www.archive.org
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415.840-0391 e-fax

Internet Archive
300 Funston Avenue
San Francisco, CA 94118

AFFIDAVIT OF CHRISTOPHER BUTLER

1. I am the Office Manager at the Internet Archive, located in San Francisco, California. I make this declaration of my own personal knowledge.

2. The Internet Archive is a website that provides access to a digital library of Internet sites and other cultural artifacts in digital form. Like a paper library, we provide free access to researchers, historians, scholars, and the general public. The Internet Archive has partnered with and receives support from various institutions, including the Library of Congress.

3. The Internet Archive has created a service known as the Wayback Machine. The Wayback Machine makes it possible to surf more than 150 billion pages stored in the Internet Archive's web archive. Visitors to the Wayback Machine can search archives by URL (i.e., a website address). If archived records for a URL are available, the visitor will be presented with a list of available dates. The visitor may select one of those dates, and then begin surfing on an archived version of the Web. The links on the archived files, when served by the Wayback Machine, point to other archived files (whether HTML pages or images). If a visitor clicks on a link on an archived page, the Wayback Machine will serve the archived file with the closest available date to the page upon which the link appeared and was clicked.

4. The archived data made viewable and browseable by the Wayback Machine is compiled using software programs known as crawlers, which surf the Web and automatically store copies of web files, preserving these files as they exist at the point of time of capture.

5. The Internet Archive assigns a URL on its site to the archived files in the format http://web.archive.org/web/[Year in yyyy][Month in mm][Day in dd][Time code in hh:mm:ss]/[Archived URL]. Thus, the Internet Archive URL http://web.archive.org/web/19970126045828/http://www.archive.org/ would be the URL for the record of the Internet Archive home page HTML file (http://www.archive.org/) archived on January 26, 1997 at 4:58 a.m. and 28 seconds (1997/01/26 at 04:58:28). A web browser may be set such that a printout from it will display the URL of a web page in the printout's footer. The date assigned by the Internet Archive applies to the HTML file but not to image files linked therein. Thus images that appear on a page may not have been archived on the same date as the HTML file. Likewise, if a website is designed with "frames," the date assigned by the Internet Archive applies to the frameset as a whole, and not the individual pages within each frame.

6. Attached hereto as Exhibit A are true and accurate copies of printouts of the Internet Archive's records of the HTML files for the URLs and the dates specified in the footer of the printout.

7. I declare under penalty of perjury that the foregoing is true and correct.

DATE: 6/15/12

Christopher Butler

CALIFORNIA JURAT WITH AFFIANT STATEMENT

See Attached Document.

State of California
County of San Francisco

Subscribed and ~~sworn to (~~or affirmed) before me this

15th day of June, 2012, by

Christopher Butler,

proved to me on the basis of satisfactory evidence to be the person who appeared before me.

Signature: _____

Exhibit A

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FDA ADVISORY COMMITTEES

[NOTE: Many of the documents are in PDF format, the ADOBE ACROBAT Reader is needed to review PDF files. Click on the ADOBE icon below and download the free reader.]

- Federal Advisory Committee Act
- Executive Secretaries (Updated 8/1/00)
- CDER Rosters
- List of Advisory Committees & Information Line Numbers
- Meeting Transcripts/Minutes/Other Docs by Center
  - 1997 [Transcripts] / [Minutes]
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http://web.archive.org/web/20010309112600/http:/www.fda.gov/ohrms/dockets/ac/acmenu.htm

2001 MEETING TRANSCRIPTS / MINUTES BY CENTER

Center for Biologic Evaluation and Research (CBER)

- Allergenic Products Advisory Committee (Updated 10/15/01)
- Biological Response Modifiers Advisory Committee (Updated 07/30/01)
- Blood Products Advisory Committee (Updated 08/14/01)
- Transmissible Spongiform Encephalopathies Advisory Committee (Updated 10/12/01)
- Vaccines & Related Biologic Products Advisory Committee (Updated 08/17/01)

Center for Drug Evaluation and Research (CDER)

- Anesthetic and Life Support Drugs Advisory Committee (Updated 08/24/01)
- Anti-Infective Drugs Advisory Committee (Updated 10/15/01)
- Anti-Viral Drugs Advisory Committee (Updated 10/17/01)
- Arthritis Advisory Committee (Updated 09/27/2001)
- Cardiovascular and Renal Drugs Advisory Committee (Updated 10/10/01)
- Endocrinologic and Metabolic Drugs Advisory Committee (Updated 09/27/01)
- Nonprescription Drugs Advisory Committee (Updated 10/18/01)
- Oncologic Drugs Advisory Committee (Updated 09/27/01)
- Peripheral and Central Nervous System Drugs Advisory Committee (Updated 07/13/01)
- Advisory Committee for Pharmaceutical Science (Updated 10/03/01)
- Psychopharmacologic Drugs Advisory Committee (Updated 7/23/01)
- Pulmonary-Allergy Drugs Advisory Committee (Updated 10/18/01)

Center for Devices and Radiological Health (CDRH)

- Anesthesiology and Respiratory Therapy Devices Panel (New 07/30/01)
- Circulatory System Devices Panel (Updated 09/27/01)
- Gastroenterology-Urology Devices Panel (Updated 09/07/01)
- General and Plastic Surgery Devices Panel (Updated 08/07/01)
- Medical Devices Dispute Resolution Panel (Updated 09/21/01)
- Microbiology Devices Panel (New 10/11/01)
- National Mammography Quality Assurance Advisory Committee (Updated 09/21/01)
- Obstetrics-Gynecology Devices Panel (Updated 6/5/01)
- Ophthalmic Devices Panel (Updated 08/14/01)
- Orthopedic and Rehabilitation Devices Panel (Updated 08/22/01)
- Radiologic Devices Panel (Updated 6/13/01)
- Technical Electronic Product Radiation Safety Standards Committee (Updated 08/07/01)

Office of the Commissioner (OC)

- Ranch Hand Advisory Committee (New 08/02/01)
- Science Board to FDA (Updated 10/11/01)

Dockets Management Branch, 5630 Fishers Lane - Room 1061- HFA-305, Rockville, MD, 20852; 301-827-6860; Fax 301-827-6870

(Updated 10/18/01)

http://web.archive.org/web/20011020203932/http:/www.fda.gov/ohrms/dockets/ac/01docsbc.htm

2001 MEETING TRANSCRIPTS / MINUTES BY CENTER

Center for Biologic Evaluation and Research (CBER)

- Allergenic Products Advisory Committee (Updated 10/15/01)
- Biological Response Modifiers Advisory Committee (Updated 11/23/01)
- Blood Products Advisory Committee (Updated 12/10/01)
- Transmissible Spongiform Encephalopathies Advisory Committee (Updated 11/26/01)
- Vaccines & Related Biologic Products Advisory Committee (Updated 11/27/01)

Center for Drug Evaluation and Research (CDER)

- Anesthetic and Life Support Drugs Advisory Committee (Updated 08/24/01)
- Anti-Infective Drugs Advisory Committee (Updated 12/10/01)
- Anti-Viral Drugs Advisory Committee (Updated 12/11/01)
- Arthritis Advisory Committee (Updated 09/27/2001)
- Cardiovascular and Renal Drugs Advisory Committee (Updated 10/24/01)
- Endocrinologic and Metabolic Drugs Advisory Committee (Updated 09/27/01)
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- Peripheral and Central Nervous System Drugs Advisory Committee (Updated 07/13/01)
- Advisory Committee for Pharmaceutical Science (Updated 12/12/01)
- Psychopharmacologic Drugs Advisory Committee (Updated 7/23/01)
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Center for Devices and Radiological Health (CDRH)

- Anesthesiology and Respiratory Therapy Devices Panel (New 07/30/01)
- Circulatory System Devices Panel (Updated 11/26/01)
- Clinical Chemistry and Clinical Toxicology Devices Panel (Updated 11/23/01)
- Gastroenterology-Urology Devices Panel (Updated 10/26/01)
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- Microbiology Devices Panel (New 11/05/01)
- National Mammography Quality Assurance Advisory Committee (Updated 09/21/01)
- Obstetrics-Gynecology Devices Panel (Updated 6/5/01)
- Ophthalmic Devices Panel (Updated 11/29/01)
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- Radiologic Devices Panel (Updated 01)
- Technical Electronic Product Radiation Safety Standards Committee (Updated 08/07/01)

Office of the Commissioner (OC)

- Ranch Hand Advisory Committee (New 08/02/01)
- Science Board to FDA (Updated 12/05/01)

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http://web.archive.org/web/20011214125612/http:/www.fda.gov/ohrms/dockets/ac/01docsbc.htm

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2001 MEETING TRANSCRIPTS / MINUTES BY CENTER

Center for Biologic Evaluation and Research (CBER)

- Allergenic Products Advisory Committee (Updated 10/15/01)
- Biological Response Modifiers Advisory Committee (Updated 11/23/01)
- Blood Products Advisory Committee (Updated 01/08/02)
- Transmissible Spongiform Encephalopathies Advisory Committee (Updated 03/29/02)
- Vaccines & Related Biologic Products Advisory Committee (Updated 01/03/02)

Center for Drug Evaluation and Research (CDER)

- Anesthetic and Life Support Drugs Advisory Committee (Updated 08/24/01)
- Anti-Infective Drugs Advisory Committee (Updated 05/23/02)
- Anti-Viral Drugs Advisory Committee (Updated 01/23/02)
- Arthritis Advisory Committee (Updated 09/27/2001)
- Cardiovascular and Renal Drugs Advisory Committee (Updated 12/21/01)
- Endocrinologic and Metabolic Drugs Advisory Committee (Updated 09/27/01)
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- Psychopharmacologic Drugs Advisory Committee (Updated 7/23/01)
- Pulmonary-Allergy Drugs Advisory Committee (Updated 10/18/01)

Center for Devices and Radiological Health (CDRH)

- Anesthesiology and Respiratory Therapy Devices Panel (New 07/30/01)
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- Clinical Chemistry and Clinical Toxicology Devices Panel (Updated 12/20/01)
- Gastroenterology-Urology Devices Panel (Updated 10/26/01)
- General and Plastic Surgery Devices Panel (Updated 12/20/01)
- Medical Devices Dispute Resolution Panel (Updated 11/26/01)
- Microbiology Devices Panel (New 11/05/01)
- National Mammography Quality Assurance Advisory Committee (Updated 09/21/01)
- Obstetrics-Gynecology Devices Panel (Updated 6/5/01)
- Ophthalmic Devices Panel (Updated 12/20/01)
- Orthopedic and Rehabilitation Devices Panel (Updated 08/22/01)
- Radiologic Devices Panel (Updated 01)
- Technical Electronic Product Radiation Safety Standards Committee (Updated 08/07/01)

National Center for Toxicological Research (NCTR)

- Ranch Hand Advisory Committee (New 08/02/01)

Office of the Commissioner (OC)

- Science Board to FDA (Updated 02/07/02)

[Accessibility] [E-mail]

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Updated 05/23/02

http://web.archive.org/web/20020602142527/http:/www.fda.gov/ohrms/dockets/ac/01docsbc.htm

CDER 2001 Meeting Documents

Anti-Infective Drugs Advisory Committee					
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4/26	4/26	Pages 1- 100 3746t1_01.pdf (10,540) Pages 101-200 3746t1_02.pdf (10,646) Pages 201-339 3746t1_03.pdf (19,170)	3746t1.rtf (388) & html (392)		Agenda 3746a1.pdf, htm Briefing Info. 3746b1.htm Roster 3746r1_01committee.pdf, htm 3746r1_02quest.pdf, htm Slides 3746s1.htm
4/23	4/23	3744t1_01.pdf & htm	3744t1.rtf		Notice of Mtg. 032301d.htm & pdf Briefing Information 3744b1.htm Agenda 3744a1.pdf, htm Roster 3744r1.pdf, htm Questions 3744q1.pdf, htm Slides 3744s1.pdf
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01/30	01/30	3719t1_01.pdf (6126) 3719t1_02.pdf (6374) 3719t1_03.pdf (6385) 3719t1_04.pdf (6428)	3719t1.rtf (439)	3719m1.doc, pdf	Briefing Package 3719b1.htm Roster 3719r1.htm Slides 3719s1.htm Agenda 3719a1.htm

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					Question 3719q1.htm

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Anti-Viral Drugs Advisory Committee					
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1/10	1/10	3676t1_a.pdf 3676t1_b.pdf 3676t1_c.pdf 3676t1_d.pdf	3676t1.rtf		Agenda 3676a1.doc, pdf Roster 3676r1.doc, pdf Briefing Information 3676b1.htm Slides 3676s1.htm 3676s1_03.pdf
	1/11	3678t1_a.pdf 3678t1_b.pdf 3678t1_c.pdf 3678t1_d.pdf	3578t1.rtf		Agenda 3678a1.doc, pdf Briefing Information 3678b1.htm Slides 3678s1.htm

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Arthritis Advisory Committee					
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2/7	2/7	3677t1_01.pdf (6421) 3677t1_02.pdf (6733) 3677t1_03.pdf (2448)	3677t1.rtf (561)		Agenda 3677a1.doc, pdf Roster 3677r1_01.doc, pdf Guest Roster 3677r1_02.doc, pdf Briefing Information 3677b1.htm Questions 3677q1.doc, pdf Slides 3677s1.htm
	02/08	3677t2_01.pdf (6774) 3677t2_02.pdf (6852) 3677t2_03.pdf (2918)	3677t2.rtf (597)		Briefing Package 3677b2.htm Agenda 3677a2.doc & pdf Questions 3677q2_01.doc & pdf 3677q2_02.doc & pdf Slides 3677s2.htm

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Cardiovascular and Renal Drugs Advisory Committee					
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Nonprescription Drugs Advisory Committee					
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06/07	06/07				Agenda 3757a1.htm & pdf Questions 3757q1.htm & pdf Briefing Information 3757b1.htm & pdf
4/24	4/24	3743t1_01.pdf 3743t1_02.pdf 3743t1_03.pdf	3743t1.rtf		Agenda 3743a1.htm & pdf Briefing Information 3743b1.htm & pdf

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6/6	6/6				Agenda 3754a1.pdf, html Rosters Members 3754r1_01.pdf, html Consultants 3754r1_02.pdf, html Public Hearing 3754r1_03.pdf, html Questions 3754q1.pdf, html Briefing Information 3754b1.htm
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	3/14	3724t2.pdf	3724t2.rtf	3724m2.htm 3724m2.pdf	Agenda (DRAFT) 3724a2.doc, pdf Roster 3724r1_02.doc, pdf Briefing Info 3724b2.htm Slides 3724s2.htm

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Pharmaceutical Science Drugs Advisory Committee

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Non-Clinical Studies Subcommittee					
5/3	5/3	3742t1.pdf (10,036)	3742t1.rtf (93)& html (100)		Agenda 3742a1.htm & pdf Roster 3742r1.htm & pdf 3742r2.htm & pdf Briefing Info 3742b1.htm & pdf Notice of Meeting 98frx032301g.htm 98frx032301g.pdf

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Psychopharmacologic Drugs Advisory Committee					
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Pulmonary-Allergy Drugs Advisory Committee					
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http://web.archive.org/web/20010617210030/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm

CDER 2001 Meeting Documents

Anesthetic and Life Support Drugs Advisory Committee					
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9/13	9/14	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date.			Draft Agenda 3778a1_draft.pdf Questions 3778q1.pdf Meeting Info m000001.pdf, htm Briefing Information 3778b1.htm Docket Number 01N-0256

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Anti-Infective Drugs Advisory Committee					
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09/12	09/12	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date.			
4/26	4/26	Pages 1- 100 3746t1_01.pdf (10,540) Pages 101-200 3746t1_02.pdf (10,646) Pages 201-339 3746t1_03.pdf (19,170)	3746t1.rtf (388) & html (392)		Agenda 3746a1.pdf, htm Briefing Info. 3746b1.htm Roster 3746r1_01committee.pdf, htm 3746r1_02guest.pdf, htm Slides 3746s1.htm
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	4/24	3744t2.pdf & htm	3744t2.rtf		Briefing Information 3744b2.htm

http://web.archive.org/web/20011004081740/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm

					Agenda 3744a2.pdf, htm Roster 3744r2.pdf, htm Questions 3744q2.pdf, htm Slides 3744s2.pdf
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10/03	10/03				Draft Agenda 3792a1.pdf & htm Final Agenda 3792a1.pdf & htm Roster Committee 3792r1_01.pdf & htm Consultants & Guests 3792r1_02.pdf Questions 3792q1.pdf Briefing Information 3792b1.htm
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	1/11	3678t1_a.pdf 3678t1_b.pdf 3678t1_c.pdf 3678t1_d.pdf	3578t1.rtf		Agenda 3678a1.doc, pdf Briefing Information 3678b1.htm Slides 3678s1.htm

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2/7	2/7	3677t1_01.pdf (6421) 3677t1_02.pdf (6733) 3677t1_03.pdf (2448)	3677t1.rtf (561)		**Agenda** 3677a1.doc, pdf **Roster** 3677r1_01.doc, pdf **Guest Roster** 3677r1_02.doc, pdf **Briefing Information** 3677b1.htm **Questions** 3677q1.doc, pdf **Slides** 3677s1.htm
	02/08	3677t2_01.pdf (6774) 3677t2_02.pdf (6852) 3677t2_03.pdf (2918)	3677t2.rtf (597)		**Briefing Package** 3677b2.htm **Agenda** 3677a2.doc & pdf **Questions** 3677q2_01.doc & pdf 3677q2_02.doc & pdf **Slides** 3677s2.htm

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http://web.archive.org/web/20011004081740/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm

					3775q1_02.pdf, htm Slides 3775s1.htm
	08/10	Pages 1-100 3775t2_01.pdf Pages 101-200 3775t2_02.pdf Pages 201-228 3775t2_03.pdf	3775t2.rtf (299)		Briefing Information 3775b2.htm Questions bosenton 3775q2.pdf, htm
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	07/27	Pages 1-100 3761t2_01.pdf (8,398) Pages 101-200 3761t2_02.pdf (8,508) Pages 201-300 3761t2_03.pdf (8,318) Pages 301-359 3761t2_04.pdf (9,991)	3761t2.htm	3761m2.pdf & htm	Agenda 3761a2.pdf, htm Questions 3761q2.pdf, htm Roster 3761r2.pdf, htm Briefing Information 3761b2.htm Slides 3761t2.htm

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Nonprescription Drugs Advisory Committee					
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Oncologic Drugs Advisory Committee					
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Pediatric Subcommittee					
06/28	06/28	Pages 1-100 3756t1_01.pdf Pages 101-200 3756t1_02.pdf Pages 201-end 3756t1_03.pdf	3756t1.rtf, 3756t1.txt		Agenda 3756a1.htm, pdf Roster 3756r1.htm, pdf Briefing Information htm & pdf Slides 3756s1.htm
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Pediatric Subcommittee					

