you have an efflux of macrolide
18 and lincosamine streptogramin-B resistance,
19 Telithromycin retain activity.

20 We have explored other drugs. When a *S.*
21 *pneumoniae* is resistant to Cefotaxime, to Penicillin
22 G, Tetracycline, Cotrimoxazole, Ofloxacin,
23 Telithromycin retained activity and is highly active.
24 So there is no cross-resistance between all these
25 drugs and Telithromycin.

1 A fourth, very important, among this class
2 of antibiotic it is the first time that we have a drug
3 with a rapid bactericidal activity at an MIC level.
4 So what is important, you have a very quick drop of
5 three or more logs after four to six hours of contact.
6 But at 24 hours with a mode MIC around 0.01 to 0.03
7 microbial we end up with Telithromycin against *S.*
8 *pneumoniae*, we still have bactericidal activity. So
9 with 800 milligrams per day, you cover the 24 hour
10 period and you expect to have a bactericidal activity.

11 All this in vitro data will confirm in
12 vivo in animal model. Disseminated infection, lung
13 infections in mouse, and we use Erythromycin
14 susceptible and Erythromycin resistant micro-organisms
15 with different mechanisms of resistance, *erm* and *mef*.
16 In a survey in North America only one strain about
17 2,000 -- out of 2,000 MIC of four, Telithromycin was
18 about 4 so only one strain. So it is today a very
19 rare occurrence.

20 But Telithromycin is not only a drug for
21 *S. pneumoniae*. It covers many micro-organisms and
22 mainly all the bugs which are involved in respiratory
23 tract infections; *S. pneumoniae*, *S. pyogenes*, *H.*
24 *influenzae*, *Moraxella catarrhalis*, and *S. pyogenes*,
25 *Legionella pneumophila*, *C. pneumoniae* and atypical

1 mycoplasma. The data you have here, I share with you
2 were obtained also by NCCLS methodology.

3 The other very important point which is
4 related and linked with the section is intracellular
5 accumulation. With Telithromycin you have an
6 accumulation or concentration in the cells in
7 phagocytes with a ratio between 350 and 400 times.
8 But the drug is also eliminated. Forty-five percent
9 of the drug is pumped out in one hour period, so no
10 accumulation in the cells. But accumulation of
11 concentration in cells doesn't mean activity. So
12 bioactivity is very high with Telithromycin
13 demonstrated in *C. pneumoniae*, bactericidal activity,
14 *Legionella pneumophila* in many models, *S. pneumoniae*
15 and other intracellular pathogens. For *S. pneumoniae*
16 it was demonstrated in the model two that it was the
17 only compound that stabilized the cells, not as a
18 compound we tested. We have tested quinolones, we
19 have tested macrolides; and it is the only one who are
20 able to do that. Even rifampin is not able to do
21 that.

22 So to sum up the antibacterial activity
23 and the mechanics of action and resistance to
24 Telithromycin; Telithromycin is the first Ketolide, a
25 new class of antibiotics. Telithromycin exhibits

1 antibacterial activity against *S. pneumoniae*,
2 resistance to other antibiotics. Telithromycin is
3 able to overcome Erythromycin A resistance and achieve
4 our targets.

5 Important bactericidal activity is
6 obtained with the major respiratory pathogens.
7 Doesn't induce ~~MLSC~~ macrolide, lincosamine,
8 streptogramin ~~to~~ resistance. A low frequency of
9 selection of resistance was noted in cellular
10 passages. And it's active against all resistance
11 pathogen with other drug. Thank you. Now I will ask
12 Vijay Bhargava to continue with pharmacokinetics.

13 PRESENTATION OF DR. VIJAY BHARGAVA

14 DR. BHARGAVA: Thank you, Andre. Good
15 morning. I will outline the key clinical pharmacology
16 data for Telithromycin. Doses ranging from 800 to
17 3200 milligrams were given in this program to
18 establish the pharmacokinetic and safety profile of
19 Telithromycin. Safety aspects of Telithromycin in
20 clinical pharmacology will be discussed by Dr.
21 Benedict.

22 First, I will present the key plasma and
23 tissue characteristics. Second, I will present the
24 disposition profile and exposure profiles when these
25 pathways are blocked either by drug interaction or

1 impairment of an eliminating organ. And third, I
2 will present support for the dose that was used in the
3 Phase III trials.

4 This slide shows the pharmacokinetics
5 after an 800 milligram single dose and as multiple
6 doses to steady state in healthy volunteers.
7 Absorption is rapid as seen in both cases as seen by
8 the t_{max} . The maximum concentration after single
9 dose is similar to that seen after steady state in
10 concentrations over two microgram per mL are achieved.
11 Trough levels and area under the curve increase upon
12 multiple dosing and steady state was rapidly achieved
13 after the second or third dose.

14 There is a bi-exponential elimination
15 with terminal half-life of seven to 10 hours. This
16 profile is reproducible and representative of that
17 scene in healthy volunteers and in patients. This
18 slide shows the tissue concentrations of Telithromycin
19 in patients when dosed with 800 milligrams once a day
20 to steady state. In the three tissues here, adequate
21 concentrations were rapidly achieved and are
22 detectible for at least 24 hours. Patient data for
23 the important target tissue epithelial lining fluid is
24 from the laboratory of Honeybourne and Wise where
25 similar data for other drugs has been reported.