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Peripheral & Central Nervous System Drugs Advisory Committee					
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6/6	6/6	Pages 1-100 3754t1_01.pdf Pages 101-200 3754t1_02.pdf Pages 201-300 3754t1_03.pdf Pages 301-381 3754t1_04.pdf	3754t1.txt	3754m1.pdf, html	Agenda 3754a1.pdf, html Rosters Members 3754r1_01.pdf, html Consultants 3754r1_02.pdf, html Public Hearing 3754r1_03.pdf, html Questions 3754q1.pdf, html Briefing Information 3754b1.htm Slides 3754s1.htm
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Advisory Committee for Pharmaceutical Science					
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07/19	07/19	Pages 1-100	3763t1.htm, txt	3763m1.htm &	Agenda

http://web.archive.org/web/20011004081740/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm

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Orally Inhaled and Nasal Drug Products Subcommittee					
7/17	7/17	Pages 1-100 3764t1_01.pdf Pages 101-200 3764t1_02.pdf Pages 201-211 3764t1_03.pdf	3764t1.htm, txt		Agenda 3764a1.htm & pdf Roster 3764r1.htm & pdf Open Speakers 3764r1.htm & pdf Questions 3764q1.htm & pdf Briefing Information 3764b1.htm Slides 3764s1.htm
Non-Clinical Studies Subcommittee					
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Psychopharmacologic Drugs Advisory Committee					
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2/14	2/14	3685t1.pdf	3685t1.txt	3685m1.pdf	Agenda 3685a1.doc, pdf Roster 3685r1.doc, pdf Questions 3685q1.doc, pdf Briefing Info 3685b1.htm Slides 3685s1.htm
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Pulmonary-Allergy Drugs Advisory Committee					
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05/11	05/11	Pages 1-100 3737t1_01.pdf Pages 101-200 3737t1_02.pdf Pages 201-300 3737t1_03.pdf Pages 301-345 3737t1_04.pdf	3737t1.rtf	3737m1.pdf, html	Agenda 3737a1.htm, pdf Planning Agenda 3737a1_planning.htm, pdf Questions 3737q1.htm, pdf Briefing Information 3737b1.htm Petition

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(Updated 10/02/01)

http://web.archive.org/web/20011004081740/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm

CDER 2001 Meeting Documents

Anesthetic and Life Support Drugs Advisory Committee

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9/13	9/14	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date.			Draft Agenda 3778a1_draft.pdf Questions 3778q1.pdf Meeting Info m000001.pdf, htm Briefing Information 3778b1.htm Docket Number 01N-0256

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Anti-Infective Drugs Advisory Committee

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09/12	09/12	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date. This meeting was rescheduled for 10/16/01.			

http://web.archive.org/web/20011116144419/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm

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http://web.archive.org/web/20011116144419/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm

		Pages 101-200 3792t1_02.pdf (9,581) Pages 201-300 3792t1_03.pdf (10,067) Pages 301-326 3792t1_04.pdf (8,207)			Final Agenda 3792a1.pdf & htm Roster Committee 3792r1_01.pdf & htm Consultants & Guests 3792r1_02.pdf & htm Questions 3792q1.pdf Briefing Information 3792b1.htm Slides 3792s1.htm
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Arthritis Advisory Committee

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07/26	07/26	Pages 1-100 3761t1_01.pdf (9,446) Pages 101-200 3761t1_02.pdf (9,613) Pages 201-300 3761t1_03.pdf (9,586) Pages 301-342 3761t1_04.pdf (8,306)	3761t1.htm	3761m1.pdf & htm	Notice of Meeting June 8, 2001 txt pdf Agenda 3761a1.pdf, htm Questions 3761q1.pdf, htm Briefing Information 3761b1.htm Slides 3761s1.htm
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Nonprescription Drugs Advisory Committee					
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Joint meeting with Pulmonary-Allergy Drugs Advisory Committee					
05/11	05/11	Pages 1-100 3737t1_01.pdf Pages 101-200 3737t1_02.pdf Pages 201-300 3737t1_03.pdf Pages 301-345 3737t1_04.pdf	3737t1.rtf	3737m1.pdf, html	Agenda 3737a1.htm, pdf Planning Agenda 3737a1_planning.htm, pdf Questions 3737q1.htm, pdf Roster Consultants 3737r1_01.htm & pdf Members 3737r1_02.htm & pdf Open Public Hearing 3737r1_03.htm & pdf Briefing Information 3737b1.htm

http://web.archive.org/web/20011116144419/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm

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Oncologic Drugs Advisory Committee					
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Pediatric Subcommittee					
11/28	11/28				Draft Agenda 3803a1.[Word version] [htm version] [pdf version] Roster 3803r1.[Word version] [htm version] [pdf version] Questions 3803q1. [Word version] [htm version] [pdf version] Briefing Information 3803b1.htm
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Peripheral & Central Nervous System Drugs Advisory Committee					
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6/6	6/6	Pages 1-100 3754t1_01.pdf Pages 101-200 3754t1_02.pdf Pages 201-300 3754t1_03.pdf Pages 301-381 3754t1_04.pdf	3754t1.txt	3754m1.pdf, html	Agenda 3754a1.pdf, html Rosters Members 3754r1_01.pdf, html Consultants 3754r1_02.pdf, html Public Hearing 3754r1_03.pdf, html Questions 3754q1.pdf, html Briefing Information 3754b1.htm Slides 3754s1.htm
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Advisory Committee for Pharmaceutical Science					
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11/13	11/13				Draft Agenda 3798a1. [htm format] & [pdf format] Roster Committee Members [htm format] & [pdf format] Guests [htm format] & [pdf format] Briefing Information 3798b1.htm
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7/17	7/17	Pages 1-100 3764t1_01.pdf Pages 101-200 3764t1_02.pdf Pages 201-211 3764t1_03.pdf	3764t1.htm, txt	3764m1.htm & pdf	Agenda 3764a1.htm & pdf Roster 3764r1.htm & pdf Open Speakers 3764r1.htm & pdf Questions 3764q1.htm & pdf Briefing Information 3764b1.htm Slides 3764s1.htm

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Non-Clinical Studies Subcommittee					
5/3	5/3	3742t1.pdf (10,036)	3742t1.rtf (93)& html (100)		Agenda 3742a1.htm & pdf Roster 3742r1.htm & pdf 3742r2.htm & pdf Briefing Info 3742b1.htm & pdf Notice of Meeting 98frx032301g.htm 98frx032301g.pdf

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Psychopharmacologic Drugs Advisory Committee					
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2/14	2/14	3685t1.pdf	3685t1.txt	3685m1.pdf	Agenda 3685a1.doc, pdf Roster 3685r1.doc, pdf Questions 3685q1.doc, pdf Briefing Info 3685b1.htm Slides 3685s1.htm
	2/15	3685t2.pdf	3685t2.txt	3685m2.pdf	Agenda 3685a2.doc, pdf Roster 3685r2.doc, pdf Questions 3685q2.doc, pdf Briefing Info 3685b2.htm Slides 3685s2.htm

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Pulmonary-Allergy Drugs Advisory Committee					
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Joint meeting with Nonprescription Drugs Advisory Committee					

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CBM of U.S. Patent No. 7,668,730
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(Updated 11/07/01)

http://web.archive.org/web/20011116144419/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm

[Federal Registers] [FDA Home Page][Dockets Home Page][CBER][CDRH][OC][Up][AC What's New] [Accessibility] [E-mail] Dockets Management Branch, 5630 Fishers Lane - Room 1061- HFA-305, Rockville, MD, 20852; 301-827-6860; Fax 301-827-6870

CDER 2001 Meeting Documents

Anesthetic and Life Support Drugs Advisory Committee

Start	Day	Transcript PDF ID (size in kb)	Transcript Text ID (size in kb)	Minutes (size in kb)	Other Docs ID (size in kb)
9/13	9/14	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date.			Draft Agenda 3778a1_draft.pdf Questions 3778q1.pdf Meeting Info m000001.pdf, htm Briefing Information 3778b1.htm Docket Number 01N-0256

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Anti-Infective Drugs Advisory Committee

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11/07	11/07	Pages 1-100 (8,448) Pages 101-200 (8,549) Pages 201-307 (17,286)	[Word version] [htm version]	[pdf version] [htm version] [Word version]	Final Agenda [Word version] [pdf version] [htm version] Draft Agenda [Word version] [pdf version] [htm version] Questions [Word version] [pdf version] [htm version] Briefing Information htm Slides
10/16	10/16	Pages 1-100 3797t1_01.pdf Pages 101-200 3797t1_02.pdf Pages 201-300 3797t1_03.pdf Pages 301-345 3797t1_04.pdf	3797t1.[Word Version] (477) & [HTML Version] (394)		Agenda htm & pdf Questions htm & pdf Briefing Information Roster Committee Members htm & pdf Slides 3797s1.htm

http://web.archive.org/web/20011218005715/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm

09/12	09/12	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date. This meeting was rescheduled for 10/16/01.			
04/26	04/26	Pages 1- 100 3746t1_01.pdf (10,540) Pages 101-200 3746t1_02.pdf (10,646) Pages 201-339 3746t1_03.pdf (19,170)	3746t1.rtf (388) & html (392)		Agenda 3746a1.pdf, htm Briefing Info. 3746b1.htm Roster 3746r1_01committee.pdf, htm 3746r1_02guest.pdf, htm Slides 3746s1.htm
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Anti-Viral Drugs Advisory Committee					
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12/12	12/12				Notice of Meeting [text version] [pdf version] Draft Agenda 3819a1_draft [pdf version] [htm version] [Word version] Roster 3819r1_committee [pdf version] [htm version] [Word version] Briefing Information 3819b1.htm
10/03	10/03	Pages 1 - 100 3792t1_01.pdf (9,207) Pages 101-200 3792t1_02.pdf (9,581) Pages 201-300 3792t1_03.pdf (10,067) Pages 301-326 3792t1_04.pdf (8,207)	3792t1.htm		Draft Agenda 3792a1.[pdf version] [htm version] Final Agenda 3792a1.[pdf version] [htm version] Roster Committee 3792r1_01.[pdf version] [htm version] Consultants & Guests 3792r1_02.[pdf version] [htm version] Questions 3792q1.pdf Briefing Information 3792b1.htm Slides 3792s1.htm
	10/04	Pages 1 - 100 3792t2_01.pdf (9,357) Pages 101-200 3792t2_02.pdf (9,375) Pages 201-300 3792t2_03.pdf (9,990) Pages 301-327 3792t2_04.pdf (8,452)	3792t2.htm		Agenda 3792a2.pdf & htm Roster Committee 3792r2_01.pdf & htm Consultants & Guests 3792r2_02.pdf Questions 3792q2.pdf Briefing Information 3792b2.htm Slides 3792s2.htm
02/27	02/27	3731t1_01.pdf (6394) 3731t1_02.pdf (6275) 3731t1_03.pdf (3920)	3731t1.rtf (271)		Agenda 3731a1.doc, pdf Slides 3731s1.htm Roster 3731r1.doc, pdf 3731r2.doc, pdf Briefing Information 3731b1.htm Questions 3731q1.doc, pdf
01/10	01/10	3676t1_a.pdf 3676t1_b.pdf 3676t1_c.pdf 3676t1_d.pdf	3676t1.rtf		Agenda 3676a1.doc, pdf Roster 3676r1.doc, pdf Briefing Information 3676b1.htm

http://web.archive.org/web/20011218005715/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm

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Arthritis Advisory Committee					
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	08/17	Pages 1-100 3779t2_01.pdf Pages 101-159 3779t2_02.pdf		3779m2.pdf & htm	Agenda 3779a2.htm & pdf Rosters Committee 3779r2_committee.htm & pdf Consultants 3779r2_consultants.htm & pdf Public Hearing 3779r1_public_hearing.htm & pdf Briefing Information 3779b2.htm
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02/07	02/07	3677t1_01.pdf (6421) 3677t1_02.pdf (6733) 3677t1_03.pdf (2448)	3677t1.rtf (561)		Agenda 3677a1.doc, pdf Roster 3677r1_01.doc, pdf Guest Roster 3677r1_02.doc, pdf Briefing Information 3677b1.htm Questions 3677q1.doc, pdf Slides 3677s1.htm
	02/08	3677t2_01.pdf (6774) 3677t2_02.pdf (6852) 3677t2_03.pdf (2918)	3677t2.rtf (597)		Briefing Package 3677b2.htm Agenda 3677a2.doc & pdf Questions 3677q2_01.doc & pdf 3677q2_02.doc & pdf Slides 3677s2.htm

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Cardiovascular and Renal Drugs Advisory Committee					
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10/11	10/11				Agenda 3793a1.htm & pdf Briefing Information Questions 3793q1.htm & pdf Slides 3793s1.htm
08/09	08/09	Pages 1-100 3775t1_01.pdf Pages 101-200 3775t1_02.pdf Pages 201-300 3775t1_03.pdf Pages 301-400 3775t1_04.pdf Pages 401-411 3775t1_05.pdf	3775t1.rtf (444)		Agenda 3775a1.htm, pdf Roster 3775r1.htm Briefing Information 3775b1.htm Questions Remondulin 3775q1_01.pdf, htm Extraneal 3775q1_02.pdf, htm Slides 3775s1.htm

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5/24	5/24	3749t1_01.pdf (9171) 3749t1_02.pdf (8690) 3749t1_03.pdf (7469) 3749t1_04.pdf (4025)	3749t1.rtf (437)		Briefing Information 3749b1.htm Agenda 3749a1.pdf & htm Questions 3749q1.pdf & htm
	5/25	3749t2_01.pdf (9171) 3749t2_02.pdf (8465) 3749t2_03.pdf (8352) 3749t2_04.pdf (7345)	3749t2.rtf (465)		Briefing Information 3749b2.htm Questions 3749q2.pdf & htm

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Endocrinologic and Metabolic Drugs Advisory Committee					
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	07/27	Pages 1-100 3761t2_01.pdf (8,398) Pages 101-200 3761t2_02.pdf (8,508) Pages 201-300 3761t2_03.pdf (8,318) Pages 301-359 3761t2_04.pdf (9,991)	3761t2.htm	3761m2.pdf & htm	Agenda 3761a2.pdf, htm Questions 3761q2.pdf, htm Roster 3761r2.pdf, htm Briefing Information 3761b2.htm Slides 3761t2.htm

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Nonprescription Drugs Advisory Committee					
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Joint meeting with Pulmonary-Allergy Drugs Advisory Committee					
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http://web.archive.org/web/20011218005715/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm

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	12/06				Briefing Information Morning Session 3815b2_01.htm Afternoon Session 3815b2_02.htm
Pediatric Subcommittee					
11/28	11/28				Draft Agenda 3803a1.[Word version] [htm version] [pdf version] Roster 3803r1.[Word version] [htm version] [pdf version] Questions 3803q1. [Word version] [htm version] [pdf version] Briefing Information 3803b1.htm Slides 3803s1.htm
09/10	09/10	Morning Session Pages 1-100 3782t1_01a.pdf (10,008) Pages 101-179 3782t1_01b.pdf Afternoon Session Pages	Morning Session 3782t1_01.htm (139) Afternoon Session 3782t1_02.htm		Agenda 3782a1.pdf & htm Revised Agenda 3782a1_revised.pdf & htm Roster

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06/07	06/07	Pages 1-100 3757t1_01.pdf Pages 101-201 3757t1_02.pdf	3757t1.txt, htm		Agenda 3757a1.htm & pdf Questions 3757q1.htm & pdf Briefing Information 3757b1.htm & pdf
		Pediatric Subcommittee			
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Peripheral & Central Nervous System Drugs Advisory Committee					
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http://web.archive.org/web/20011218005715/http:/www.fda.gov/ohrms/dockets/ac/cder01.htm

		3754t1_03.pdf Pages 301-381 3754t1_04.pdf			Consultants 3754r1_02.pdf, html Public Hearing 3754r1_03.pdf, html Questions 3754q1.pdf, html Briefing Information 3754b1.htm Slides 3754s1.htm
3/13	3/13	3724t1.pdf	3724t1.rtf	3724m1.htm 3742m1.pdf	Agenda 3724a1.doc, pdf Roster 3724r1_01.doc, pdf Briefing Info 3724b1.htm Slides 3724s1.htm
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Advisory Committee for Pharmaceutical Science					
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11/28	11/28				Revised Agenda [pdf version] [htm version] [Word version] Draft Agenda 3804a1 [pdf version] Rosters Committee: 3804r1 [pdf version] [htm version] [Word version] Guests: [pdf version] [htm version] [Word version] Briefing Information 3804b1.htm Slides
	11/29				Revised Agenda [pdf version] [htm version] [Word version] Committee: 3804r1 [pdf version] [htm version]

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11/13	11/13	Pages 1-100 (10,038) Pages 101-148 (6,901)	[htm version] [Word version]	[pdf] [htm] [Word]	Draft Agenda 3798a1. [htm format] & [pdf format] Roster Committee Members [htm format] & [pdf format] Guests [htm format] & [pdf format] Briefing Information 3798b1.htm
07/19	07/19	Pages 1-100 3763t1_01.pdf Pages 101-200 3763t1_02.pdf Pages 201-300 3763t1_03.pdf Pages 301-313 3763t1_04.pdf	3763t1.htm, txt	3763m1.htm & pdf	Agenda 3763a1.htm & pdf Roster 3763r1.htm & pdf Guest Roster 3763r1_guest.doc & pdf FDA Roster 3763r1_fda.doc & pdf Questions 3763q2.htm & pdf Briefing Information 3763b1.htm Slides 3763s1.htm
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			Orally Inhaled and Nasal Drug Products Subcommittee		
7/17	7/17	Pages 1-100 3764t1_01.pdf Pages 101-200 3764t1_02.pdf Pages 201-211 3764t1_03.pdf	3764t1.htm, txt	3764m1.htm & pdf	Agenda 3764a1.htm & pdf Roster 3764r1.htm & pdf Open Speakers 3764r1.htm & pdf Questions 3764q1.htm & pdf Briefing Information 3764b1.htm Slides

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Non-Clinical Studies Subcommittee					
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Psychopharmacologic Drugs Advisory Committee					
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Pulmonary-Allergy Drugs Advisory Committee					
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Joint meeting with Nonprescription Drugs Advisory Committee					
05/11	05/11	Pages 1-100 3737t1_01.pdf Pages 101-200 3737t1_02.pdf Pages 201-300 3737t1_03.pdf Pages 301-345	3737t1.rtf	3737m1.pdf, html	Agenda 3737a1.htm, pdf Planning Agenda 3737a1_planning.htm, pdf Questions 3737q1.htm, pdf Roster

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		3737t1_04.pdf			**Consultants 3737r1_01.htm & pdf** **Members 3737r1_02.htm & pdf** **Open Public Hearing 3737r1_03.htm & pdf** **Briefing Information** 3737b1.htm Petition **Slides** 3737s1.htm **Open Public Hearing Presentations** 3737op1.htm

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(Updated 12/12/01)

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CDER 2001 Meeting Documents

Anesthetic and Life Support Drugs Advisory Committee

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9/13	9/14	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. This meeting has been rescheduled for January 30-31, 2002. You may find additional information at CDER 2002 page.			Draft Agenda 3778a1_draft.pdf Questions 3778q1.pdf Meeting Info m000001.pdf, htm Briefing Information 3778b1.htm Docket Number 01N-0256

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Anti-Infective Drugs Advisory Committee

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10/16	10/16	Pages 1-100 3797t1_01.pdf Pages 101-200 3797t1_02.pdf Pages 201-300 3797t1_03.pdf Pages 301-345 3797t1_04.pdf	3797t1.[Word Version] (477) & [HTML Version] (394)		Agenda htm & pdf Questions htm & pdf Briefing Information Roster Committee Members htm & pdf Slides 3797s1.htm

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09/12	09/12	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date. This meeting was rescheduled for 10/16/01.			
04/26	04/26	Pages 1- 100 3746t1_01.pdf (10,540) Pages 101-200 3746t1_02.pdf (10,646) Pages 201-339 3746t1_03.pdf (19,170)	3746t1.rtf (388) & html (392)	pdf htm doc	Agenda 3746a1.pdf, htm Briefing Info. 3746b1.htm Roster 3746r1_01committee.pdf, htm 3746r1_02guest.pdf, htm Slides 3746s1.htm Questions pdf htm doc
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Arthritis Advisory Committee					
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Joint meeting with Pulmonary-Allergy Drugs Advisory Committee					

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Joint meeting with Nonprescription Drugs Advisory Committee					

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9/13	9/14	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. This meeting has been rescheduled for January 30-31, 2002. You may find additional information at CDER 2002 page.			Draft Agenda 3778a1_draft.pdf Questions 3778q1.pdf Meeting Info m000001.pdf, htm Briefing Information 3778b1.htm Docket Number 01N-0256

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09/12	09/12	Due to the events of this week, this meeting has been postponed. It will be rescheduled in the future. Please check here for the new date. This meeting was rescheduled for 10/16/01.			
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Joint meeting with Pulmonary-Allergy Drugs Advisory Committee					

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Peripheral & Central Nervous System Drugs Advisory Committee

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PERIPHERAL & CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

June 6, 2001

Briefing Information

Consideratin of NDA 21-196, Xyrem (sodium oxybate, Orphan Medial Inc.), proposed to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness for persons wit narcolepsy.