1 Levels in the ELF as high as 14.9 microgram per mL
2 were observed. In other tissues high levels of
3 Telithromycin were also achieved.

4 Regarding other key pharmacokinetic
5 characteristics, absolute viable ability of
6 Telithromycin is high, about 60 percent in both the
7 young and elderly subjects. Protein binding is
8 approximately 70 percent meaning that binding
9 interactions are unlikely. Pharmacokinetics between
10 men and women were similar and no food interaction was
11 observed with this drug.

12 In the next few slides, I'd like to show
13 you the multiple pathways of Telithromycin
14 disposition. I will also present exposure profiles in
15 population where these disposition pathways can be
16 impaired. After an oral dose, over 90 percent of the
17 drug is absorbed through the gastrointestinal tract.
18 Prior to reaching systemic circulation about 33
19 percent of the drug is metabolized in the liver or
20 gastrointestinal tract resulting in a systemic
21 bioavailability of 57 percent. Once the drug reaches
22 systemic circulation it can be eliminated by the GI
23 tract or biliary secretion about seven percent, it can
24 be renally eliminated as unchanged drug in the urine,
25 about 13 percent.

1 Telithromycin can also be metabolized in
2 the liver and excreted as several metabolites that add
3 up to about 37 percent. The metabolites of
4 Telithromycin are equally mediated by cytochrome P450,
5 mainly 3A4 and non-cytochrome P450 pathways. Non-
6 cytochrome P450 pathways are rarely associated with
7 clinically relevant drug interactions or inhibitions.
8 In clinical studies, the non-cytochrome P450
9 metabolite was not inhibited with Ketoconazole or in
10 hepatic impairment.

11 Since the exposure of Telithromycin to
12 CYP3A4 isozyme is limited, its potential for increased
13 exposure when this pathway is blocked is minimal.
14 This contrast with other drugs such as Cisapride and
15 terfenadine where CYP3A4 is the primary isozyme for
16 elimination. The effect of Telithromycin when given
17 with or without 3A4 inhibitors on cardiac
18 repolarization will be discussed by Dr. Benedict. Two
19 other important points regarding Telithromycin
20 metabolite to note; first SYP2D6 is not involved in
21 its metabolism and secondly, due to minimal exposure
22 metabolites do not contribute to the activity.

23 In the next few slides I will show you the
24 exposure in populations where one of the disposition
25 pathways could be impaired. Having established that

1 the contribution of CYP3A4 is limited, we wanted to
2 validate this in clinical studies with several drugs
3 that are known to be potent inhibitor of this enzyme.
4 This slide shows the effect of Ketoconazole , one of
5 the most potent CYP3A4 inhibitors on the
6 pharmacokinetics of Telithromycin at steady state to
7 mimic the clinical situation. Area under the curve
8 increased two-fold. Importantly the increase in C max
9 which may be more relevant to safety was less at about
10 1.5 fold. As indicated earlier, this contrast with
11 drugs where CYP3A4 is the primary pathway, fluoxetine
12 Cisapride levels increased eight-fold and terfenadine
13 levels 16 to 73-fold when they are co-administered
14 with Ketoconazole.

15 With other potent inhibitors such as
16 itraconazole, we saw a lesser interaction and also
17 very importantly with grapefruit juice, we saw no
18 change in exposure of Telithromycin. Regarding
19 hepatic impairment, the maximum concentration in AUC
20 values indicated no change in exposure after a single
21 dose of Telithromycin. Interestingly the renal
22 clearance of Telithromycin in subjects with hepatic
23 impairment increased about 60 percent when compared to
24 the age and sex matched controls in this study.

25 A multiple dose study in patients with

1 hepatic impairment has been completed and data
2 recently shared with the agency. Similar to the
3 single dose results, in this multiple dose study where
4 800 milligrams once a day was administered for seven
5 days, exposure did not change in the hepatically
6 impaired subjects either on day one or on day seven.
7 Increases in renal clearance of Telithromycin were
8 clearly seen in this study both at day one and day seven
9 in subjects with hepatic impairment compared to the
10 age and sex match control. Similar findings for
11 Clarithromycin have been documented.

12 Pharmacokinetics were investigated in
13 subjects with different degrees of renal impairment.
14 The Cmax and AUC increased about 1.5-fold in the group
15 with creatinine clearance of 11 to 40 mils per minute
16 and lesser increases were observed with the group
17 creatinine clearance of 41 to 80 mils per minute.
18 Thus, we have now seen that when a Telithromycin
19 elimination route is blocked the risk of increased
20 exposure is limited due to the multiple pathways.

21 One other point regarding the limited risk
22 of exposure for Telithromycin due to drug interaction
23 is its high absolute bioavailability of about 60
24 percent. Inhibition of first pass metabolism with
25 Telithromycin will result in less than a two-fold

1 increase unlike drugs with low bioavailability for
2 example, Semvastatin and Cisapride and Terfenadine
3 where changes of six to eight-fold or greater are
4 observed.