Orphan Medical Presentations

Disclaimer

The statements contained in this document are those of the product's sponsor, not FDA, and FDA does not necessarily agree with the sponsor's statements. FDA has not made a final determination about the safety or effectiveness of the product described in this document.

Briefing Information pdf

Xyrem Prescription and Distribution Process, *Video Script 2/2/01)* html pdf

Video

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Overview Memo pdf

Efficacy Review pdf

Safety Review pdf

Major Amendment Review pdf

Controlled Substance Overview pdf

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PERIPHERAL & CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

June 6, 2001

Briefing Information

Consideratin of NDA 21-196, Xyrem (sodium oxybate, Orphan Medial Inc.), proposed to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness for persons wit narcolepsy.

Orphan Medical Presentations

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Briefing Information pdf

Xyrem Prescription and Distribution Process, *Video Script 2/2/01)* html pdf

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Major Amendment Review pdf

Controlled Substance Overview pdf

http://web.archive.org/web/20010811143424/http:/www.fda.gov/ohrms/dockets/ac/01/briefing/3754b1.htm

PEDIATRIC SUBCOMMITTEE OF THE

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

June 6, 2001

Slides

Consideration of (NDA) 21-196, Xyrem® (sodium oxybate, Orphan Medical, Inc.), proposed to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness for persons with narcolepsy. A main focus of the deliberations will be on risk management issues.

Orphan Medical Presentations ppt html

Disclaimer

The statements contained in this document are those of the product's sponsor, not FDA, and FDA does not necessarily agree with the sponsor's statements. FDA has not made a final determination about the safety or effectiveness of the product described in this document.

NDA 21196 Xyrem for Narcolepsy, Orphan Medica, Inc., Comments About Sleepwalking, Ranjit Mani, MD pdf htm

Effect of GHB on Measures of Daytime Sleepiness in Narcolepsy, Ranjit Mani, MD pdf htm

GHB the CEWG Perspective, Carol Falkowski pdf

GHB Abuse in the United States, Carol Falkowski ppt htm

Gamma Hydroxybutyrate, Jo Ellen Dyer, PharmD ppt htm

Public Hearing

Written Testimony of Sharon A. Fitzgerald pdf

Testimony by Abbey S. Meyers, National Organization for Rare Disorders, Inc. pdf

Statement of Robert L Cloud, Narcolepsy Network pdf

Statement of Cindy Pekarick pdf

Statement of Eric C. Strain, MD, College on Problems of Drug Dependence pdf

Public Statement of Deborah Zvosec, PhD, Hennepin County Medical Center pdf

Zvosec, Deborah L. PhD, Stephen W. Smith, MD. et al, "Adverse Evens, Including Death, Associate with the Use of 1,4-butanediol," *N Engl J Med*, Vol. 344, No. 2, January 11, 2001, pp 87-94.*

Statement of Trinka Porrata pdf

Testimony of Richard L Gelula, MSA, National Sleep Foundation pdf htm

"Living with Narcolepsy," National Sleep Foundation*

Statement of Matt Speakman pdf

Statement of Charles F Cichon, National Association of Drug Diversion Investigators Inc pdf

Michael's Message Foundation Inc., Debbie Alumbaugh pdf

Statement of Brian A Hunter, Young Adults with Narcolepsy - YAWN pdf

Statement Regarding GHB (Xyrem) Approval, Joe Spillane, PharmD, ABAT pdf htm

* Copyrighted material may be view at: Dockets Management Branch, Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20857, Public hours are 9:00 am – 4:00 pm Monday through Friday except for Federal Holidays.

http://web.archive.org/web/20010806024315/http:/www.fda.gov/ohrms/dockets/ac/01/slides/3754s1.htm

Pediatric Subcommittee of the

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

April 23, 2001

Slides

Review of Meeting Agenda/Background Information and Overview, Russ Fleischer, PA-C, MPH, FDA ppt html

Hepatitis C in Children, Maureen Jonas, MD, Children's Hospital, Boston, MA ppt html

Pediatric Drug Development: Overview of FDA Initiatives, Karen Weiss, M.D, FDA ppt html

http://web.archive.org/web/20020306081400/http:/www.fda.gov/ohrms/dockets/ac/01/slides/slides/3744s1.htm

Pediatric Subcommittee of the

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

April 23, 2001

Slides

Review of Meeting Agenda/Background Information and Overview, Russ Fleischer, PA-C, MPH, FDA ppt html

Hepatitis C in Children, Maureen Jonas, MD, Children's Hospital, Boston, MA ppt html

Pediatric Drug Development: Overview of FDA Initiatives, Karen Weiss, M.D, FDA ppt html

Virology and Immunology of Hepatitis C Virus Infection, Dr. Barbara Rehermann, MD, NIH pdf

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Calendar of CDER Advisory Committee Meetings

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This area includes meetings and events that are related to CDER's mission. It is advised that participants verify the time and location of meetings and events. There are other meetings and events listed on the FDA Meetings Page.

Tentative Advisory Committee Meetings (updated 5/8/2001)

- Advisory Committee Agendas
- Advisory Committee Information
- Advisory Committee Transcripts

CENTER FOR DRUG EVALUATION AND RESEARCH
FOOD AND DRUG ADMINISTRATION
ADVISORS AND CONSULTANTS STAFF

May 2001 Meetings

Cardiovascular and Renal Drugs Advisory Committee

May 24, 2001, from at 8:30 a.m. to 5 p.m. and on May 25, 2001, from at 9 a.m. to 3:30 p.m., National Institutes of Health, 9000 Rockville Pike, Building 10, Clinical Center, Jack Masur Auditorium, Bethesda, MD. **ADDITIONAL INFORMATION:** Joan C. Standaert, Center for Drug Evaluation and Research (HFD-110), 419-259-6211 or John M. Treacy (HFD-21), 301-827-7001. Oral presentations from the public will be scheduled between approximately 8:30 a.m. and 9:00 a.m. on May 24, 2001.
Agenda: On May 24, 2001, the committee will discuss: (1) published interim analyses of ALLHAT (antihypertensive and lipid lowering treatment to prevent heart attack trial) sponsored by the National Heart, Lung, and Blood Institute, National Institutes of Health; and (2) Response to the Citizen's Petition of Lawrence D. Bernhardt and Arnold Liebman, regarding new drug application (NDA) 19-668, Cardura (doxazosin), Pfizer Inc. On May 25, 2001, the committee will discuss NDA 20-920 Natrecor (nesiritide), Scios Inc., for treatment of acute heart failure.

June 2001 Meetings

Peripheral and Central Nervous System Drugs Advisory Committee

June 6, 2001, 8 a.m. to 5 p.m., Holiday Inn, 8120 Wisconsin Avenue, Bethesda Maryland. The hotel phone number is 301-652-2000.
ADDITIONAL INFORMATION: Sandy Titus, Center for Drug Evaluation and Research (HFD-21), 301/827-7001 or e-mail: Tituss@cder.fda.gov.
Oral presentations from the public will be scheduled between approximately 1

p.m. to 2 p.m.
Agenda: On June 6, 2001, the committee will consider the safety and efficacy of new drug application (NDA) 21-196, Xyrem®, (sodium oxybate, Orphan Medical, Inc.) proposed to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness for persons with narcolepsy. A main focus of the deliberations will be on risk management issues.

Background material from the sponsor and the FDA will be posted 24 hours before the meeting in the "Peripheral and Central Nervous System Drugs Advisory Committee" section of the Dockets site. This is the same web site where you can find the minutes, transcript, and slides from the meeting. This material is generally posted about three weeks after the meeting.

The **June 14-15, 2001** meeting of the Anesthetic and Life Support Drugs Advisory committee meeting has been cancelled. The meeting will be rescheduled for Fall 2001.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS

ADVISORY COMMITTEE

Wednesday, June 6, 2001

8:15 a.m.

Holiday Inn
Bethesda, Maryland

PARTICIPANTS

Claudia H. Kawas, M.D., Consultant and Acting Chairman
Sandra Titus, Ph.D., Executive Secretary

MEMBERS:

Ella P. Lacey, Ph.D., Consumer Representative,

http://web.archive.org/web/20010806060337/http:/www.fda.gov/ohrms/dockets/ac/01/transcripts/3754t1.txt

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LaRoy P. Penix, M.D.
Richard D. Penn, M.D.
Gerald Van Belle, Ph.D.

CONSULTANTS:

Gustavo C. Roman, M.D.
Jerry S. Wolinsky M.D.

XYREM CONSULTANTS:

VOTING:

Pippa Simpson, Ph.D.
Carol Falkowski, Ph.D.

NON-VOTING:

Christine A. Sannerud, Ph.D.
Jerry Frankenheim, Ph.D.
Jo-Ellen Dyer, Ph.D.

ON PONE-LINK - NON-VOTING:

Ronald Chervin, M.D.
Christian Guilleminault, M.D.

FDA:

Robert Temple, M.D.
Russell Katz, M.D.
Ranjit Mani, M.D.
John Feeney, M.D.
Deborah B. Leiderman, M.D.

C O N T E N T S

http://web.archive.org/web/20010806060337/http:/www.fda.gov/ohrms/dockets/ac/01/transcripts/3754t1.txt

P R O C E E D I N G S

Call to Order and Introductions

DR. KAWAS: Good morning, everyone, and welcome to the Wednesday, June 6, 2001 meeting of the Peripheral and Central Nervous System Advisory Committee. My name is Claudia Kawas, and I think we can begin with introductions, please, perhaps over by Dr. Temple's side.

DR. TEMPLE: Bob Temple, I am the Office Director.

DR. KATZ: Russ Katz, Division of Neuropharmacological Drug Products, FDA.

DR. FEENEY: John Feeney, neurology team leader, FDA.

DR. MANI: Ranjit Mani, medical reviewer, Neuropharm., FDA.

DR. LEIDERMAN: Deborah Leiderman, Director, Controlled Substance Staff, FDA.

DR. SIMPSON: Pippa Simpson, University of Arkansas Medical Sciences, biostatistician.

DR. FALKOWSKI: Carol Falkowski, drug

http://web.archive.org/web/20010806060337/http:/www.fda.gov/ohrms/dockets/ac/01/transcripts/3754t1.txt

abuse researcher, Hazelden Foundation.

DR. ROMAN: Gustavo Roman, Professor of Neurology at the University of Texas, San Antonio.

DR. WOLINSKY: Jerry Wolinsky, Professor

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of Neurology, University of Texas, Houston.

DR. TITUS: Sandy Titus, FDA, the administrator of the Peripheral and Central Nervous System Committee.

DR. PENN: Richard Penn, neurosurgeon at the University of Chicago.

DR. LACEY: Ella Lacey, professor emerita, Illinois University, Carbondale, Illinois.

DR. VAN BELLE: Gerald Van Belle, Department of Biostatistics, from the University of Washington.

DR. PENIX: LaRoy Penix, Associate Professor of Neurology at Moorehouse School of Medicine.

DR. SANNERUD: Christina Sannerud, Drug and Chemical Evaluation Section, Drug Enforcement Administration.

DR. DYER: I am Jo Dyer, with the University of California, San Francisco and the San Francisco Poison Control System, California.

DR. FRANKENHEIM: Jerry Frankenheim, pharmacologist, National Institute on Drug Abuse.

DR. KAWAS: Today we have met to discuss the consideration of Xyrem, proposed to reduce the incidence of cataplexy and to improve the symptom

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of daytime sleepiness for persons with narcolepsy. The main focus of the deliberations will also be on risk management issues.

If we could ask Dr. Titus to begin with

http://web.archive.org/web/20010806060337/http:/www.fda.gov/ohrms/dockets/ac/01/transcripts/3754t1.txt

the conflict of interest statement?

Conflict of Interest Statement

DR. TITUS: Before I begin the conflict of interest statement, I just want to announce that we have two people on line with us, Dr. Chervin and Dr. Guilleminault. They are both in a room listening to us and will participate with us on the mikes.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

The special government employees participating in today's meeting have been screened for interests in Orphan Medical's Xyrem and for interests in the products and sponsors deemed by the agency to be competing. Based on the agency's review of each participant's response to the conflict of interest screening, it has been determined that there is no potential for a

conflict of interest with regard to this meeting.

With respect to FDA's invited guests, there are reported affiliations which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Ronald Chervin would like to disclose for the record that he has a contract with Cephalon to study Provigil, but not for use in narcolepsy. He is the principal investigator, however, no funds from Cephalon, present or past, have contributed to his personal salary and none have been made available for his non-research related use. Further, in previous years Dr. Chervin was a

http://web.archive.org/web/20010806060337/http:/www.fda.gov/ohrms/dockets/ac/01/transcripts/3754t1.txt

co-investigator with Cephalon in a narcolepsy clinical trial.

Christian Guilleminault has been the administrator of the Sleep Disorder Clinic in Palo Alto, California, where the study of Xyrem was performed by a team of researchers.

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

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

DR. KAWAS: Thank you very much, Dr. Titus. We will begin with Dr. Russell Katz, of the FDA, who will give us the FDA overview of the issues. I want to point out to the committee members that they have much of the materials that they will be seeing during this meeting in front of them.

FDA Overview

DR. KATZ: Thanks, Claudia. First, I would like to welcome the committee back. You were here just a few months ago so I appreciate your coming back so soon.

We have a number of invited guests who are augmenting the committee today, and many of them are experts in the evaluation of issues related to drug abuse, and I would just like to welcome them,

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in particular Drs. Simpson, Sannerud and Frankenheim.

We have two other experts who will actually be speakers later this morning. Dr. Dyer

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will speak on her experience with GHB use and misuse in cases she has seen, and Dr. Falkowski will talk about the epidemiology of GHB abuse in the United States.

Finally, as Dr. Titus mentioned, we have two acknowledged experts in sleep disorders who are attending the annual sleep meetings in Chicago, but who have agreed to sit in a hotel room for however long this takes and participate by phone. So, Drs. Guilleminault and Chervin, wherever you are, thank you. Thanks for being here.

As you know and as you have heard, today we will ask you to discuss NDA 21-196, which was submitted by Orphan Medical for the use of Xyrem, gamma hydroxybutyrate or better known as GHB, for the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy.

GHB is a simple molecule and it is ubiquitous in mammalian tissues, its function though is not really well known. Its relevant regulatory history goes back to about 1990, and prior to that date it was freely available in health food stores. But in 1990 the agency began to receive reports of widespread recreational use in a number of different types of folks, for a

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number of different types of reasons, or GHB and began to get numerous reports of serious adverse events associated with its misuse.

It was not entirely clear that all of

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these events were necessarily related to GHB. It was difficult to interpret some of these reports because there were concomitant medications that were unreported and it wasn't entirely clear whether or how much GHB was in a particular preparation that someone had taken. Those sorts of issues made it difficult to completely interpret the reports, but many of the reports were of events that were known to be consistent with GHB's effect as a potent CNS depressant, including things like respiratory depression, coma and other decreased levels of consciousness. So, it was reasonable to believe that GHB was at least in part responsible for some of these reports.

As a result of these reports, the agency withdrew GHB from health food shelves and made it illegal to use. However, illicit use continued and continues to this day, not only with GHB but with two related drugs which are precursors, GBL and 1,4-butanediol, and there have been similar reports of serious adverse events associated with the use

of those products.

So, against this background of use, the investigation of GHB as a treatment for cataplexy began. Based on the results of a single trial performed by the sponsor and their commitment to perform additional trials, the sponsor was granted a treatment IND in December of 1998. For those of you unfamiliar with a treatment IND, it is basically a mechanism to permit use of an investigational drug outside the context of a controlled trial for a serious disease for which there aren't other available treatments. It is usually granted relatively late in the development

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of a drug so that by the time you grant it you have some reasonable idea, based on controlled data, that the drug is probably effective and reasonably well tolerated.

Just another relevant piece of history, in 2000 Congress passed a law which placed GHB in Schedule I and also placed it into Schedule III for any approved uses that may be granted.

The NDA that we are discussing today was submitted in September of 2000 by the company, and it contains the results of four controlled trials which the sponsor believes establish substantial

evidence of effectiveness for cataplexy and excessive daytime sleepiness in patients with narcolepsy. It also contains, obviously, safety experience.