5 Next we will look at Telithromycin in the
6 elderly. The Phase I data are outlined in your
7 briefing document and show that the elderly have a
8 modest increase when compared to the young. Data
9 shown here are from our Phase III study in community-
10 acquired pneumonia patients where risk factors for
11 increased exposure may have been present -- were
12 present, for example, concomitant medication,
13 infections or decrease renal and/or hepatic function.

14 When comparing the CAP patient under 65 to
15 over 65, we see a 1.4-fold increase in AUC and more
16 importantly, a 1.2-fold increase in Cmax which was
17 lower. The safety of Telithromycin in the elderly
18 will be discussed by Dr. Leroy and Dr. Benedict.

19 The next few slides illustrate data that
20 was used to establish the dose and regiment for the
21 clinical efficacy trial. Telithromycin was evaluated
22 using the well-known mouse thigh infection model in
23 Professor Craig's unit. The pharmacologically
24 effective dose was similar irrespective of the
25 frequency of dosing. That is, when similar doses were

1 given, divided into three, six, 12 or 24 hours, the
2 outcome was similar.

3 Area under the curve over MIC and Cmax
4 over MIC were better predictors of efficacy than time
5 over MIC. This indicated that the efficacy of
6 Telithromycin is concentration dependent like that of
7 azithromycin rather than time dependent like that of
8 clarithromycin. Therefore, this model indicated that
9 a once daily dose that would achieve adequate Cmax and
10 AUC values would be efficacious in the clinical
11 studies.

12 Once the pharmacokinetic, pharmacodynamic
13 data were established, the human dose was chosen so
14 that the unbound AUC over MIC values would be similar
15 to or higher than the AUC over MIC values at the
16 effective dose in mice. Eight hundred milligram given
17 once daily met this criteria. In addition, as shown
18 earlier, the tissue concentrations after the 800
19 milligram dose in Phase I studies were adequate to
20 achieve the MIC 90 for *S. pneumonia*. Hence, the doses
21 predicted by the model were validated by levels
22 observed in humans after the 800 milligram
23 Telithromycin given once daily.

24 A few points need to be made regarding the
25 dose selection in *H. flu.* Contrary to the *S.*

1 pneumonia situation, there is no well-validated model
2 for predicting the therapeutic dose for lower
3 respiratory tract infection caused by H. Flu. Non-
4 typable H. Flu is rarely isolated in the blood stream
5 of infected patients. Hence, the drug levels in
6 respiratory tissues are important in the treatment of
7 this pathogen. The ELF levels of Telithromycin after
8 the 800 milligram dosed once a day exceed the MIC
9 value for H. Flu.

10 Plasma and extra cellular concentration of
11 Telithromycin are higher than those for Azithromycin
12 which is one of the better in vitro macrolide for H.
13 Flu. The efficacy of the chosen dose will be
14 discussed by Dr. Leroy.

15 In summary, Telithromycin rapidly achieved
16 the targeted plasma and respiratory tissue
17 concentrations. Telithromycin has a well
18 characterized and reproducible pharmacokinetic profile
19 with a high bioavailability. Telithromycin has
20 multiple pathways for elimination and its metabolism
21 by CYP3A4 is limited. It is significantly metabolized
22 by non-cytochrome P450 pathway and also eliminated as
23 unchanged drug, unlike other drugs where CYP3A4
24 interactions have been an issue.

25 Pharmacokinetic and pharmacodynamic data

1 were used to support the 800 milligram dose given once
2 daily during the clinical efficacy program. Thank you
3 and I'd like to turn it to Dr. Leroy.

4 PRESENTATION OF DR. BRUNO LEROY

5 DR. LEROY: Thank you, Vijay. My subject
6 now is the clinical efficacy of Telithromycin in
7 respiratory infections and I will start with the
8 common element of study design and then cover efficacy
9 in each of the four indications. The dose of 800
10 milligrams was chosen for all indications. And in
11 this program we also studied the efficacy of short
12 five-day treatments cause for common infections other
13 than pneumonia. This was based on the potent in vitro
14 activity of Telithromycin as well as its high and
15 prolonged diffusion in tissue.

16 The benefit targeted with the short
17 treatment duration was an improve patient compliance
18 as well as a decrease of antibiotic exposure. In the
19 pneumonia trials, a seven to 10 days regiment was
20 maintained to insure that enrollment will not be
21 biased to want patients with mild diseases. Some key
22 elements of the study design was standardized across
23 studies and indications. There were five study visits
24 and you know in accordance to the FDA drug guidelines
25 for Anti-Infectives, the test of cure was performed at

1 the post-therapy visit between day 17 and day 21.

2 In studies where five-day Telithromycin
3 was used, a placebo peer at five days was added in
4 order to maintain the blind and the test of cure was
5 performed in the studies at the same time after the
6 start of treatment in both groups. And this was the
7 most stringent approach allowing to capture the early
8 relapses.