I just want to talk about the safety experience for just a little bit. As you know from the briefing documents, much of the safety data in the application was not generated by the company but by an individual investigator under his own individual investigator IND. This is Dr. Scharf, and he is an acknowledged expert in the use of GHB and he has been treating patients under his IND for about 16 years. His data comprise almost 30 percent of the patient safety database in the NDA. If one looks at patient time, his experience constitutes about 70 percent of the total patient exposure.

As part of a routine investigation of the NDA to look at source documents, the agency investigators found that they were unable to locate some critical source documents of Dr. Scharf's IND,

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and it was difficult to confirm the sponsor's submission of Dr. Scharf's data. However, subsequent to that, Dr. Scharf has made extensive efforts to provide the additional source documents

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and agency investigators have reinspected that data. I believe the conclusion of that investigation is that we find that the records, for the most part, do support the sponsor's descriptions of Dr. Scharf's data. And, we believe we can make certain statements about that data at this point.

We were particularly interested in the 80 or so patients that Dr. Scharf treated that did not move on into the company's treatment IND. He treated a total of 143, or thereabouts, patients, 60 of whom went into the sponsor's treatment IND. So, we had a good idea of what was happening to those patients but there were about 80 that didn't and who were basically discontinued from treatment under Dr. Scharf's own IND.

So, except for a handful of patients, we believe we know why those 80 patients discontinued and their status. I believe we can say reasonably comfortably say that nothing catastrophic that we don't know about happened to those patients but, unfortunately, we have relatively little well-documented data regarding other less serious adverse events in that cohort of 80. Other than patient diaries, we have essentially no

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documentation about exactly what dose those patients took and for how long.

I have gone into this at some depth because the safety experience in the NDA is

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relatively small as compared to a typical NDA, and that is by agreement. This is an orphan product. Based on the sponsor's estimated prevalence of cataplexy of about 25,000, it received orphan designation and one wouldn't necessarily expect that a safety database of a typical size, which is somewhere in at least 10000 to 2000 patients in the typical NDA, would be submitted in an orphan application. So, we agreed with the sponsor that about 500 patients treated for appropriate durations, at appropriate doses would be acceptable.

But, given the relatively small database and some of these residual questions about a reasonable proportion of it, that is to say Dr. Scharf's data, that may take on some additional meaning and we would like you to think about that as the day goes on.

In addition to the safety and the effectiveness data which is required in an NDA of course, the sponsor has proposed a detailed risk

management program, and that has three goals: to inform patients and physicians about the risks of GHB; to minimize the risks to those patients; and also to minimize the likelihood that subjects for whom the drug has not been prescribed will be exposed to it. This latter point not only refers to diversion and its use illicitly by folks who shouldn't be taking it, but also to the accidental use of GHB in the home, perhaps by small children, and you will hear how GHB is administered and what form it is prepared in, and we think that is a potential risk. So, we would like you to think about that as the day goes on too.

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As far as the risk management program, you will hear about it in great detail from the company but, in brief, it consists of a couple of sort of major components. One is that the product will be made available through a central pharmacy and will be shipped directly to the patient at home. Physicians and patients will also receive detailed materials about the risks and the appropriate use of the drug after the first prescription is filled. Actually, they will receive those materials initially and all subsequent refills of prescriptions will be contingent upon patients and

physicians documenting that they have read these materials, and they understand the risks and how to take the drug appropriately.

All patients and physicians will be entered into a registry, and there will be close surveillance instituted to ensure that untoward events are minimized, for example, to ensure that patients don't go from doctor to doctor trying to get refills of prescriptions that are inappropriate.

So, with these data and against the background of misuse of GHB out in the population at large, we bring you today's application and we will ask you to formally vote on three questions. One is whether or not you think that substantial evidence of effectiveness has been submitted for the indications that the sponsor has proposed, that is to say, cataplexy and excessive daytime sleepiness in patients with narcolepsy. If you find that they haven't, we would be very interested to know whether or not you feel that substantial

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evidence has been submitted for either of those two indications.

While you listen to the effectiveness data, we would like you to pay particular attention

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to the question of dose and for which dose you think evidence of effectiveness has been submitted. If you find there is substantial evidence of effectiveness for a particular indication, we need to ask you whether or not GHB can be considered safe in use given appropriate labeling. Now, we are not going to discuss necessarily the specifics of proposed labeling but, nonetheless, we ask you to think of it in that context.

Again, in assessing the safety of the product, we ask you to concentrate on at least the question of what dose you have found to be effective and whether or not there is sufficient safety experience at that dose for the drug to be approved.

Finally, we want to take a formal vote on the question of whether or not you think it is required or should be required that the drug be approved only with the risk management program of some type, not necessarily the one specifically proposed by the company. Obviously, the company has proposed a risk management program but we need to know whether or not you think it is mandatory that it be approved with such a program in place. If you do, we have a number of questions that we

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would like you to discuss -- not necessarily take a formal vote on but discuss with regard to a risk management program and some of the provisions that the sponsor has proposed.

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There are some aspects of the program that they have proposed that we would like you to pay particular attention to and discuss. For example, there is some considerable sympathy in the agency for including a provision in the risk management program that would restrict the use of the drug to patients with whatever indication you believe has been supported, that is to say, to restrict as much as possible off-label prescribing. That is one possibility.

There is also some enthusiasm internally for physicians and patients to document that they have reviewed the relevant materials before the first prescription is filled. So, we would like you to think about that as well as we talk about the risk management program.

So, as you can see from the agenda, the company is going to present the safety and effectiveness data, after which Dr. Mani, from the Division, will come up and present briefly some of our views about the data you will have just heard.

Specifically, I believe we have some different views about the evidence submitted for establishing a claim for excessive daytime sleepiness in narcolepsy, and there may be other additional safety issues that we would like to bring up at that time, in particular the question of an event that has been called sleep walking.

I think with that as background, I will turn it back to Dr. Kawas. Thank you.

DR. KAWAS: Thank you, Dr. Katz. Orphan Medical presentation is to follow. Dr. David Reardan, Orphan Medical?

Orphan Medical Presentation

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DR. REARDAN: Hi. Good morning. Good morning, ladies and gentlemen, members of the committee and FDA.

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My name is David Reardan, and I represent Orphan Medical as head of regulatory affairs. Orphan Medical is a small, 60-person firm, dedicated to the development of orphan drugs. We have obtained marketing approval for six orphan products from FDA since we were founded, in 1994.

The firm became involved with Xyrem when approached by FDA that same year, and Xyrem was

designated an orphan drug in 1994. Today we will share with you the data that has been collected with respect to the efficacy and safety since our IND was submitted, in 1996.

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Dr. Mignot, director of the Narcolepsy Institute at Stanford University, will present a picture of a narcoleptic patient and the serious medical need such patients have for new therapeutic treatments.

Dr. Houghton is the chief medical officer and chief operating officer at Orphan Medical, and he will present next on the efficacy that has been collected. Dr. Houghton was chair of anesthesia and critical care in Australia.

Dr. Black, director of the Stanford Sleep Clinic and an investigator for several trials, will share with you the EEG pharmacology of Xyrem. Dr. Houghton will then present the safety data and finish up with a benefit/risk assessment.

Following presentations by two FDA invited

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speakers with respect to GHB abuse, Dr. Balster, director of the Institute for Drug and Alcohol Studies at the Medical College of Virginia, will share with you his views on abuse liability.

Since there is public abuse of GHB and its analogs, the company has developed a risk management program for Xyrem that will be presented by Patti Engel, our vice president of marketing and sales.

[Slide]

In addition to those presenting today, the following experts are available in the audience to answer questions from the committee or FDA: Dr. Emsellem, Dr. Hagaman and Dr. Ristanovic are all directors of their respective sleep institutes, and have been investigators in our clinical trials. Dr. Okerholm is a consultant in the area of pharmacokinetics and drug metabolism; Dr. Reno in the area of toxicology; and Dr. Richard Trout, who is a professor emeritus in statistics from Rutgers, is here if there are any statistical questions.

[Slide]

This is the chemical structure of sodium oxybate, more commonly known as gamma hydroxybutyrate, or GHB. Notice that it is a simple 4-carbon hydroxy fatty acid and, as such, quite easy to synthesize. In fact, kits have been illegally promoted on the Internet for its manufacture. If an amino group were to replace

this alcohol functional group at position 4, you would have GABA, gamma aminobutyric acid, another CNS active chemical. Oxybate is a natural compound in the human body.

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Gamma hydroxybutyrate was first discovered in the 1960's by Dr. Labore, in France, and was investigated as an analog for GABA. It was found to have hypnotic properties and was first approved in France, and later a few other countries of Europe, as an adjunct in anesthesia. It was used in labor and delivery for quite a few years. The injectable form is still available today in parts of Europe.

In the 1970's initial work was begun in Canada to test its properties in narcolepsy. Following initial promise for use in patients with narcolepsy two controlled trials were conducted by independent investigators, one in the U.S. and one in The Netherlands. In 1994, due to the promising investigator trials, FDA Office of Orphan Products approached Orphan Medical to consider the compound for development.

Since there was no patent protection and the market was very small, no other firms were

willing to consider the development of GHB for narcolepsy at the time. Orphan Medical agreed to sponsor this medication. Our new drug application was submitted in October of 2000 and was designated by FDA for priority review.

The clinical development has been fairly straightforward and all controlled trials conducted to date have shown sodium oxybate to be effective and safe for the treatment of narcolepsy. This project has been made more difficult because of the abuse situation.

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Let me explain why Xyrem is not going to

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be a factor in the abuse of GHB and its precursors. Orphan Medical was aware abuse existed at the time the company agreed to sponsor development of Xyrem. At this same time, Internet was burgeoning. Due to its ease of synthesis and ready availability of precursor chemicals, GHB was initially an easy target for promoters of illegal drugs.

But GHB is not the only problem. GBL and 1,4-butanediol are precursor chemicals that can be easily converted to GHB and are, in fact, converted to GHB in the human body. These precursors are widely available as bulk chemicals and are being

illegally used in the United States, and the abuse problem is growing.

Federal legislation, enacted in 2000, helped to control the availability of GHB and GBL but not 1,4-butanediol and other precursor chemicals that can be used for the same purpose. In many states, even with GHB schedules, GBL and 1,4-butanediol are not controlled.

We believe that approval of Xyrem for use by patients with narcolepsy will not add to the general abuse problem of GHB and its numerous precursors.

[Slide]

The proposed indication for which we are asking FDA for marketing approval is to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy.

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Narcolepsy fits the definition of orphan disease in the United States, with less than 200,000 patients. There are estimated to be about

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135,000 patients, of which 55 percent are diagnosed, with about 24,000 seeking treatment for cataplexy.

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I would now like to introduce you to Dr. Emmanuel Mignot, from Stanford. Dr. Mignot has been widely published in this area and is considered one of the premiere international experts on narcolepsy. He has not participated in any of our clinical trials.

Medical Need

DR. MIGNOT: It is my privilege to talk to you today about narcolepsy. I have been working on narcolepsy for about 15 years, both at the level of basic research as well as clinical care. I am a medical doctor and I see patients with narcolepsy.

[Slide]

I am going to try to summarize in a few minutes really a lot of data about narcolepsy and how it impacts people.

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First, I would like to start briefly by reviewing the symptoms of narcolepsy. Narcolepsy is usually associated with 5 different symptoms. The most disabling and the most problematic in patients with narcolepsy is sleepiness. Patients with narcolepsy are sleepy all the time; tired; they have sleep attacks; they cannot stay awake for a long period of time, and it is usually why they

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come to see the doctor. They just cannot live a normal life. Especially in work conditions, as you probably know, it is very difficult -- you have to be awake all day long and it is a major problem in

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narcolepsy.

Now, it is not enough to diagnose narcolepsy. Narcolepsy is not just sleepiness and there are a lot of other medical conditions that are associated with sleepiness. Patients with narcolepsy also have a series of symptoms that correspond to the fact that they go very quickly into rapid eye movement sleep. As probably many of you know, rapid eye movement sleep is a stage of sleep that only occurs 1.5 or 2 hours after you fall asleep where you are actively dreaming but your body is completely paralyzed and you have these rapid eye movements.

Patients with narcolepsy go into REM sleep extremely quickly, sometimes in a few minutes, and that leads to a series of symptoms where patients sometimes are half way through REM sleep, being still awake. Consequently, they may experience odd symptoms that we call the dissociated REM sleep event, abnormal REM sleep event. Those are cataplexy, hypnagogic hallucinations and sleep

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paralysis.

An example is cataplexy. When a patient gets emotionally excited, typically when they are happy, they meet a good friend, sometimes when they are angry but most often when they are joking, in a nice environment and happy about something, they may feel suddenly weak; they become paralyzed; sometimes they fall down to the ground, completely paralyzed and they cannot move. In very rare cases they may even go into REM sleep. We believe somehow being emotionally excited stimulates the paralysis of rapid eye movement sleep that every one of us experiences during sleep, except that in

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patients with narcolepsy it may occur in the middle of the day in response to emotion.

Also, when they fall asleep they sometimes have hallucinations because they go so quickly into REM that sometimes they dream while they are still awake. I remember a patient, for example, who every night would fall asleep and he would see someone coming and strangling him. Or, they may hear people talking; or see people walking in the room. It can be very frightening and it can be a very terrible experience for patients with narcolepsy.

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Another symptom of abnormal REM sleep that patients with narcolepsy have as well is called sleep paralysis. When they wake up from a nap or when they fall asleep, sometimes they again go so quickly into REM and disassociated REM sleep events that sometimes they may be paralyzed from REM but still be awake. Basically, they would wake up from sleep and they cannot move, not even their little finger. It can be very scary. It lasts a few minutes and then finally they can move. Some patients with narcolepsy have multiple episodes of sleep paralysis when they nap during the day, and so forth, and that is another very bothersome symptom.

Finally, patients with narcolepsy, contrary to what people way, don't sleep too much; their main problem is that they just cannot stay awake. They fall asleep very quickly in many circumstances, but they are unable to stay asleep for a long period of time. In fact, patients with narcolepsy don't sleep 20 hours a day. What

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happens is that at night they don't sleep well. Often that is another symptom that is very bothesome. They fall asleep very quickly at night but after one hour they cannot sleep again. They

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are just awake and cannot sleep.

Then, all these symptoms are quite severe and, of course, affect the lives of patients. And, since GHB is recommended in cataplexy, which is muscle atonia triggered by emotion, I will just show you a quick video of a patient with cataplexy.

This is a boy, a 9-year old. Narcolepsy usually starts during adolescence and here the clinicians are trying to make him laugh to just try to elicit the symptom, and you see he is falling down and he is completely paralyzed and he is losing his muscle tone. Some of these patients have that many time per day and it can be extremely socially disabling. You can imagine being at a party or being with some friends and having this happen to you. In this kid it was particularly severe.

Most cases of narcolepsy start during adolescence but occasionally it starts as early as 5 years of age. It peaks around 15 years of age. It is often extremely problematic because I am sure you realize when you have this type of thing happening to you and sleepiness at school, especially when you are 15 years old, when you are an adolescent, it really wrecks your life apart,

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especially when it is not properly diagnosed.

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There have been a number of studies, and I won't have time to review them, that have shown

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that the quality of life of patients with narcolepsy is extremely impaired, as much as depression, epilepsy or other reference conditions in almost all the scales that you look at. Clearly, it is a very socially disabling disorder.

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It is also, of course, a disorder that impacts just your daily life. For example, driving -- patients with narcolepsy have a very increased rate of accidents and sometimes many of them refuse to drive just because of falling asleep or having cataplexy while driving.

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We have objective tests for diagnosing narcolepsy. In fact, it is not just a psychological disorder. You can actually use a test like the Multiple Sleep Latency Test, where you ask patients to come to the sleep lab. You check that they sleep normally and the following day you ask them to nap every two hours and you measure how fast they fall asleep. You see,

normally people won't fall asleep or nap in the middle of the day, or they would fall asleep with a 15-minute latency in the dark. A patient with narcolepsy, as soon as you switch off the light, they are sleeping. In a few minute latency, they are asleep. So, we have objective ways to show that these people have a problem.

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Also, in this nap you see that they go very quickly into REM sleep. Normal people won't have REM sleep before one hour after falling asleep, but patients with narcolepsy will go straight into REM. You can actually demonstrate --

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we call that sleep onset REM period -- that patients with narcolepsy have all this sleep abnormality and REM abnormality using sleep testing.

[Slide]

Current treatment for narcolepsy is completely symptomatic. We don't treat the cause of the disease; we only treat the symptoms. Typically, the treatment now uses two drugs, two lines of drug. A patient with cataplexy will be treated usually with two drugs. One is a stimulant which would be a classical amphetamine-like

stimulant or this more recent drug that was just approved that is called modafinil, Provigil, which works on sleepiness. It will keep a patient awake but will never normalize him; it only improves him. And, they all have a lot of side effects. You know, the stimulants can even produce psychosis in some rare cases but, of course, they raise blood pressure. They produce psychological changes. They have a lot of other side effects.

We all know now that they all increase dopamine in the brain. We have done a series of studies which have shown that. Even modafinil, the most recent drug -- we know now that it works by increasing dopamine in the brain. And, they don't have anything different from each other so some of them are definitely safer than others.

For the antidepressants, for the treatment of cataplexy -- this works well on sleepiness but it doesn't work on cataplexy or nightmares, or hallucination or sleep paralysis. For this you use antidepressants. Why? Because antidepressants

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depress REM sleep and they also suppress cataplexy and all the other abnormal dreaming that patients with narcolepsy have. The problem is they also have a lot of side effects. Actually, the new

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SSRI, they don't work as well as the old tricyclines. Often you even have to use the old tricycline antidepressants because norepinephrine uptake inhibition seems to be the mode of action of these drugs, more than serotonin. They don't really work that well and, of course, they have a lot of side effects and a lot of different problems.

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Finally, I want to stress again that we need new treatments for narcolepsy just because all the treatments we have now just don't make people normal. They just help them to be better. You can best illustrate that using the MSLT/MWT, which is a slightly different test where, instead of measuring how fast people fall asleep in the dark, you ask people to try to stay away in the dark and you see that normal people can stay awake. They don't fall asleep in 20 minutes, whereas patients with narcolepsy fall asleep very dramatically after a few minutes in the dark.

Even if you treat them with modafinil which is a very good treatment for narcolepsy, which was recently approved, you improve them but they never become normal. Then, it is clear that

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what we have is not enough. We just need better, and this would be the same for amphetamines. Even high dose amphetamines don't normalize these patients. That has been shown by multiple studies.

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[Slide]

We have worked for more than 15 years trying to find the cause of narcolepsy, and recently we have isolated the gene for narcolepsy in a canine model where the disease is genetically determined, and we found that it was a receptor for a norpeptide that is called hypocretin. We found that in humans with narcolepsy it is not like dogs with narcolepsy; it is not the receptor but a peptide called hypocretin which is expressed in about 10,000 cells in the brain, here in the hypothalamus, which is missing in patients with narcolepsy.

This is brain tissue of a patient with narcolepsy. You see here is the normal; everything is gone. If you measure in the cerebrospinal fluid, this is a normal level in a normal person, or in patients with MS or other neurological symptoms, and you see in all patients with narcolepsy that this hypocretin molecule is gone. We know now that the cause of narcolepsy is not

dopamine or norepinephrine, which is the current treatment for narcolepsy, which are stimulants and antidepressants acting through these neurotransmitters, and probably replacing this hypocretin would be an ideal treatment for narcolepsy. But this finding was only made one year ago and it is going to take probably 10 years or many years before we actually have a treatment based on this new discovery.

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To summarize the medical need, I think I have convinced you that narcolepsy is a serious and disabling condition that needs treatment, and these

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patients are in desperate need of better treatment. As you will see from the presentation afterwards, GHB is one of the effective treatments which helps a lot of people. So, current treatments like amphetamines and antidepressants don't work well in terms of efficacy. They have a lot of side effects. They all work the same way but they don't act on the cause of the disease and, clearly, we know that GHB, even though it probably doesn't act on hypocretin, acts differently from other drugs. And, it is one more drug that would be available to help a lot of patients with narcolepsy.

Finally, even though there have been numerous, very recent developments that are very exciting in the hypocretin area, unfortunately, you all know it takes a long time until drugs are available and it is going to take probably many years until this available.

This is a very quick summary of what we know about narcolepsy to date. Thank you.

DR. REARDAN: Thank you, Dr. Mignot. Dr. Houghton will now present the data which has been assembled in support of the efficacy of Xyrem. Dr. Houghton is a qualified anesthesiologist, with 18 years of clinical experience in critical care medicine and numerous years experience in pharmaceutical drug development. Bill?

Efficacy

DR. HOUGHTON: Good morning.

[Slide]

I am sorry to start with such a complex diagram but this just outlines the pattern of studies that we will be talking about this morning.

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On the left-hand side here are the 4 controlled studies on which the assessment of efficacy will be based, but what is unusual about this program is that patients, in an uncommon way, move to

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extension protocols. So, as Dr. Katz pointed out, even though the total database may be small, the total duration of exposure of patients is quite promising.

The first study that I will talk about is entitled OMC-GHB-3, and the patients, at the completion of this short-term treatment study did progress to a long-term, open label study and then had the opportunity to move into one of the treatment IND protocols, with some of them still participating in that study.

A second contributor to that protocol was the patients who completed the first 6-month safety treatment IND protocol, and the significance of all of that is that it was from this protocol that the patients are represented in the long-term pivotal blinded efficacy study that supports the long-term efficacy of Xyrem.

[Slide]

The first and pivotal study is a randomized, double-blind, placebo-controlled, parallel group, multi-center trial comparing the effects of three doses, 3 g, 6 g and 9 g of orally administered Xyrem with placebo for the treatment of narcolepsy. As I mentioned, this was a study

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conducted in 136 patients in 16 centers.

[Slide]

The primary efficacy parameter was the change in the number of total cataplexy attacks in

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the last two weeks of the treatment period compared to the two weeks of the baseline period.

Secondary efficacy parameters that were considered included complete and partial cataplexy attacks; daytime sleepiness; inadvertent sleep attacks during the day; hypnagogic hallucinations; sleep paralysis; and a clinical global impression of change.

[Slide]

Patients naive to sodium oxybate therapy were chosen with a bona fide diagnosis of narcolepsy for at least 6 months. They were required to have a record of a polysomnograph or Multiple Sleep Latency Test within the last 5 years to exclude other causes of daytime sleepiness, and particularly sleep apnea.

They were required to have a history of daytime sleepiness and cataplexy for at least 6 months, and recurrent daytime naps that occurred almost daily in the preceding 3 months.

[Slide]

The overall study design was divided into 5 stages. Firstly, there was a screening period in which the patients were required to qualify for entry criteria and then withdrawn from their existing anti-cataplectic medications over a 4-week period to avoid rebound phenomena which were considered a safety consideration. At the end of this withdrawal period they entered a washout period, which was determined by at least 5 times the half-life of their preceding drug to remove any effects of those drugs. However, if patients weren't on any cataplectic medications, they were still required to remain 5 days in that washout

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period to familiarize themselves with the use of diaries.

They then proceeded to a baseline period of 2 to 3 weeks, using daily diary recording to establish the severity of their disease and to confirm that they had reached a stable stage in their disease. They then entered a 4-week blinded, randomized treatment period, with a visit at 2 weeks, a telephone call the day after commencing treatment, and then safety telephone calls 3 times a week during the treatment period, at the end of which they were abruptly withdrawn from drug and

followed up 3 to 5 days later to assess any rebound phenomena and any adverse experiences that may have ensued.

[Slide]

As is shown here, the patient groups were very evenly balanced at baseline. They represented a fairly severe group of narcoleptics, with an average incidence of cataplexy of around 34 per week at baseline.

There was a dose-response relationship across the doses based on median change in the total number of cataplexy attacks that, when compared to placebo, approached significance at the 9 g dose, with a p value of 0.0529, and achieved highly significant change at the 9 g dose.

[Slide]

This dose relationship is clearly shown in the plot of median change from baseline in the number of cataplexy attacks per week, and the spread of the data is demonstrated as the quartile lines around these median values.

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[Slide]

A more clinically relevant presentation of the data is the percentage change in the number of cataplexy attacks from baseline. This was

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calculated as the distribution of percentage change values for each individual patient and is again presented as the medians. This representation clearly shows that the major change in cataplexy occurs in the first 2 weeks, but with ongoing change in the subsequent 2 weeks, as represented in 2 of the dose groups.

[Slide]

Secondary efficacy variables included assessment of excessive daytime sleepiness using the validated Epworth Sleepiness Scale which rates the patient's feeling of daytime somnolence by scoring on a scale of 0-3 the probability of falling asleep in the circumstances of 8 common life scenarios. This results in a potential maximum score of 24.

[Slide]

This slide demonstrates a clear dose-related reduction in the Epworth Sleepiness Scale, reaching a significant level of 0.0001 in the 9 g group compared to placebo. This change was incremental beyond the effects of stable dosing of stimulants because stimulant medications were maintained constant throughout the study. In all Xyrem-treated groups some patients improved beyond

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the defined narcolepsy range, with some patients in the 6 g and 9 g groups actually improving into the normal range as rated by the Epworth Sleepiness Scale.

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The second component of daytime sleepiness, the number of inadvertent naps during the day, was also significantly reduced compared to placebo in the 6 g group and 9 g dosing.

[Slide]

The severity of the disease at baseline was rated by the principal investigator according to the following validated scale. Then, at the end of the treatment period a blinded global impression of change according to the rating shown here was made, rating from very much improved through no change to very much worse.

[Slide]

Assignment of these modal values indicated a primary distribution of the placebo patients mainly to no change or minimally improved, but there is an obvious predominance of assignment in the 9 g dose to very much improved and much improved.

[Slide]

Because of the complexity of presenting

these assigned categories, a post hoc simplification was applied to group the patients that showed clear clinical improvement into a responder group, and all others were called non-responders. This again displays the dose-response trend in the categorical data, with a clear statistical difference between the 9 g group and the placebo group.

[Slide]

Other secondary measures that achieved significant change included the number of awakenings at night, subjective sleep quality, morning alertness, the ability to concentrate.

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Hypnagogic hallucinations and sleep paralysis, which had a much lower incidence at baseline, showed a non-significant trend towards improvement.

[Slide]

The next study that I would like to present is the study that was suggested by the FDA to provide evidence of long-term efficacy of Xyrem based on the return of cataplexy following the cessation of long-term treatment with the active drug.

[Slide]

Patients entered this blinded, randomized

study from the long-term open-label study I showed you initially having completed the GHB-2 protocol and proceeded into the GHB-3 protocol for periods up to 2 years, or from the initial treatment IND protocol. This provided assessment of potential adverse consequences of the abrupt withdrawal of long-term therapeutic doses of Xyrem as well.

Patients having taken the drug for 6 months to 3.5 years were screened, and after blinded randomization entered a single blind baseline period in which daily diaries were used to record the severity of their cataplexy. They then entered a double-blind phase of 2 weeks wherein they were randomized in a 50 percent ratio to either continued, unchanged dose of Xyrem in a blinded fashion or to placebo. Randomization was performed in a centralized manner to ensure equal representation of dosing in the comparative groups.

[Slide]

The primary efficacy variable was the change in the number of cataplexy attacks in the

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double-blind period compared to baseline. There was a median change of zero in the Xyrem group but, as seen, there was a marked increase in the incidence of cataplexy in those randomized to

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placebo. This was highly significant.

[Slide]

When the median change from baseline by week was calculated, you can see that there was a step-wise increase in cataplexy which supported the long-term efficacy of the drug in a statistically significant manner, but they represent a gradual return of cataplexy rather than an acute rebound phenomenon.

[Slide]

I will now present very briefly some supportive data from 2 early controlled, crossover design studies that have been published, and for which Orphan Medical purchased the databases and included in the NDA submission.

[Slide]

The first was a study conducted by Dr. Lawrence Scrima, then of the University of Arkansas, in 20 patients, 10 males and 10 females, using a dose of 50 mg/kg, much lower than some of those in the previous studies and equivalent to about 3.5 g per day in a 70 kg man.

Following the withdrawal of anticataplectic medications, he recorded a baseline period during which the patients were required to

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have a minimum of 10 cataplexy attacks, then were randomized into an initial treatment period of 29 days, followed by a washout period of 6 days, and then crossed over to the alternate treatment, again

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followed by a washout of 6 days. Stimulants were continued throughout this study and all patients were actually transferred to methylphenidate as their stimulant.

[Slide]

The primary efficacy measures are identified, with the average number of cataplexy attacks compared to baseline and objective sleepiness index as determined by the Multiple Sleep Latency Test. This was to represent a measure of daytime sleepiness.

Because of logistic issues in the study conduct and methodologic issues in design and definition, this is presented as supporting data only to represent cataplexy response at a lower dose. As can be seen, this patient group again represented a reasonably severe narcoleptic population. They had a baseline measure of 20 cataplexy attacks per week. There was an initial fairly significant placebo response, as was shown in the previous studies, but by week 3 and week 4

statistically significant differentiation between placebo and active treatment was shown, and there was a statistically significant overall response in the study. There was no significant change in the sleepiness index as the measure of daytime sleepiness, however, in this study.

[Slide]

The second study that I will present very briefly was conducted by Dr. Lammers, in The Netherlands. It is, again, a randomized, blinded, crossover design study in 24 narcoleptics. The other significant difference in this study was that concomitant medications for both cataplexy and

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excessive daytime sleepiness were continued throughout the study.

Following a 1-week baseline to establish disease severity, the patients were randomized to a 4-week treatment period at a dose of 60 mg/kg in divided nightly doses, followed by a washout period of about 3 weeks, and then a baseline period of 1 week again preceding a second treatment period of 4 weeks.

[Slide]

As is obvious here, the severity of cataplexy during the baseline period was much lower

in this study, potentially the consequence of continued anticataplectic medication in some patients. But, again, there is a significant response. According to the statistical plan which was very scant that was represented in the published study, and agreed to by the FDA, there was an incorrect or unsatisfactory statistical management of this study. The change in cataplexy was not statistically significant. When the results of this study were submitted by Orphan, they were reanalyzed with an ANCOVA analysis as had been applied in the GHB-2 study, and this change was significant according to the ANCOVA analysis.

[Slide]

Other measures that showed significant improvement included hypnagogic hallucinations and daytime sleep attacks again.

[Slide]

Although not eligible for determination of efficacy since it is an open-label study, I would like to briefly mention three aspects of the

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follow-on study to the pivotal GHB-2 study. And, 117 patients chose to participate entering the study at the 6 g per day dose and then slowly titrating to clinical efficacy between the doses of

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3 g and 9 g. This study, therefore, represents the proposed clinical use of the drug and, although primarily a safety study, represents some important dynamic information.

[Slide]

This slide shows the response in cataplexy over the 12-month period. What is surprising is that the maximum nadir occurred at about 8 weeks, and then the sustained efficacy was maintained across the 12 months in all dose groups.

[Slide]

A similar pattern was seen in the Epworth Sleepiness Scale, which shows the same time frame with maximum response at about 8 weeks, and then maintained efficacy over the course of 12 months in this open-label study. What is also interesting to note is that most of the patients in most dose groups were maintained beyond the defined narcolepsy range.

[Slide]

When the distribution of doses to which the patients were titrated is shown, it is seen that 6 g per day is the most common dose, followed by the 9 g dose group.

[Slide]

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This represents the pattern of dosing seen in other open-label studies where doses were titrated to clinical response. What is important to note is that there is not a change in dosing

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between the 6-month and the 12-month dosing groups, suggesting no tolerance development to maintain the dynamic effects shown.

[Slide]

This slide represents the cohort of patients that entered the SXB-21 protocol via the GHB-2 and then GHB-3 protocol. Represented here is the incidence of cataplexy for each individual patient at the baseline in GHB-2. They were then maintained in the study I have just shown you over the course of up to 2 years, and this is the incidence of cataplexy of each of the individual patients in the single-blinded baseline in the SXB-21 protocol. When the paradigm of random assignment to placebo is shown, then there is certainly a demonstration of efficacy between those who were randomized to the placebo group in SXB-21 versus those that maintained their Xyrem treatment, which certainly helps to support the efficacy statement in the GHB-3 protocol.

[Slide]

Finally and to summarize, we have presented data to show efficacy of sodium oxybate to reduce cataplexy in 4-week treatment periods in a dose-related manner that is highly statistically significant at the 9 g dose, and approaching statistical significance at the 6 g dose.

We have presented supportive data demonstrating statistically significant efficacy of the lower doses, and demonstrated statistically significant efficacy in terms of daytime sleepiness, using the Epworth Sleepiness Scale, again at 9 g. In a scale used in the Lammers study at 60 mg/kg daytime sleep attacks were

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statistically significantly reduced in all 3 studies. We supported the long-term efficacy of Xyrem with return of cataplexy when blindedly assigned to placebo in the SXB-21 protocol.

[Slide]

I would now like to very briefly summarize the pharmacokinetics studies that were conducted by Orphan Medical.

[Slide]

In total, we conducted 8 clinical pharmacokinetic studies, including 2 studies in narcoleptic patients and 6 in healthy human

volunteers. This slide lists the 8 pharmacokinetic studies by their primary objective.

The studies included a single dose pilot study in 6 narcoleptics, and a second study in narcoleptic patients comparing acute and chronic dosing over an 8-week period. Normal volunteer studies were conducted to examine the kinetics of Xyrem with respect to gender differences, dose proportionality and the effects of food. Also, 3 drug interaction studies were performed with Zolpiden, protriptyline and modafinil as representatives of the 3 classes of drugs used commonly to treat the symptoms of narcolepsy. Lastly, an in vitro study, using human hepatic microzymes, was conducted to assess the effects of oxybate.

[Slide]

I will only present the studies that have a significant message, and in very brief summary form. This slide displays the results of the dose proportionality study that compared nightly dose of

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4.5 and 9 g given in 2 equally divided doses at bedtime and 4 hours later. A randomized, 2-day crossover design was utilized, and doubling the dose from 4.5 to 9 g resulted in a nearly 4-fold

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increase in the area under the time concentration curve. The peak plasma concentration and the time to peak concentration changed significantly with doubling the dose, the latter suggesting capacity-limited absorption. C_{max} was higher after the second dose than with the first nightly dose, as has been seen in other studies with divided dosing.

These findings indicate non-linear kinetics and capacity-limited elimination and absorption, as reported in previously published studies.

[Slide]

The results of the effect of food study are displayed graphically on this slide. In this randomized, crossover study 34 healthy subjects were dosed with 4.5 g of Xyrem on 2 occasions 1 week apart, either after an overnight 10.5 hour fast or immediately following a high fat standardized breakfast. After the high fat meal the peak plasma concentration decreased by almost 60 percent. The median time to achieve peak levels increased from 45 minutes to around 2 hours, and the AUC decreased by 37 percent. All of these differences were statistically significant. The

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apparent half-life was not significantly altered. Thus, the presence of food significantly reduces systemic exposure to GHB, a finding not previously reported.

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In the 3 volunteer kinetic studies the urinary excretion of Xyrem was measured, and renal excretion was shown to be a minor pathway of elimination, accounting for less than 5 percent of the administered drug.

[Slide]

As an example of the drug interaction studies, on this slide we present the modafinil results. The upper graph indicates that co-administration of 200 mg of modafinil had no impact on the kinetics of Xyrem. The lower graph demonstrates that 4.5 g of Xyrem had no clinically significant effect on the kinetics of a standard dose of modafinil.

Likewise, in the Zolpiden protriptyline interaction studies, no significant kinetic interactions were found. In the separate in vitro study using human hepatic microzymes, sodium oxybate was found to have no effect on 6 cytochrome p450 enzymes either to inhibit or induce their activity.

[Slide]

So in summary, Xyrem oral solution is rapidlyh absorbed and eliminated with a half-life of about one hour. The drug displays non-linear, dose-dependent kinetics, indicative of capacity-limited absorption and elimination. Xyrem kinetics are similar in men and women and do not change with chronic administration at therapeutic doses.

[Slide]

Chronic dosing did not change the kinetics of Xyrem in a patient population, and a high fat

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meal appreciably delayed absorption and reduced total systemic exposure to the drug. Three separate in vivo drug interaction studies, as well as the in vitro p450 enzyme study, would suggest the probability of significant drug-drug interaction with Xyrem is minimal. Thank you very much.

DR. REARDAN: Thank you. I would now like to introduce Dr. Jed Black, from Stanford University Sleep Center, and he will present on the polysomnographic effects of Xyrem and GHB.

Polysomnographic Effects of Xyrem

DR. BLACK: Good morning, ladies and

gentlemen. I would like to summarize the body of data that has been collected over the past 25 years which characterizes the effects of gamma hydroxybutyrate or sodium oxybate on sleep parameters. I will then speculate briefly on a possible mechanism whereby these effects on sleep result in a robust improvement in daytime narcolepsy symptoms seen with this agent.

This has been a particular focus of my research in sleep over the past years. That is, how does what happens in the brain at night affect various aspects on daytime function and alertness?