9 This approach was also recommended by the
10 FDA. There were three main analysis populations. The
11 mITT population corresponds to the intent to treat
12 population excluding subjects who did not have the
13 disease or did not receive treatment, the PPc
14 corresponds to the mITT excluding subjects who had
15 major protocol violation or an indeterminate response
16 and this was the primary analysis population in all
17 indications except in tonsillitis/pharyngitis and I
18 will focus on this population during the presentation.

19 Results of the mITT analyses, which are
20 presented in the briefing document, were consistent
21 with the PPc analyses. The protocol population was
22 the primary analyses for tonsillitis/pharyngitis. Let
23 us first consider the efficacy of Telithromycin in
24 community acquired pneumonia. There were three
25 controlled double blind comparative studies; 3001

1 compared 10 days of Telithromycin with 10 days of
2 amoxicillin high doses, one gram three times daily.
3 This comparator is increasingly considered as the best
4 therapy in countries with high prevalence of *S.*
5 *pneumonia* resistant to penicillin. 3006 compared 10
6 days of Telithromycin with 10 days Clarithromycin
7 given 500 milligrams twice daily and 3009 was
8 performed with Trovafloxacin as a comparator because
9 of its efficacy against resistant strains of *S.*
10 *pneumonia*.

11 This study was stopped before the planned
12 sample size was reached when the FDA restricted the
13 use of Trovafloxacin because of post-marketing safety
14 concerns.

15 Three open-label studies were also
16 performed, 3000 designed to obtain some
17 pharmacokinetic data in patients with pneumonia. 3009
18 open-label which was performed only in South Africa,
19 was aimed at gathering additional cases of *S.*
20 *pneumonia* resistant to Erythromycin or penicillin and
21 in this study consolidation on chest x-ray was
22 required in all patients at entry. This study was an
23 extension of 3009 with Telithromycin but no subjects
24 of 3009 were included in 3009 open label.

25 Data from a dose comparison study

1 performed in pneumonia in Japan 2105 will be also
2 presented in agreement with the FDA. In total, more
3 than 1300 subjects were treated with Telithromycin for
4 pneumonia.

5 Looking at criteria associated with an
6 increased severity, we can see that risk factors for
7 morbidity summarized here for the mITT population were
8 well balanced between Telithromycin and the
9 comparative groups in comparative studies. And
10 turning now to the pool of Telithromycin patients, you
11 can see that the significant numbers of outpatients at
12 risk of complication were included in the program.
13 For example 16 percent of subjects had a fine score of
14 three and a above, 56 subjects had an associated
15 pneumococcal bacteremia. And this to our knowledge is
16 one of the highest number of pneumococcal bacteremia
17 submitted in an NDA for an oral antibiotic.

18 Therefore, we believe that the upper end
19 of severity expected for outpatients with pneumonia in
20 the community has been well-captured in this program.

21 On this slide the bar represents the cure
22 rates with Telithromycin in blue and the comparator in
23 gray. And at the bottom of the bars are the study
24 numbers and the comparator used. At the top of the
25 bars are the cure rates and the 95 percent confidence

1 interval of the difference.

2 Analysis of the PPC population
3 demonstrated equal balance between Telithromycin and
4 high dose Amoxicillin and Clarithromycin with clinical
5 cure rate with Telithromycin of 95 percent in studies
6 greater than one and 81 percent in studies greater
7 than six. In both studies the lower bounds of the
8 confidence interval was well within trial limits.

9 In 3009 versus Trovafloxacin both
10 treatments gave high cure rates exceeding 90 percent.
11 However, the planned size was not reached for the
12 reason explained earlier. But the results also
13 support efficacy of Telithromycin in this indication.
14 Clinical cure rate in the uncontrolled studies were
15 consistent with the comparative studies and of note in
16 study 3009 open-label where consolidation was required
17 at entry, the cure rate was high with 94 percent in
18 the PPC population.

19 In the Telithromycin group the clinical
20 cure rate by pathogens for the most frequently
21 isolated organism varied between 87 percent and 95
22 percent with the highest rate observed for *S.*
23 *pneumonia*. Stringent serology criteria were used for
24 the diagnosis of atypical pneumonia, which are
25 detailed in the briefing document. Only patients with

1 no common pathogens were considered for this diagnosis
2 and the cure rate was over 90 percent for these
3 pathogens.

4 Interestingly, 12 subjects were diagnosed
5 with Legionella infection by serology or antigen
6 soluble and these number of -- these pathogens are
7 less observing of patients than in those hospitalized
8 patients, but still ought to be considered as they
9 represent a threat in the out-patients with pneumonia.
10 All these 12 subjects were cured. This table
11 summarizes the efficacy in the out-patients most
12 likely to develop complications. In the Telithromycin
13 group the cure rate, a test of cure, was high, 90
14 percent and above in elderly subjects. In subjects
15 with Pneumococcal bacteremia in the PPb population,
16 any subjects with fine score greater or equal to
17 three.

18 Of particular note is the outcome of
19 serving subject with Pneumococcal bacteremia.
20 Efficacy in this subject may result from the
21 combination of the excelling in vitro activity of the
22 Telithromycin as well as its substantial plasma
23 results and we believe that that differentiates
24 Telithromycin from isolates compound giving low class
25 labels and that it provides a high level of confidence

1 in the treatment of out-patients with pneumonia in the
2 community.