It is unexpected that a medication that objectively markedly improves sleep quality also improves measures of daytime alertness as this finding has never been observed with traditional hypnotics or sleep aids. To pursue an understanding of this possible interaction, 6 investigations have been conducted in humans. These studies explored the effect of sodium oxybate on a variety of nocturnal sleep parameters, using

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electroencephalography during sleep and a laboratory test known as polysomnography.

The first 3 studies found an increase in slow wave sleep. Slow wave sleep, also known as

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stages 3 and 4 sleep, is the deepest portion of sleep and correlates positively with functions of daytime concentration, attention and alertness in normal subjects. These studies also reveal a reduction in nocturnal awakenings with GHB.

The more recent studies of Scrima, Lammers and Orphan Medical explored both measures of nocturnal sleep as measured by polysomnography, or PSG, and measures of daytime sleepiness with the Multiple Sleep Latency Test, or daytime alertness with the Maintenance of Wakefulness Test.

[Slide]

These 2 studies, the design of which has been reviewed by Dr. Houghton, again found significant reductions in slow wave sleep, that is to say stage 3-4 sleep or slow wave sleep, and reductions in nocturnal awakenings. Additionally, the Scrima group reported a reduction in stage 1 sleep, a very light stage of sleep, and the Lammers group noted significant reduction in the percentage of time patients spent awake during nocturnal polysomnography.

[Slide]

The most recent study, a multi-center trial performed at 4 sites with an enrollment of 25

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patients, was designed to further explore the effects of sodium oxybate on nocturnal sleep parameters and daytime measures of sleepiness and alertness. In this open-label study patients were

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kept at a stable stimulant dose throughout the protocol. Cataplexy medications were tapered, followed by a 2-week washout and baseline period. Sodium oxybate was initiated at 4.5 g in a divided nightly dose for 4 weeks, then increased to 6, then 7.5, then 9 g for 2 weeks each. Nocturnal polysomnography and the Maintenance of Wakefulness Test, or MWT, were obtained at the time points noted here.

[Slide]

This study revealed the expected increase in slow wave, or stages 3-4 sleep, and increase in delta power. Delta power is the measure of the depth of sleep. It incorporates the combination of the amplitude of the slow frequency waves and the prevalence of those waves through the night to produce a single number called delta power. Delta power is another measure found in a variety of animal and human studies to correlate positively with sleep quality. The calculation of this value requires sophisticated processing which was

unavailable for the prior studies. The increments in slow wave sleep and delta power were found to be dose related. Dose-related improvements in daytime alertness and subjective sleepiness were also observed.

[Slide]

The dose-response increase in the number of minutes of slow wave sleep is illustrated in this slide, with an increase from 6 g up to the 9 g dose. The total duration of slow wave sleep increased to over 5-fold that of baseline at the 9 g dose.

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It is important to note that while these results are predicted to be dose related, time on medication cannot be factored out as a potential contributor to these increments.

[Slide]

Delta power, which characterizes slow wave activity throughout the entire sleep period, not just during stages 3 and 4, was also found to increase in a dose response fashion with a 50 percent increase noted at the 9 g dose over baseline.

[Slide]

The Maintenance of Wakefulness Test, or

MWT, is a daytime evaluation which places the patient in a dimly lit room in a semi-recumbent position, with nothing to do and with the instruction to remain awake. The duration of sustained wakefulness was measured in this study over 40-minute intervals across 4 periods, spaced 2 hours apart during the day. Substantial dose-related increases in the ability to remain awake were observed at both the 4.5 g and 9 g doses.

[Slide]

As previously noted, the MWT was not performed at the 6 g nor 7.5 g doses in this protocol. Similar marked reductions were found in the Epworth Sleepiness Scale scores. In this measure the individual rates their own potential to fall asleep in a variety of more sedentary daytime activities.

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A post hoc analysis of the possible correlations between sodium oxybate-related changes

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in nocturnal parameters with changes in daytime measures revealed the strongest correlation occurring with delta power and Epworth Sleepiness Scale scores. This was a negative correlation,

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such that the greater the delta power, the lower the daytime sleepiness. In addition, trends toward significant correlations between delta sleep and MWT scores, and between slow wave sleep and Epworth and MWT scores were observed.

[Slide]

In conclusion, studies of sodium oxybate's effects on sleep demonstrate increases in measures of restorative sleep, including dose-related increments in slow wave and delta sleep, coupled with and correlated with improvements in measures of daytime alertness and sleepiness.

It is postulated that sodium oxybate works directly to enhance brain neurochemical activity critical to the restorative mechanisms of slow wave sleep and of slow wave activity during the total sleep period. Such enhanced activity may be the cause of substantial improvement in both subjective and objective measures of sleepiness and alertness observed with sodium oxybate in narcolepsy.

DR. REARDAN: Thank you, Dr. Black. Dr. Houghton will now present the safety summary overview of Xyrem and finish up with a benefit/risk assessment.

Safety Overview and Summary of

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Risk/Benefit Assessment

DR. HOUGHTON: Thank you.

[Slide]

I am sorry to horrify you with this

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complex diagram again but it is just to outline the 15 studies that will be referred to today as the updated safety database. The Lammers study was excluded because adverse events were not recorded in the classical way and, as Dr. Katz explained, the Scharf study was separated and will be explained again later.

[Slide]

The safety profile was reported based on exposure of 479 narcoleptic patients and 125 healthy volunteers from the pharmacokinetic studies. This represents an exposure of greater than 6 months in 360 patients in total, and greater than 12 months in 296 patients, which represents a total patient-year exposure of 1328 years with the Scharf database included.

[Slide]

When exposures were restricted to the studies other than the Scharf database, 399 narcoleptics and 125 subjects represent exposure in 524 persons. This represents exposure of greater

than 6 months in 296 patients and greater than 12 months in 223 patients, for a total exposure of 330 patient-years.

[Slide]

In the open-label studies patients were titrated between the doses of 3-9 g in divided dose at night. This slide represents the distribution of patients across this defined dose range and, again, identifies the 6 g dose as the most commonly used, followed again by the 9 g dose. In fact, approximately 80 percent of patients were titrated within the 6-9 g range.

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In the updated integrated safety database, composed of 402 patients, 399 of whom were treated with active drug and 3 patients received placebo only, it can be seen that 65 percent of patients completed therapy or were ongoing in the treatment IND study. Thirty-five percent have discontinued treatment for the reasons noted here, with 13 percent discontinuing due to adverse events; 2 percent discontinuing because of lack of efficacy; and there were 2 deaths that occurred in the treatment IND studies, both due to suicide.

[Slide]

Across all of these studies, 82 percent of treated patients reported any adverse event, as did 70 percent of patients exposed to placebo. It is important to note that the placebo exposure represents 4 weeks as compared to active drug treatment over a much longer period of up to 4 years. Hence, severe adverse event discontinuations and serious adverse events are significantly greater in the active treatment groups.

[Slide]

When considered in terms of dose at onset, there seemed to be a slight preponderance of incidence in the 9 g group.

[Slide]

This slide represents the most frequent adverse events reported across the integrated database. There was a consistent pattern of events across the study. Nausea, dizziness, sleep walking, are represented here as a partial representation of the term sleep disorder, enuresis

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and confusion were most frequently considered dose related, while others represent intercurrent illness.

[Slide]

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This profile is reinforced by consideration of the controlled trials in which there is represented a balanced exposure to placebo and active medication. Again, dizziness, nausea, pain, sleep disorder, confusion, infection, vomiting and urinary incontinence separate. A dose relationship was shown introduction eh GHB-2 trial for confusion, nausea, dizziness and urinary incontinence.

[Slide]

In the SXB-21 trial the most common adverse events that were reported are shown here. The incidence was very low in this study of patients on long-term treatment, but what is relevant is the data that looks at the possible presentation of a withdrawal syndrome with the abrupt cessation of long-term therapy.

[Slide]

This is in marked contrast to a severe syndrome that is being described in the abuser population who have significantly escalated both dose and frequency of dosing. When we looked at symptoms that could relate to a withdrawal phenomenon, we saw only 2 patients with anxiety in a circumstance of escalating cataplexy, 1 patient

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with dizziness, 1 insomnia, 1 sleep disorder that actually in verbatim terms, was increased awakenings, and 1 patient with somnolence as their narcolepsy worsened.

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[Slide]

I would like to now address the Scharf database. This was conducted under an investigator IND commencing about 10 years before Orphan's involvement, without any of the rigors of external monitoring, and really represents over 16 years experience in the use of the drug rather than drug development clinical research with regulatory disciplines.

Patients were scattered all over the country and, hence, the data is based primarily on diary recordings without medical review and interpretation, leading to a significant discontinuation rate for lack of compliance. Dose accountability and titration were less clearly defined and less controlled. Patients had less defined entry criteria and represent a broader profile of associated pathologies. On this basis, the study data has been reported separately to the integrated database, as Dr. Katz had suggested.

[Slide]

We will address the Scharf open-label experience in terms of dosing exposure, patient disposition, adverse event incidence over 16 years, and then to try and establish some parity with the integrated database. We have considered the adverse event experience reporting in just the first 6 months of the study.

[Slide]

Patient disposition in the Scharf database is represented in this slide. At the time of database closure 63 patients transferred into the SXB-7 protocol. The FDA expressed concern

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regarding the accountability of the 80 patients that did not continue. We provided a narrative account for each individual patient, with updated status where possible, in the form of a major amendment. In addition, FDA requested further clarification of adverse events initially deemed uaevaluable, which we have also provided.

Of these 80 patients, 8 continued in the Scharf trial under his treatment IND. The 71 patients who withdrew had received oxybate for from 5 days to 10 years, and the reasons for early withdrawal of the 71 patients were primarily classified into non-compliance, adverse event and

cost.

[Slide]

The adverse event profile reflects the length of the study. The relatively large numbers of viral infection, flu syndrome, pharyngitis, etc. shouldn't be worrisome considering the 16 years duration of the study. However, of particular interest is the unusual incidence of sleepwalking and urinary incontinence and these will be discussed in some detail later.

[Slide]

The most frequent adverse events in the first 6 months of the Scharf trial are shown here. When compared to the integrated safety database, few adverse events separate in incidence. Most notable are somnolence, infection, viral infection and malaise. There were few new adverse events reported after the first 6 months.

The FDA requested further information regarding the following adverse events of particular interest. They were represented by

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incontinence and convulsions, confusion, neuropsychiatric events and sleepwalking.

[Slide]

I will address incontinence first. In

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their review of the GHB-2 trial, submitted in October, 1998, the FDA requested an analysis of adverse event terms for incontinence in association with central nervous system adverse events suggestive of seizure.

[Slide]

We responded by initiating the following: a questionnaire to all investigators to review the history of abnormal nocturnal observations that could be suggestive of seizures; a detailed urologic history preceding oxybate therapy and any new neurologic symptoms.

Examination of the databases for potential correlation between central nervous adverse events that could be related to seizures and incontinence, either urinary or fecal, was undertaken. Review of both preclinical and clinical data in the literature was performed and an overnight EEG recording after a 9 g dose was conducted in 6 patients who had reported incontinence during their oxybate therapy. An expert opinion was provided by Dr. Nathan Chrone, a neurologist of Johns Hopkins University.

[Slide]

The issue as represented is shown here.

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Urinary incontinence was presented by 8 patients reporting 15 events in the GHB-2 study, by 13 patients reporting 51 events over the 2-year period of GHB-3, and in the Scharf study by 33 patients

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reporting 140 events.

When central nervous system events were analyzed for contemporaneous reporting, 2 patients in each of the GHB-2 and -3 trials recorded such events corresponding to episodes of incontinence, as did 7 patients in the Scharf database. Relatively few incontinence events were temporally associated with the CNS adverse events suggestive of seizure. No potential seizure genesis was reported by bed partners in response to specific questions, and many of the partners reported relevant urinary symptoms such as frequent nocturia preceding the Xyrem treatment.

[Slide]

Single events of fecal incontinence occurred in 4 patients in 4 different trials. Association between these incontinence events and central nervous system adverse experiences were present only in 1 patient in the Scharf trial and 1 in the pharmacokinetic SXB-11 trial. In this patient the event of fecal incontinence was

definitely associated with a seizure in a patient with a known pre-study history of seizures. The subject in the SXB-11 effect of food study was a patient who, while significantly obtunded and with respiratory obstructive symptoms, had a brief episode of fecal incontinence.

[Slide]

In conclusion, there was limited support for a relationship between incontinence and seizures from the clinical trials, the prospective EEGs or from the literature.

[Slide]

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The vast majority of events that could have been coded as convulsions were actually recorded under the COSTART dictionary as cataplexy events. One patient in the integrated trial database did not represent this classification and he has been investigated by a neurologist for seizure genesis. His fugue state and automatic behavior episodes have been deemed part of his narcolepsy syndrome.

In the Scharf database two patients with definite seizures recorded history of preexisting disease, and two other patients recorded seizure events without definitive diagnosis but with

complicated polypharmacy.

[Slide]

To now address confusion, in the integrated safety database 30 patients or 70 percent reported 48 events recorded as confusion, leading to discontinuation from study in 3 patients. A possible dose relationship was suggested by a review of the entire database. In the Scharf database, again 7 percent of patients reported 15 such events, with no discontinuations and no dose relationship pattern observed.

[Slide]

The coding of confusion embodied a wide range of verbatim terms, as shown here. These do not represent confusion based on a standard medical status examination. They do not differentiate between nighttime events from those of awakening or arousal parasomnias. These events led to no dosage adjustment in 37 instances, but dose was reduced in 4 events, led to temporary discontinuation following 4 events, and 3 patients discontinued

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permanently because of a side effect of confusion.

[Slide]

When the GHB-2 controlled trial was considered with respect to confusion, the highest

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incidence in the databases is represented in this 4-week study by 10 patients. The highest incidence was seen in the 9 g dose, and 6 of the 10 developed during the first week of treatment. Seven of these 10 events were in patients over the age of 50. The difference in this study, of course, was the assigned doses rather than dose titration. It is important to note that 1 event was reported in a placebo patient.

[Slide]

In conclusion, the term represents a symptom report rather than confusion defined in a medical sense by formal mental status examination, and all resolved usually without interruption of therapy or dose modification. Confusion and other associated symptoms are not unexpected with sedating medications. The blinded, controlled trial results suggest that a higher incidence may result without dose titration.

[Slide]

Neuropsychiatric events will now be reviewed. The adverse event database was searched for terms that could represent neuropsychiatric symptoms, and this led to the classification shown in this slide. Fifty-two patients reported 57 such

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events in the integrated safety database, of whom 12 discontinued as a result of these events. In the Scharf database 41 patients reported 84 such events, leading to 2 patient discontinuations.

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[Slide]

Of these 57 events, 1 occurred while a patient was on placebo. This slide lists the terms examined and some, such as stupor and coma, failed to represent neuropsychiatric events. Many represented symptoms of narcolepsy such as hypnagogic hallucinations COSTART-coded to the term hallucinations. The most frequent was clinical depression, and this represents a symptom rather than a diagnosis of major depressive disorder. Depressive symptoms are frequent accompaniments in narcolepsy, and this is well recorded in the literature. Suicide was attempted in 4 patients with major preexisting psychiatric history, and resulted in death in 2 of these patients. The other representations of psychotic disorders and the patient with manic depressive disorder also occurred in patients with preexisting major psychiatric disease. As is shown, a similar profile of reported symptoms is found in the Scharf database.

[Slide]

In conclusion, most patients with major events had a preexisting psychiatric disorder. Many events do not qualify as neuropsychiatric disorders, as was represented by the terms pointed out. Assignment of causality is very difficult because narcolepsy is associated with depression and even mechanistically there has been an association between psychosis and the central processes in narcolepsy. As Dr. Mignot mentioned, stimulant medications are associated with central nervous system side effects that are represented by

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neuropsychiatric symptoms. And, it is true to say that in many patients, particularly in the Scharf database, pre-study screenings were deficient.

[Slide]

To lastly address sleepwalking, in the integrated safety database 7 percent of patients reported such events, whereas in the Scharf database 32 percent of patients reported events that were listed as sleepwalking. In the Scharf trial, however, these reports were primarily data listings in patient diaries in response to a specific leading question, listed as a line item in the diary.

[Slide]

The listing of this term did not receive the benefit of medical consideration of a differential diagnosis of somnambulism, and since most patients were not seen by the investigator no clarification was provided. Post hoc consideration was rendered impossible given the lack of information regarding sleep stage, time of night, relationship to drug dosing, and could be representative of any of the differential diagnoses listed on this slide.

[Slide]

In the controlled trials only 3 sleepwalking events were reported, 2 of which occurred on active treatment and 1 occurred in a patient during placebo treatment.

[Slide]

Hence, in conclusion, the incidence in the integrated safety database of 7 percent is not particularly dissimilar to the range reported in the literature for normal patients. This was

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reported by Dr. Mahowald, of Minneapolis, as between 4-10 percent in a publication in 1998, and between 1-7 percent by Dr. Roger Broughton of Canada.

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Diary recording without medical classification represents a potential increased reporting in the Scharf trial. The slight increase in incidence over the general population may certainly be representative of Xyrem effects with increase in slow wave sleep, but REM behavior disorder, common in narcolepsy, mayou be a separate consideration.

[Slide]

To summarize the safety profile of this drug, we based our assessment to date on 604 patients, which represents 524 patients excluding the Scharf database. Dosing was between 3-9 g per day in divided nightly dosing. The common adverse events were certainly headache, unspecified pain, nausea, dizziness, and less common but important adverse events were vomiting, confusion, restlessness, agitation, sleepwalking and enuresis.

[Slide]

All events have been reversible. There were no significant changes in lab values or vital signs identified across the studies. There was no evidence of organ toxicity outside the pharmacologic effects in the central nervous system. There was no diversion or consumption of

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clinical trial supplies by any family members during the trials, and there was certainly no evidence of Xyrem diversion in our database.

[Slide]

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I would like to conclude with the statement that Xyrem was generally well tolerated.

[Slide]

To commence a risk/benefit assessment, I would like to remind you of the indication proposed by Orphan Medical for the use of Xyrem. That is, to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy.

[Slide]

As has been pointed out, narcolepsy is an uncommon disease, with an incidence of around 0.05 percent and, as such, has been qualified for orphan designation. There are no therapies approved for the treatment of cataplexy. Because of this, the FDA were very kind to apply a priority review to our submission and we are very appreciative of that recognition. Current off-label therapies, so well described by Dr. Mignot, are unsatisfactory. Excessive daytime sleepiness has approved therapies but these do not address cataplexy. There is

clearly a medical need existing beyond the therapies available.

[Slide]

The benefits of Xyrem in the trials presented were based on patient diary recordings, investigator ratings of overall clinical improvement in overall disease severity, and objective measures of changes in sleep architecture and daytime response.

[Slide]

Clinical benefit in the short-term reduction in cataplexy was shown by the

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dose-related reduction in cataplexy in the GHB-2 and Scrima studies and in the long-term efficacy in the SXB-21. Subjective changes in the Epworth Sleepiness Scale have been well demonstrated, and reduction in daytime sleep attacks have accompanied this change. Early objective Maintenance of Wakefulness Test data supported these changes in daytime sleepiness. The global impression of the investigators for overall changes in disease severity also showed a significant dose relationship.

[Slide]

Xyrem was generally well tolerated when

used in the proposed dose range, with the most common side effects reported including nausea, dizziness, headaches, pain and confusion. Less common but important associated effects include enuresis and sleepwalking, with a possible dose relationship suggested. Although there were 11 deaths in the Scharf trial over 16 years and 2 deaths by suicide in the integrated database, no deaths were associated with Xyrem.

[Slide]

In relation to the specific FDA inquiries, there is a possible relationship between Xyrem therapy and somnambulism but further definition is required. There is a marked discrepancy between the reported incidence in the Scharf study of the 32 percent, recorded solely by diary entry in response to a leading question, and the 7 percent in the integrated database, which is really in the range in public literature for the normal population. In the controlled trials there were only 3 such reports in total, 2 recorded in active

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treatment and 1 during placebo treatment.

[Slide]

Confusion is also an adverse accompaniment of sedative hypnotic drugs and has been identified

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as an occasional side effect of Xyrem. Dose titration may assist in limiting this side effect but it remains an important component of patient and physician education.

[Slide]

The incidence of enuresis with Xyrem treatment supports an association that may be dose related, but any association of these events with seizure activity is very weak. In terms of Xyrem causing seizures at the therapeutic doses, there was no reliable support for such causality. In this regard, the coding to the COSTART dictionary terms of cataplexy as convulsion was confusing. However, there were 2 patients recording seizures with preexisting causes. Two further patients in the Scharf database reported seizures where confounding contributions rendered assignment very difficult. One patient in the Orphan studies represented a complex history of symptoms characterized by fugue state and these symptoms have been attributed to his narcolepsy syndrome.

[Slide]

No significant measures were seen in laboratory measures, vital signs or ECG measures and these changes were comparable across the

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treatment groups. There was no evidence of organ toxicity at therapeutic doses that were not part of the central nervous system pharmacology of the drug.

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We did not identify any evidence of kinetic or dynamic tolerance in the narcoleptic populations studied and the absence of drug-drug interactions in the 3 classes of drugs commonly used in narcolepsy, along with the absence of either induction or inhibition of the oxybate p450 enzyme system make it possible to predict that drug-drug interactions should be minimal.

[Slide]

Although a serious withdrawal syndrome has been described in the abuser population that relates to escalation in both dose and frequency of dosing, no evidence of withdrawal has been demonstrated in patients maintained on long-term therapeutic doses in narcolepsy. Following abrupt discontinuation of long-term dosing in the blinded study, only 2 patients reported anxiety but in the presence of worsening cataplexy, with 1 patient reporting mild dizziness and 1 report of insomnia.

[Slide]

We have not attempted in any way to minimize the issue of abuse with GHB or its precursors. We recognize that this is a serious problem, but stress the fact that this has been peripheral to the development program in narcolepsy. We have detected no evidence of abuse, diversion or self-escalation of dosing in patients in clinical trials. Great efforts have been applied to working with the appropriate expert bodies to plan a restricted distribution system to support in every way the unique bifurcated scheduling legislated by Congress and to plan

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physician and patient education to minimize the possibility of diversion. This will be greatly facilitated by the documentation centrally of prescribing and patient use. This will be described in detail to you later.

[Slide]

In conclusion, I would propose that we have established statistically and clinically significant evidence for the reduction in cataplexy, and for improvement in daytime sleepiness when used concomitantly with stimulant medications.

Xyrem is generally well tolerated, with a

safety profile well characterized in this orphan population by long-term exposure. The medical benefits clearly outweigh the risks for a therapeutic agent that may be the first single agent to address the multiple symptoms of narcolepsy. Thank you very much.

DR. REARDAN: I would just like to thank the committee and FDA for your attention. I believe Dr. Mani has some comments, or we are now happy to take questions from the committee.

DR. KAWAS: The FDA will give us a response to the presentation, and then we will probably take a break before we have questions, unless the committee has anything burning they need to ask now. Dr. Ranjit Mani will present for the FDA.

FDA Response to the Presentation

DR. MANI: What I propose to do in the next few minutes is address two issues where our views diverge somewhat from those of the sponsor.

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The first is the effect of GHB on measures of daytime sleepiness in narcolepsy.

[Slide]

This overhead illustrates how many

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measures of daytime sleepiness there were in the GHB efficacy trials. As you can see, GHB-2 had 3 measures of daytime sleepiness; the Scrima study had 2, of which 1 was primary; and the Lammers study had 2. I will draw your attention to the fact that, with the exception of the Scrima study, the remaining measures were all designated as being secondary.

[Slide]

Because what is considered statistically significant does depend or could depend on the number of comparisons made, I think it is also important to illustrate how many secondary efficacy measures there were in each trial. In the GHB-2 trial I was able to count a total of 10; in the Scrima study 17; and in the Lammers study 7.

[Slide]

This is based on data provided by Orphan. As you can see, in the GHB-2 trial the Epworth Sleepiness Scale measure did reveal a fairly clear-but efficacy for GHB but only at the 9 g dose. The p value of 0.001 probably remains statistically significant even when adjustment is made for multiple comparisons.

On the other hand, the frequency of

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daytime sleep attacks and duration of daytime sleep attacks should probably be considered negative evidence of efficacy if adjustment is made for multiple comparisons.

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[Slide]

Again, in the Scrima study one primary efficacy measure was sleepiness index of the Multiple Sleep Latency Test. Here, the results must be considered negative whether adjusted for multiple comparisons or not.

[Slide]

The other measure was the frequency of daytime sleep attacks, again negative whether adjusted for multiple comparisons or not.

[Slide]

In the Lammers study the severity of daytime sleepiness was 1 of 7 secondary efficacy measures which is probably negative when adjusted for multiple comparisons. On the other hand, the frequency of daytime sleep attacks was positive, but using an ANCOVA which was not a protocol specified analysis.

[Slide]

So, here are the problems as we see them with the proposed claim for excessive daytime

sleepiness. Most measures were secondary. The only measure that was primary was negative. The majority of measures were negative after adjustment of the Type 1 error for multiple comparisons. The effects were inconsistent across studies, and the clearly positive results on the GHB-2 trial on the Epworth Sleepiness Scale were not replicated. As mentioned, the approval of modafinil for the treatment of excessive daytime sleepiness was based on replicated results in 2 efficacy studies. And a minor point, the results on the GHB-2 study were, to some extent, confounded by concurrent stimulant

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use, raising the question, among other questions, of whether Xyrem is effective as monotherapy for the treatment of excessive daytime sleepiness.

[Slide]

The second issue that I want to address briefly is that of sleepwalking. As you can see, I have put it in quotes. As Bill Houghton has already emphasized, we do not know what these episodes represent. They have not been clinically characterized.

[Slide]

The term sleepwalking does not correspond to the medical entity of somnambulism. The term is

based entirely on patient diary entries, and there has been no attempt to characterize the episodes further and define what clinical entity they correspond to.

The incidence of these episodes, whatever they may represent, was approximately 32 percent. The majority of patients did list as having more than one episode. A single patient had a total of 346 episodes over a 5-year period. As already said, an adequate clinical description is lacking, and the episodes cannot be said to be completely benign.

There was one patient who is reported to have overdosed twice during two consecutive episodes of sleepwalking. During one episode the patient became comatose and needed to be hospitalized, needed to be on a ventilator for some hours but completely recovered. A second pat had multiple episodes of sleepwalking. She was found by her husband to be smoking, apparently inadvertently. During one such episode her clothes

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were set on fire. The fire was put out. She was taken off GHB and did not have any further such episodes. A third patient is reported to have swallowed nail polish remover during an episode,

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without any serious consequences.

I would also like to add one minor point in response to Dr. Houghton's presentation. That is, I believe that in the Scharf study there was one patient who was withdrawn from the study because he felt that he had benefitted from Xyrem and decided that these benefits could be extended to a circle of friends who also received part of his own supply, again apparently without serious consequences. Thank you. That is really all I have to say.

DR. KAWAS: Thank you, Dr. Mani. Does the committee have any questions they would like to ask before the break? If not, we will reconvene this meeting at 10:30 sharp.

[Brief recess]

Committee Discussion

DR. KAWAS: Will you please have a seat so we can reconvene this session? This meeting of the Peripheral and Central Nervous System Advisory Committee is now reconvened. We appreciate the presentations from the sponsor and the FDA, and the floor is open for questions. The first question is going to come from someone who has been patiently sitting on the phone. Dr. Chervin, can you hear

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me?

DR. CHERVIN: Yes, thank you.

DR. KAWAS: Dr. Chervin, we can't year you yet, if you will give us a moment to do whatever it

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is we have to do?

DR. CHERVIN: Can you hear me now?

DR. KAWAS: Give it a shot.

DR. CHERVIN: I have a question perhaps for Dr. Houghton. In regard to the safety experience with the 1328 patient years, were there any reports that alcohol was taken in the evening in combination with GHB? If so, what was the outcome?

DR. HOUGHTON: It was certainly recommended as a contraindication in our protocols. The advice to the patient was that they not consume alcohol during the studies. I can't vouch for the fact that it was entirely complied with, but we don't have protocol or database record of consumption of alcohol during the trials. There certainly is record of patients having imbibed during the Scharf study and I am not in a position to clarify that.

DR. GUILLEMINAULT: This is Dr. Guilleminault. I have also a question, and it is

for Dr. Mani, about the sleepiness data. Was there the slow wave sleep information looked at for sleepiness? As you know, delta power greatly improves alertness and there are many studies, sleep deprivation studies and investigation into sleep disorders such as obstructive sleep apnea, where it is very clear that decrease in delta power and in slow wave sleep has a big impact on the alertness, and the more delta power you have and the more slow wave sleep you have, the better alertness the next day.

So, one of my understandings is that this

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drug has an impact on slow wave sleep and delta power. Was there any analysis of that in data looking at alertness?

DR. MANI: To the best of my knowledge, it was not listed as an efficacy measure in any of the controlled studies that I looked at.

DR. GUILLEMINAULT: Okay. The second question is maybe a question about my ignorance. I did not understand exactly the statistic about the ESS because in the investigation of the results of the ESS there was an investigation with negative studies. All the results, when you look at everything there, was there a positive p value?

Was there a statistical difference? Because I don't understand the manipulation which was done. Maybe through poor knowledge, I have never seen this type of manipulation.

DR. REARDAN: Dr. Guilleminault, which study are you referring to when you ask about the Epworth Sleepiness score?

DR. GUILLEMINAULT: I think OMS-2.

DR. REARDAN: Is that for Dr. Mani, or do you want to pose that to the company?

DR. GUILLEMINAULT: No, I was asking that because Dr. Mani reported that he looked at that study and classified the results, and my understanding, and it may be a wrong understanding, is that he made a subdivision in looking at the results and I did not see completely the statistical rationale for that approach.

DR. MANI: Are you referring to the statistical adjustments for multiple comparisons? Is that what you mean?

DR. GUILLEMINAULT: No, the Epworth

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Sleepiness Scale study in GHB-2, secondary efficacy daytime sleepiness on your slide, and I did not understand exactly how that was analyzed, the type of analysis that was done or redone.

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DR. MANI: Perhaps I should ask the Orphan statisticians to explain that in greater detail, but the analysis was an ANCOVA.

DR. GUILLEMINAULT: The microphone must be poorly placed because we cannot hear the response.

DR. MANI: Can you hear me now?

DR. GUILLEMINAULT: Yes.

DR. MANI: The analysis was an ANCOVA. I mean, perhaps I should get the Orphan study statistician to explain the analysis to you in greater detail.

DR. REARDAN: I am just asking Dr. Richard Trout, the statistician, to comment on how the Epworth Sleepiness score was statistically analyzed.

DR. TROUT: Hi. My name is Dick Trout. First of all, the analysis was just as you described, that is to say it was an analysis of covariance which was preplanned. I think the concern that you expressed was the fact that it was listed as a secondary efficacy measure --

DR. GUILLEMINAULT: Right.

DR. TROUT: -- as compared to a primary, and there was a number of secondary efficacy measures, but even if one adjusted for the multiple

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testing which I think you were concerned about, the 9 g separation from the placebo group would still be significant. We already adjusted for the multiple testing with regard to the dosing issue,

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using Dunnett's test, but your concern was with regard to the fact that there were a number of secondary efficacy measures which would then diminish the effect.

DR. GUILLEMINAULT: Okay, thank you.

DR. PENN: I can see that the claim for helping daytime sleepiness is going to be one that we will want to look into very carefully, and I want to ask our FDA statistician a question about that in a general sort of way. If you were a gambling person, which I assume a statistician would not be --

[Laughter]

-- from the data that you have looked at for 9 g, would you say that in a good controlled trial you would bet on it working to decrease daytime sleepiness? It looks like the strongest data is at 9 g and that is what the company is suggesting. I am going to ask you to bet on that, and then I am going to make a point.

DR. MANI: You addressed the question to a

statistician; I am not a statistician.

DR. PENN: Oh, I am sorry. Anybody else want to gamble with this?

DR. REARDAN: Coming up to the podium is Dr. Sharon Yan, who is the FDA statistician that has been working on the Xyrem program.

DR. YAN: Basically we rely on the results that were prespecified, and a lot of results that we looked at -- and you want me to bet -- after looking at those results, most people would bet that the data shown, for example, the 9 g it seems that it is highly positive; it is highly

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significant, but we rely on the analysis which is prespecified. Without that, the data information -- it is hard to bet on anything.

DR. PENN: But I am asking you how you would bet on that if you had to make a bet now in Las Vegas, and the point I am trying to make is that it seems to me a reasonable bet that it does help daytime sleepiness but that they haven't presented two clean studies that show at 9 g that that is the case. And, is there going to be some middle ground to this where that claim can be put in language that would be acceptable later on? So, I wanted to see if you agree that that analysis

then presenting of the problem is the correct one, that is, that there is very strong suggestive evidence, not as strong as we often want for a claim, that it helps daytime sleepiness. When you sit back and you look at all the data, would you bet on that helping daytime sleepiness?

DR. KAWAS: Perhaps Dr. Katz could help with this response.

DR. KATZ: Yes, again, I will just sort of reiterate something that Dr. Yan has already said, which is that whether or not we personally believe something is true or what we would bet on is not really the standard. The standard which we apply is what the law requires, which is substantial evidence of effectiveness, ordinarily defined, unless there is some compelling reason to do otherwise, as data from at least two adequate and well-controlled trials demonstrating effect. We have adopted by tradition a usual sort of statistical rule by which we decide whether or not a study is "positive" for a particular indication.

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So, I think that is the standard. Unless there is some, as I say, very compelling reason to apply some different standard, like what would I bet on or what my personal belief is, that is the standard

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we need to apply. Again, unless there is a view that there is some compelling reason to apply some different standard, we would ask you as a committee whether you think that the evidence for that particular claim meets that standard.

DR. PENN: So, once again the question should go then to Orphan, whether or not they feel they have met that standard on two separate occasions using their 9 g amount, and I haven't gotten a clear-cut idea in my mind whether they are really claiming that or just showing us data that would be for a good bet.

DR. YAN: May I clarify one thing? For the analysis for daytime sleepiness for GHB-2 the sponsor showed it was highly significant, with a p value of 0.001, and I analyzed the data with the original scale and, as I analyzed it, it shows that the normal assumption was validated and then the log transformation to then improve the data, and I used nonparametric analysis to analyze the p value, and it is not that small. As I remember, the p value is 0.03 or something.

DR. REARDAN: I can comment on the trials. We have GHB-2, obviously, where the trial was very effective. I don't think there is a dispute with

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FDA on that. The question is do we meet the standard of two well-controlled trials for that indication. The data in support of that comes from the Lammers study. The sleepiness scale used there

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was something he developed, not a validated scale but it was statistically significant for daytime sleepiness, albeit in a very small, 24-patient crossover trial.

So, we have a small supportive study. We have the large controlled study, GHB-2. That is the evidence basically. Bill, do you want to comment?

DR. HOUGHTON: Yes. We are not trying to make this something that it is not in any way, and if you apply the absolute, most rigorous standards of normal drug development to our database, we have a small database. We did have the two components that were statistically significant. This was supported by the reduction in daytime sleep attacks which are very clinically significant to the patient, and we had two components of statistical significance there.

The other issue, and I know that this from a pure mathematical sense is problematic, is the evidence of long-term support in daytime sleepiness

claim with the GHB-3 protocol, which showed the Epworth Sleepiness Scale and the daytime sleepiness reduced and maintained over the long period of time. The fact then that the objective data in SXB-20 was so strongly supportive and the change in Maintenance of Wakefulness Test is an objective measure and was clearly positive was very important.

The part that concerns me from a clinical point of view is if you look at the patient profiles as they enter the studies, they are on stable doses of stimulants and, yet, their ratings

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are very low. The real issue is that daytime sleepiness with current medications isn't well addressed. So, the question is not only have we shown absolute irrevocable evidence of long-term efficacy for daytime sleepiness with the existence of the present treatments for long-term effectiveness, what we didn't do is ask for a claim in daytime sleepiness.

[Slide]

Our proposed indication was to improve the symptom. We didn't attempt to do studies that displaced the stimulant therapies. What we are really looking at is a hand-in-glove approach that

actually makes patients better as an incremental change, and all therapies up to now have been very separate. The symptoms of daytime sleepiness and those of the associated REM phenomena have been treated by entirely separate medications. If there is a component of Xyrem that assists in daytime sleepiness as an incremental change, we think it is very clinically important and that is what we sought to present today. I want to stress very clearly that we are not looking for the claim of daytime sleepiness; we are looking at an improvement in the symptom thereof.

DR. KAWAS: Dr. Houghton, can I ask you then, to my reading, that indication is actually two indications, I mean, cataplexy and sleepiness being a separate one. When I was reading the materials that you very carefully provided us, obviously for cataplexy the GHB-2 and the SXB-21 study speak to that issue as pivotal trials. I was going to ask you which were the two that speak to the issue of daytime sleepiness. Now I understand

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them to be the GHB-2 and the Lammers small trial with the questionnaire that was developed there. In both of those cases, however, we are talking about subjective sleepiness from the Epworth scale

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and the other question. Since there are factors that can influence someone's subjective feelings of sleepiness, do you have any objective measures that support the indication of daytime sleepiness? Specifically, the one trial that I am aware of that had an MSLT and did daytime sleepiness as a primary outcome measure, in fact, appears to be not supportive of the indication.