3 Now we will turn to the outcome in
4 subjects with resistant isolate of *S. pneumoniae* who
5 are treated with Telithromycin. A summary of the
6 results obtained in Western and Japanese studies are
7 shown on this slide. Now looking first at all
8 resistant pathogens including both single and multiple
9 pathogen infections, we can see that 19 strains were
10 resistant to penicillin, 16 of which were associated
11 with clinical cure, 25 strains were resistant to
12 Erythromycin, 21 of these strains were associated with
13 a clinical cure and of note, a total of 18 strains
14 resistant to Erythromycin had an MIC greater or equal
15 to 8 microgram per ML and 15 of these strains were
16 associated with a clinical cure.

17 Results for infections due to single
18 pathogens are given below with similar cure rates to
19 single and multiple infections. If we look at the
20 sub-set of subjects with resistant *S. pneumoniae* and
21 documented bacteremia the number are limited but still
22 substantial given that these were out-patients treated
23 orally. Seven out of the nine subjects with *S.*
24 *pneumonia* resistant to penicillin or Erythromycin were
25 cured.

1 In one of the two subjects categorized as
2 failure which are counted in all the rolls, and these
3 subjects had an *S. pneumonia* resistant to both
4 Penicillin G and Erythromycin A, the *S. pneumonia* was
5 eradicated from the blood with a documented negative
6 blood culture and an improvement of clinical symptoms.
7 But these subjects had a secondary infection with SRAs
8 isolated in culture leading to the prescription of an
9 anti-infective.

10 In summary, efficacy was demonstrated with
11 seven to 10 days of treatment with Telithromycin in
12 pneumonia due to common and atypical pathogens. Cure
13 rate in patients with pneumonia, with *S. pneumonia* and
14 *Legionella pneumophila* which are the two pathogens
15 associated with the risk of morbidity, were excellent.
16 Efficacy was demonstrated in subjects with *S.*
17 *pneumonia* resistant to Penicillin G or Erythromycin A
18 and efficacy was also shown in the most vulnerable of
19 patients such as the elderly, subjects with
20 pneumococcal bacteremia and subjects with *Legionella*
21 *pneumophila*.

22 I will now present the results obtained in
23 subjects with acute exacerbation of chronic
24 bronchitis. Two control studies were performed.
25 Study 3003 compared five days of treatment with

1 Telithromycin to 10 days of treatment with
2 Amoxicillin/Clavulanic acid given 500 milligram three
3 times daily and this was performed in subjects with
4 the documented bronchial obstruction by lung function
5 tests.

6 In 3007 the comparator was Cefuroxime
7 axetil given 500 milligram BID for 10 days and
8 patients were enrolled in these studies with a
9 criterion of exacerbation type one or two. In the PPc
10 population of both studies the clinical cure rate
11 after the short five-day treatment with Telithromycin
12 was equal to the longer 10-day treatment with the
13 comparators, Amoxicillin/Clavulanic acid or Cefuroxime
14 axetil.

15 In the PPb population which was selected
16 according to strict criteria, clinical cure rate by
17 pathogens with Telithromycin ranged from 68 to 100
18 percent. In the pooled population for both studies
19 the cure rate was slightly lower for *H. influenzae*
20 than for other pathogens. This was true also for the
21 comparative treatment. As explained in the briefing
22 document, this lower rate for *H. influenzae* was due
23 mainly to the lower eradication rate observed in study
24 3003 in patients with community -- with COPD and
25 documented obstruction.

1 In 3007 the eradication rate with
2 Telithromycin was higher than with Cefuroxime axetil.

3 For atypical pathogens, the clinical cure rates
4 exceeded 90 percent in the 11 subjects with chlamydia
5 infection diagnosed by serology with a four-fold
6 increase of IGG. Looking at the out-patients most
7 likely to develop complications in this indication
8 efficacy was high in the elderly patients, in patients
9 with one or at least two risk factors and in patients
10 with bronchial obstruction.

11 To summarize, Telithromycin 800 milligrams
12 given for five days once daily is effective in the
13 treatment of acute exacerbation of chronic bronchitis
14 due to these pathogens in patients with exacerbation
15 requiring antibiotic treatment that is to say with
16 type one or two. Efficacy was also observed in the
17 out-patients most likely to develop complications at
18 trials, the elderly and patients with documented
19 obstruction.

20 Let us now turn to the acute sinusitis
21 indications. Three studies were performed to support
22 this claim. Study 3002 compared five days and
23 treatment and 10 days of treatment with Telithromycin
24 and this study was performed in patients and all the
25 patients had bacterial documentation by sinus

1 puncture. Study 3005 had three treatment groups,
2 five-day and 10-day Telithromycin and 10 days with
3 Amoxicillin/Clavulanic acid, 500 milligram given three
4 times daily. Finally a second comparative study,
5 3011, was performed comparing Telithromycin for five
6 days with Cefuroxime given for 10 days and this study
7 also included bacterial documentation at entry.

8 In the comparative studies equivalence was
9 demonstrated between Telithromycin for -- given for
10 five days and the two goal standard in the
11 Amoxicillin/Clavulanic acid and Cefuroxime. ~~etil.~~
12 Cure rates after five and 10 days with Telithromycin
13 were also equivalent in study 3005 and in study 3002.
14 Clinical cure rate by pathogens were high and
15 comparable for the five-day and 10-day treatment
16 regimen with Telithromycin for all targeted pathogens
17 in this syndications with rates over 85 percent for *S.*
18 *pneumonia* and *H. influenza*.

19 This slide summarizes the results obtained
20 in subjects with *S. pneumonia* resistant to Penicillin
21 G or Erythromycin which are of increasing prevalence
22 in the syndication in the U.S. in our experience.
23 Focusing first on the large population of subjects
24 with single and multiple pathogen infections in the
25 pool five and 10 days treatment with Telithromycin,

1 which have been shown to have the same efficacy for
2 the other pathogens, 11 out of 13 subjects with
3 strains resistant to Penicillin G were cured.
4 Eighteen out of 21 subjects with transference to
5 Telithromycin A were cured and effectiveness was also
6 shown in the five-day treatment group and in single
7 pathogen infections although the numbers -- the
8 experiments involves smaller numbers.

9 In summary, Telithromycin given at 800
10 milligram once daily for five or 10 days is effective
11 in the treatment of acute sinusitis due to the main
12 pathogens isolated in this indication. Telithromycin
13 also proved to be effective against *S. pneumonia*
14 resistant to Penicillin A or Erythromycin A. An
15 important point to make for this indication is that
16 equal balance was demonstrated in two controlled
17 comparative studies between Telithromycin given once
18 daily for a short treatment duration of five days and
19 a standard treatment given two to three times daily
20 for 10 days.

21 Telithromycin represents therefore, an
22 effective alternative in this indication where the
23 number of antibiotics demonstrating in vitro activity
24 against all the key pathogens I related is becoming
25 limited.

1 I will now summarize briefly the
2 experience in tonsillitis/pharyngitis due to *S.*
3 *pyogenes*. Two controlled studies were performed
4 comparing Telithromycin for five days with Penicillin
5 G given 500 milligram three times daily for 10 days or
6 Clarithromycin given at 200 milligrams twice daily for
7 10 days. This was the main study performed to support
8 the claim in this indication. Equivalence in efficacy
9 which is the primary end point in this indication was
10 demonstrated between the five day Telithromycin and
11 the 10 day treatment with Penicillin VK or
12 Clarithromycin. Reasons for type of therapy are given
13 in the briefing document and confirmed the equal
14 balance between Telithromycin five days and the two
15 comparators used indicating that the short treatment
16 duration with Telithromycin was not associated with a
17 higher rate of relapses.

18 To summarize, Telithromycin, 800 milligram
19 once daily given for five days is effective at
20 treating tonsillitis/pharyngitis and is equivalent to
21 the standard 10-day treatment with Penicillin VK or
22 Clarithromycin given two to three times daily
23 respectively. Eradication of *S. pyogenes* with the
24 short five-day treatment duration given once daily is
25 of particular importance in this indication where in

1 practice compliance to a full 10-day treatment is
2 rarely observed as a clinical symptoms result
3 particularly in the adolescents.

4 This review has shown that the efficacy of
5 Telithromycin given at 800 milligrams once daily was
6 consistent in 13 Phase III studies across four
7 indications where compared to a broad range of
8 comparators that are well-recognized for their
9 efficacy. A short treatment duration with
10 Telithromycin given once daily for five days was
11 effective in three respiratory tract indications and
12 equivalent to 10 days of treatment with comparators
13 given two to three times daily.

14 The most recent of efficacy within the
15 treatment duration consistently non-pneumonia
16 indication is important because this short treatment
17 duration may favor better compliance resulting in
18 increased efficacy and also it may decrease the
19 potential to select resistant strains that can be
20 savored misdoses at the end of a prolonged treatment.

21 In pneumonia, Telithromycin given for
22 seven or 10 days showed excellent efficacy but most of
23 all in this indication Telithromycin was effective in
24 the out-patients most likely to develop complications.
25 In pneumonia it was elderly subjects and subjects with

1 pneumococcal bacteremia or Legionella infections, in
2 chronic bronchitis, elderly subjects or subjects with
3 significant obstruction.

4 Finally, Telithromycin was effective in
5 patients with *S. pneumonia* resistant strain to
6 Penicillin G or Erythromycin A with cure rates over 80
7 percent in pneumonia and acute sinusitis. I will now
8 present the key 50 results of Phase III studies
9 starting with an overview of the adverse event profile
10 and for this I will focus on treatment-related events
11 observed in controlled studies. Then I will discuss
12 the serious adverse events followed by key results of
13 laboratory investigations and the review of ECG
14 analysis will be presented separately by Dr. Benedict.

15 The safety population included all
16 subjects who received at least one dose of study
17 medication and had a subsequent safety assessment.
18 And that's shown here to the left, a total of 3,265
19 subjects were analyzed with approximately two-thirds
20 of them in controlled studies. Number of men and
21 women were equal and the population of elderly
22 subjects was substantial with 372 subjects analyzed.
23 In addition, 95 subjects are aged 13 to 18 year olds
24 were also included.

25 This table shows treatment emergent

1 adverse events considered possibly related to the
2 study medication and observed in more than two percent
3 of the subjects. Gastrointestinal events were the
4 most common events observed with Telithromycin with a
5 slightly higher frequency than in the comparable
6 groups in particular for diarrhea and nausea. But
7 most of these events were mild or moderate in
8 intensity and mild cases accounted for most of the
9 difference between Telithromycin and the comparatives.

10 Also added to this table is the rare event
11 of blurred vision observed with Telithromycin in 0.5
12 percent of subjects and events were generally mild and
13 resolved during treatment. An association with
14 trouble in accommodations of subject, especially in
15 high doses in Phase I studies, points to what is a
16 condition of transient myopia as reported for example,
17 with some of the compounds -- marketed compounds.

18 Overall the adverse events observed in
19 both Telithromycin and the comparatives were generally
20 mild and moderate in intensity and rate.
21 Discontinuation due to adverse events were low with
22 Telithromycin at about five percent for all events.
23 In both treatment groups, gastrointestinal events were
24 the most frequent events leading to discontinuation.

25 This graph shows the percentage of

1 subjects with diarrhea on each day of treatment,
2 focusing on Telithromycin, Clarithromycin, Cefuroxime
3 axetil and Amoxicillin/Clavulanic acid. Note that the
4 prevalence of diarrhea with Telithromycin is lower
5 than for Amoxicillin/Clavulanic acid which is one of
6 the most widely used antibiotic treatment of out-
7 patients with respiratory tract infections. It is
8 slightly higher than that of Clarithromycin and
9 Cefuroxime axetil.

10 Considering the distribution of treatment
11 related adverse event by age group, events in both
12 treatment groups were less frequent in the elderly
13 subjects and in subjects age 13 to 18 years old than
14 in the population of young adults. Eleven deaths
15 reported for all treatment groups in the entire
16 development program. In the controlled studies two
17 deaths occurred with Telithromycin and four deaths
18 with the comparatives. There were five deaths in the
19 uncontrolled studies, all in the pneumonia indication.

20 None of these deaths were considered
21 treatment related and the overall rate of deaths in
22 pneumonia patients in the Telithromycin group was
23 around 0.5 percent with corresponds to the expected
24 rate of death in pneumonia in the out-patients. There
25 was no imbalance between Telithromycin and the

1 comparatives in the occurrence of serious adverse
2 events considering all events, all treatment related
3 events and the rate of all treatment-related events
4 was low at .04 percent for Telithromycin and .02
5 percent for the comparatives as it is expected for
6 oral antibiotics.

7 In the uncontrolled studies the rate of
8 serious adverse events was similar. In one of the
9 uncontrolled studies a 53-year-old male treated for
10 pneumonia in Finland was enrolled with a normal
11 transaminase at baseline and also elevated
12 eosinophilia at baseline. He had a history of
13 diabetes, asthma and three previous courses of
14 macrolide in the previous year. Four days after the
15 end of treatment he had an episode of gastritis
16 similar to what was observed in several members of his
17 family but this episode was followed by fever and
18 transaminase increased with a peak eight days at
19 approximately 1500 unit per liter. The biopsy showed
20 centrilobular process and plasma cell infiltration
21 with those inner fields.

22 Transaminase returned to baseline levels
23 approximately eight weeks later and then the subject
24 presented a second episode of transaminase increase
25 nine months after the first episode with a peak at

1 around 1300 units per liter. Biopsies performed seven
2 weeks after the peak transaminase showed plasma cell
3 infiltration and fibrosis.

4 In summary these subjects with
5 transaminase increase at baseline and eosinophilia
6 increase at baseline presented two episodes of
7 transaminase increase with return to baseline after
8 the first episode and a second episode occurring nine
9 months later and to our knowledge there has been no
10 published report of drug induced liver injury or two
11 distant episodes were triggered by one drug intake.

12 Therefore, we believe it is unlikely that
13 Telithromycin is the etiology of the hepatitis episode
14 observed in this patient. Looking at treatment
15 related hepatic adverse events reported in comparative
16 studies, we can see that they were well balanced
17 between Telithromycin and comparatives with an
18 occurrence of two percent in both groups. Also there
19 was no imbalance in the occurrence of event leading to
20 discontinuation. The effect on hepatic enzymes was
21 also evaluated in detail in Phase III studies and
22 increasing transaminase greater than three times the
23 upper limit of normal as summarized here in controlled
24 studies.

25 As you can see the rate of transaminase

1 increase was similar between Telithromycin and the
2 comparatives at .05 percent and -- for Telithromycin
3 and .04 percent for the comparatives in subjects with
4 normal transaminase at baseline and 8.5 percent for
5 Telithromycin, 11.1 percent for the comparatives in
6 subjects with elevated transaminase at baseline which
7 were mainly enrolled in pneumonia studies.

8 In these subjects there were no case with
9 transaminase increase of greater than three times the
10 upper limit of normal and bilirubin greater than 1.5
11 times the upper limit of normal. These graphs show --
12 allow a more precise comparison of the different level
13 of increase in transaminase during the course of the
14 study between Telithromycin and the comparatives. I'm
15 presenting the subjects with normal transaminase at
16 baseline were less likely to have confronting factors
17 that complicate interpretation.

18 And since transaminase increase is
19 frequently observed in pneumonia, we've analyzed the
20 subject in controlled pneumonia studies and non-
21 pneumonia studies separately. We can see a small
22 difference in the transaminase increase above two
23 times the equivalent of normal similar to what is
24 observed with a macrolide but no signal above three
25 times the upper limit of normal.

1 To summarize, Telithromycin was generally
2 well tolerated, with a pattern of adverse events
3 similar to that of macrolides. Frequency of these
4 transaminase events was slightly higher with
5 Telithromycin than with comparatives but within the
6 range expected for antibiotics. The adverse event
7 profile was similar in different age groups and the
8 rate of transaminase elevation was similar to the
9 comparators.

10 Finally, and most importantly, the rates
11 of serious adverse events and discontinuation were low
12 and similar to the comparators. I'd like now to hand
13 it over to Dr. Benedict.

14 PRESENTATION OF DR. CLAUDE BENEDICT

15 DR. BENEDICT: Good morning. I would now
16 present the second part of the safety update, the ECG
17 analysis. Macrolides have been associated with
18 changes in cardiac repolarization. Telithromycin was
19 -- has structural similarities and derived from
20 macrolides. Because of this we performed an extensive
21 pre-clinical and a prospective clinical investigation
22 of the potential effect of Telithromycin on cardiac
23 repolarization and compared it to different
24 comparative macrolides and non-macrolides in our
25 program.

1 This program was designed in accordance
2 with the EU guidelines and FDA recommendations. Let
3 me now first present to you the pre-clinical data. We
4 performed extensive evaluation of the pre-clinical
5 properties of Telithromycin. This included binding to
6 the different membrane ionic channels, interaction
7 with cloned channels particularly the Ikr or HERG
8 channel but also Kv1.5 and Ikr. We also performed
9 studies in isolated human atrial cells, studies in
10 rabbit Purkinje fibers under different conditions of
11 hyperkalemia, different anti-arrhythmic drugs and in
12 the presence of low pacing rates of bradycardia as
13 well as interaction, studies with Sotalol and
14 quinidine. We also performed studies in awake
15 animals.

16 The results of these studies are
17 summarized in your briefing document but here I would
18 like to especially present the data on Ikr or HERG
19 channel. This slide gives the results of four
20 different variables for some of the commonly used
21 antibiotics except maybe Sparfloxacin. The first
22 column is oral dose, the second the peak free plasma
23 concentration, the third, the concentration required
24 to inhibit the HERG channel by 50 percent and fourth,
25 a ratio that relatively ranks these compounds by the

1 amount that is required for 50 percent inhibition
2 which is the plasma concentration that would be
3 achieved.

4 Please note Telithromycin falls between
5 Clarithromycin and Erythromycin. Please recall from
6 Dr. Jeremy Ruskin's presentation, he said we need to
7 also know not only the effect of the parent compound
8 on the Ikr channel, but also its metabolite. We also
9 looked at the effect of metabolites on the Ikr channel
10 and even at 300 micromolar concentration, the effect
11 was less than 20 percent inhibitory activated.

12 Let me now turn and present the Phase III
13 data. As sponsor, we feel we have done a large
14 extensive program in Phase III. We have gathered an
15 unusually large number of patients. We have looked at
16 the QT changes. In addition to that, we have also
17 gathered PK/PD relationship in over 1500 subjects.
18 ECGs were performed, pre and on-therapy usually days
19 3 to 5 when a steady state was reached. As indicated
20 by Dr. Ruskin, it's important to read these
21 electrocardiographic changes carefully. Therefore, it
22 was all read by a single reader who was blinded to the
23 treatment assignment and read in a random order.

24 There were approximately 1800 subjects in
25 this group. Recall the emphasis or the need to know

1 the information in patients with high risk factors.
2 Our study program had fairly relaxed inclusion
3 criterias, therefore, we were able to capture a large
4 number of patients with high risk factors. In
5 addition, about two-thirds of the way through the
6 program, after safety review, the inclusion criterias
7 were eliminated except for some drugs and congenital
8 QT prolongation giving us a total of about 600
9 subjects to evaluate which will be presented
10 subsequently.

11 QT was measured as the longest and the
12 shortest interval from the 12 leads averaged and
13 corrected by the heart rate using the Bazett's
14 formula. To place the data in perspective, we are
15 giving the data here as QTc but your briefing document
16 also has a calculation by other formula which I'll be
17 discussing shortly.

18 This shows the distribution of the QT
19 measured at entry and on treatment in all of the
20 patients who received Telithromycin. Baseline is
21 orange, treatment is green. Notice very importantly,
22 there is lack of emergence of a shorter, suggesting an
23 emergence of a special population with abnormal QT
24 prolongation. Overall the change was small, one
25 millisecond, in keeping with what Dr. Ruskin has