DR. HOUGHTON: Yes, in the Scrima trial he used the MSLT measure and that was not statistically significant, as shown. The objective data that we propose supports very strongly the effect of adequate dosing of GHB was the SXB-20 trial that Dr. Black discussed. That is not only a profound improvement in the MWT at the 9 g dose but a defined dose response across all doses. That is very positive data.

DR. KAWAS: In ten patients, it appears.

DR. HOUGHTON: Twenty-one.

DR. MANI: May I also add that that was an open-label, non-randomized study?

DR. HOUGHTON: Sure, but using an objective measure.

DR. RISTANOVIC: I am I am Ruzica Ristanovic, medical director of Sleep Disorders

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Center, in Evanston, Illinois. I would like to comment on add-on Xyrem in the presence of other stimulants. Other studies attempt to try to document the effectiveness of other stimulants in

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narcolepsy-related sleepiness documents, including the most rigorous trial of modafinil in double-blind, placebo-controlled studies. They document that these drugs improve sleepiness but very seldom outside of the range of pathological sleepiness as measured by Multiple Sleep Latency Test and Maintenance Wakefulness Test. So, the patients remain sleepy. That is the message. Add-on treatments are approved for other indications in other neurological diseases, such as epilepsy. So, I assume that this application for that particular indication is not for monotherapy but as an add-on to concurrent use of stimulants. I would like to bring this to your attention. So, patients do remain sleepy on stimulants and they need additional treatments.

DR. KAWAS: Dr. Temple?

DR. TEMPLE: Dr. Houghton also seemed to be distinguishing between monotherapy and add-on therapy. That is not the problem. The problem is whether there is adequate support for use as an

addition for whatever else the patient is on, and whether there are well-controlled studies that support that. So, add-on would be perfectly fine. That is usually true in a lot of conditions, not just neurological ones, where you continue to give standard therapy and try to improve it.

I just want to make one observation about the evidence. We do expect to see replicated or reproduced findings. Some of the issues here are whether the fact that the endpoints are secondary and need some correction means that there isn't adequate support. A lot of these things are

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matters of judgment that the committee can weigh in on. Not everything is, you know, a yes/no. Some of the things are moderately subtle and that is why this is being brought to you for judgment. There is one study that is obviously stronger than the rest but the others can be considered, and you sort of have to think about how many real endpoints there really are; how much of a correction is needed. Those are difficult discussions but worth considering.

DR. KAWAS: Dr. Katz?

DR. KATZ: I agree, but I think we would still have to have the application meet the

standard of independent replication, in other words two trials. You can decide that one of the other trials actually does meet the usual standard, again, taking into consideration the multiplicity and that sort of thing. All I am saying is that I don't think we can say we have one study that looks good. If you believe that GHB looks good and the others sort of contribute to a feeling that it probably is okay, I mean, we really need two independent sources that you believe demonstrate the effectiveness.

The only other point I wanted to add is to something, Claudia, you said which has to do with Dr. Houghton's view that they are not going for a claim of daytime sleepiness; they just want, I guess, to have language in the labeling that says that it improves that symptom. Most of the drugs we approve are for symptomatic claims, so there is no question that the inclusion of this language in the indication is a claim as we always understand that term.

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DR. KAWAS: Dr. Guilleminault, followed by Dr. Wolinsky, please.

DR. GUILLEMINAULT: If you look at all the published data on modafinil, on amphetamine, on

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methylphenidate, none of these drugs ever normalized all the objective tests on alertness and daytime sleepiness. None of them, including the modafinil data which were approved by the FDA. The MSLT and MWT for all these drugs are pitiful. The only data which shows significance was the Epworth Sleepiness Scale, which is a subjective scale, in all these trials. So, we cannot expect to have any positive result with subjective tests in any of these drugs. We will always have to rely on subjective tests even if the subjective test is not great. Everybody in the field agrees that the Epworth Sleepiness Scale is the most used scale despite the fact that it has a lot of downfall, and we have to remember that when we look at what has been approved and what is being used.

DR. KAWAS: Thank you, Dr. Guilleminault. I think that many people would agree with those comments, but my question to you would be not whether or not the Epworth Scale subjective measurements are good but do we have two randomized, controlled trials that show an improvement in subjective sleepiness.

DR. GUILLEMINAULT: That was my initial question because my understanding is, when the

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statistician from the FDA responded, she said that when she did a nonparametric analysis she found out that she had a p value of 0.03. So, my understanding is that she had a significant finding

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even when she did the reanalysis. That was my understanding of her response.

DR. KAWAS: Would you like to comment, Dr. Yan?

DR. YAN: I am sorry, the previous number is not right. I checked. The number for the nonparametric analysis, the p value was 0.0109.

DR. WOLINSKY: I have a couple of questions first for some information before I ask the real question. For the informational questions perhaps Dr. Mignot could help with. So, the first question I have is if you could enlighten us or re-enlighten us about how many patients that have narcolepsy have had cataplexy as a component symptom. What proportion?

DR. MIGNOT: In most case series it is about 70 percent.

DR. WOLINSKY: The second question is that at least for most of these studies which were done and presented to us since cataplexy was being measured, as is appropriate, the number of

cataplectic attacks was relatively high. I think in these studies it was around 20 cataplectic attacks per week. So, how many of the 70, 75 percent of patients with narcolepsy who have cataplexy have cataplectic attacks at that level?

DR. MIGNOT: I would guess 20 percent.

DR. WOLINSKY: Thank you very much.

DR. MIGNOT: Yes, roughly.

DR. WOLINSKY: And then they would fall down below that level for the remainder of the 55 percent of narcoleptics with cataplectic attacks.

DR. MIGNOT: If you analyze the spread of

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the number of cataplexy episodes per week, but you have to balance that also with the efficacy of current treatments. A lot of people that currently have cataplexy that is relatively mild just don't want to take the antidepressants because they have so many side effects, especially sexual side effects, dry mouth, all these problems --

DR. WOLINSKY: This is not the question though. So, now the question to Orphan which has really, truly become an orphan drug question, is since all of the studies that have been done have enriched for cataplexy, do we have any data that would suggest that if cataplexy is adequately

controlled or if there is no cataplexy so we don't have to worry about the control of cataplexy there would be any effect of the drug on daytime sleepiness in non-cataplectic narcoleptics?

DR. REARDAN: I think Jed Black wants to make a comment on that.

DR. BLACK: Just a comment on the prevalence of cataplexy in the 70-75 percent of folks with narcolepsy that had cataplexy, the frequency of events -- this is something that Dr. Mignot is not aware of, the cataplexy was subdivided into major events and minor events. About 20 percent or so would have the major events to that level, but when we look at the minor events a far greater percentage of that 70 percent, which may be up to 80, 90 percent of that 70 percent, will have that number of minor effects. Those are not complete attacks where they fall down. In fact, with most narcoleptic patients, they distinguish between the two and they will often only report to the physician the major events. But

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in the diaries that Orphan had set up all the events are characterized.

DR. WOLINSKY: So, the second question --

DR. BLACK: We have no idea. That is an excellent question that I think needs to be determined, but in the studies that have been completed that question cannot be answered.

DR. REARDAN: Jed, the only study I can think of maybe is SXB-20 where cataplexy was not an entry criterion and I don't know what the cataplexy incidence in that trial was. Bill is shaking his head -- we didn't record it and we didn't quantitate it.

DR. BLACK: We can't comment on that.

DR. REARDAN: It is true that in most of our studies patients were selected because at entry criteria they had to have a baseline cataplexy.

DR. KAWAS: Dr. Penix?

DR. PENIX: Before we address the two separate indications issue -- and I guess, Dr. Black, I could direct this question to you -- in the GHB-2 study you did look at all cataplexy events, I guess, and then total and partial cataplexy. In the background material, in the separation of the two it appeared that there was no significant difference in any of the three doses of GHB on total or complete cataplexy but your effect was primarily in partial cataplexy. Is that correct?

[No verbal response]

So, my question in that regard is what is the clinical significance of partial cataplexy, and you mentioned that patients frequently do not want

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treatment for partial cataplexy. So, is this a big problem? I presume that the patients that would perceive a problem would be the ones with the complete cataplexy but there we see no significant difference. So, is there a problem there with that?

DR. BLACK: I think this is a good point, and the difficulty comes in trying to separate the two because it is not sort of a box of partial and a box of complete; it is a gradation, you know, ranging from small partials to large partials and the completes. So, I think this analysis is difficult to perform. Clinically the degree of improvement with traditional anticataplectic medications that we use is similar. So, the reduction in partial -- if that is all that is being seen here and I am not convinced that clinically that is the case -- while the statistical analysis didn't demonstrate a significant difference in the complete cataplexy attacks, clinically there is an improvement in all

the different categories, and it is very substantial in traditional anticataplectic medications as well as with GHB.

DR. PENIX: Could Dr. Mignot comment on the clinical significance of partial cataplexy? Is it a big problem?

DR. MIGNOT: Yes, it is a big problem. In fact, the problem is especially the social aspect of cataplexy, when you have to realize that you are just in the middle of a crowd and are meeting some friends, and you can never tell when it is going to happen. It may happen in very odd circumstances.

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So, often even the doctors don't know what it is and they just look at it and they wonder why this person is kind of losing slight control and has to sit down. There is also almost a social aspect with fear of cataplexy that can occur at any time, any moment and, yes, it is a very significant problem.

Again, it is a balancing act because the drugs that we use are somewhat effective but they have all these side effects and you just have to choose between two evils. I am pretty sure that, for example, GHB, based on my relatively limited experience, has less side effects than

anticataplectic classical tricyclic antidepressants, and that a lot of patients would prefer to take GHB even for partial cataplexy.

DR. PENIX: The case that you showed of the nine-year child I assume is complete cataplexy --

DR. MIGNOT: Yes.

DR. PENIX: -- but you are also saying that patients with partial cataplexy have a significant impairment of their life.

DR. MIGNOT: Absolutely. But, as Dr. Black mentioned, it is not an "all or none." I mean, most patients, the ones that are complete, have a lot of partial cataplexy. You never know how bad it is going to be. Most of them are small, little attacks, and sometimes they may even be perceived only by the patient. Sometimes the face may melt; the head drops. Sometimes they just have to sit down; sometimes they don't have to sit down. I showed a young kid because it is more dramatic, but you would see the same thing in some of the

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patients with partial cataplexy occasionally.

DR. BLACK: I am realizing that a definition may be useful here. In general when we were describing patients who documented the partial

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versus complete, we told them to think about complete as an episode where they fall to the ground with complete paralysis or where, if they weren't sitting, they would have fallen to the ground with complete paralysis. Otherwise, anything else is partial -- so, slurred speech, head drops, dropping things are the partials, and those become very important for quality of life and daytime performance. Driving, those kinds of things can become a very significant event for partials.

DR. MIGNOT: Yes, one thing I should also emphasize is that in a very large number of series that, for example, have analyzed several hundred patients with narcolepsy and cataplexy, as a mean the large majority of patients have several attacks per day, several attacks per week. Between several attacks per day and several attacks per week, that is generally partial or complete attacks and it is not something that appears just once, you know, every ten years. It is really something that occurs regularly and sometimes totally unexpectedly.

DR. KAWAS: Dr. Falkowski?

DR. FALKOWSKI: That leads me to a

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question just for clarification. For the purposes of these clinical trials, were the cataplectic events something that was just perceived by the patient and recorded in a diary, or were they

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verified by some third party?

DR. REARDAN: These were taken from patient diaries. So, it is patient recorded episodes.

DR. HAGAMAN: I am Dr. Hagaman and I just wanted to address the partial versus the complete cataplectic events. I think that you have to take it on an individual basis. We have patients that come in that are teenagers that have tests in front of them and they have a partial cataplectic event and they drop their pencil; people that cut hair that have scissors in their hands and they drop their scissors. So, even though they have not had a complete event, this has been a very debilitating event in their lives. So, it is a continuum and I think you just have to really look at each person as an individual and what they are doing.

DR. KAWAS: Dr. Dyer?

DR. DYER: How variable in the same patients are the number of cataplectic attacks per week? What is the variance in that?

DR. MIGNOT: We have looked at that quite a bit.

Actually, I did some diaries in a large number of patients with cataplexy. It is really totally unpredictable and that is one of the most scary parts about cataplexy when you have narcolepsy. Of course, if something emotional is going to happen, say a patient is going to go to a wedding, often they will kind of fear that event much more because they think it is very likely that they are going to have cataplexy in front of everyone and, indeed, they may actually have a lot more cataplexy because

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it is an emotional event.

Still, I have followed, for example, patients and sometimes they may have like 80 for one week and then the following week they may have only three or four. I mean, it can really vary quite a bit. And, one of the main reasons is really that emotion is something that is very variable. In fact, someone mentioned how easy it is to observe cataplexy. It is very difficult to get it on tape because typically the patient come to your office; he really wants to show you what it is but, you know, he is tense and it just will not occur but as soon as he leaves the office and

something happens -- boom, he is going to collapse. So, it is very difficult to predict and it is quite variable.

DR. ROMAN: For Dr. Mignot also, you mentioned that cataplexy probably is the result of what you called dissociated REM. However, if I recall correctly, the polysomnographic analysis has shown that Xyrem actually decreases the amount of REM sleep and increases delta sleep. Would you like to speculate on what could be the mechanism of action to improve the cataleptic component?

DR. MIGNOT: That is a very, very difficult question. One of the difficult questions, of course, is the mode of action of GHB. I have looked into it myself for quite a while because I was trained as a pharmacologist, and it is not clear. There are two camps. Some people think it acts on GHB receptors, specific receptors; others think that it acts through the GABA-B receptors. We know that it has some strong effect on dopamine transmission. If you inject GHB in

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animals the rate of activity of dopaminergic cells shuts down and dopamine can increase in the brain proportionally to the dose. We have done quite a bit of studies that have shown that the

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dopaminergic system is very important to regulate both wakefulness and also cataplexy and the regulation of emotion. I believe it is by changing the balance of the dopaminergic system, that improves cataplexy the following day maybe by increasing dopamine in the brain during the night, but this is highly speculative and a lot more research needs to be done.

The fact that it does not increase REM -- first, it is quite variable because some studies have shown that it does increase REM and this contrasts dramatically with what all hypnotics do. If you take MVN or all the other benzodiazepine-like hypnotics, what they do is actually, rather, reduce slow wave sleep and reduce REM sleep. Xyrem doesn't do that. It actually promotes slow wave sleep and, if anything, would promote REM sleep or doesn't change it. That is still, you know, much more in the right direction of promoting normal sleep, including REM sleep.

The last comment I want to mention is that it is not sufficient -- if you know a lot about narcolepsy, it is not sufficient to just explain narcolepsy as a disorder of REM sleep. Indeed, they have all this transition to REM sleep but they

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also have impaired wakefulness per se. For example, if you do MSLTs they don't always go into REM. They will often just fall asleep into normal sleep. So, it is not only REM sleep that is

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disregulated in narcolepsy, it is also wakefulness and by improving slow wave sleep you presumably also can improve the wake aspect of narcolepsy. My answer may be a little complicated but I would be happy to discuss it in more detail.

DR. KAWAS: Dr. Van Belle?

DR. BLACK: Just another comment on that, the Broughton study showed an increase in REM at a lower dose. The first dose of the SXB-20 that I participated in showed at 4.5 g the first night an increase in REM, which was then followed by a dose-related decrease in REM over time, which is very different from REM suppressant agents where there is a robust, or in fact the largest effect that can often be seen on the first night of administration.

So, we don't know exactly why it is that over time the REM with higher doses is reduced, and why with the first dose, and with the lower doses, as has been demonstrated here with Roger Broughton's work, why the REM is increased. There

has been established sort of a competitive reaction between slow wave sleep and REM sleep. It appears that there may be factors that regulate slow wave sleep that also are important in regulating the appearance, or lack thereof, of REM sleep. It may be that gama hydroxybutyrate is sort of normalizing slow wave activity which then results in a more normal control or regulation of the REM or REM-related events.

DR. KAWAS: Can I ask for my clarification, what dose the company is proposing?

DR. REARDAN: Bill, can you take that

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question?

DR. HOUGHTON: Yes, the dosage regimen that we are proposing is that patients be started at 4.5 g and then titrated between the range of 3-9 g to clinical efficacy. Although in the strictest mathematical sense the only statistical efficacy in the GHB-2 study was clearly defined at 9 g, that may well represent that the study was too short because in the open-label study that followed, as I showed, the maximum nadir occurred at 8 weeks, and when those patients were followed over the course of 12 months they maintained efficacy across the dose range. Certainly, there is an advantage in

terms of the important side effects to dose titration. In all of the treatment IND protocols and the safety studies the data was generated at between 3-9 g. Now, 80 percent of the patients were maintained between 6 g and 9 g, but there was certainly facility for down-titration from the 4.5 or maintenance there as well.

DR. KAWAS: Thank you. Dr. van Belle?

DR. VAN BELLE: It seems to me that there is reasonable agreement with respect to efficacy for cataplexy at least between the FDA and the sponsor. So, I would like to get back to the secondary endpoints. I would like to ask a question to the sponsor's statistician, Dr. Trout, as to whether he thinks that multiple comparisons is a problem. Secondly, if multiple comparisons are a problem, how he would adjust.

DR. REARDAN: Do you want to put this in relation to a specific trial or all the trials in general?

DR. VAN BELLE: Well, I bring it up in

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connection with the analysis of Dr. Mani where he clearly comes to conclusions that differ from yours with respect to the efficacy of some of these secondary endpoints.

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DR. TROUT: You know, it is hard to answer that question. I think the way I would answer that is as follows: The GHB-2 analysis, the results that we found and also that were expressed earlier were very strong. So, even with the fact that there is some multiplicity, we also have, remember, some other outcome measures which were related to this particular general area in terms of daytime sleep attacks. So, there were at least two measures that suggested improvement with respect to that particular outcome.

The other second study that has been discussed is the Lammers study, and that study is obviously much smaller. It is obviously a weaker study, and there is some issue with regard to whether the appropriate method of analysis was there. So, I think that is a harder one to address.

Now, there are two kinds of multiplicity going on here, which you are well aware of. One is the multiplicity with regard to the multiple dosing levels and that was accounted for in our analyses. The question that was brought up by Dr. Mani with regard to the multiplicity of secondary endpoints, and I am not a betting man but I think there is

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certainly evidence to suggest that daytime sleepiness is being affected possibly. But I don't go to Las Vegas nor Atlantic City.

DR. KAWAS: Actually, while we have Dr.

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Trout up, I would ask him with regard to excessive sleepiness on the Epworth Scale in the GHB-2 study, while there certainly was a difference in the two groups, there were also major baseline differences in sleepiness for the responders and the non-responders. In fact, those that appeared to respond had a baseline that was better than the improvement in the other group. There was a significant difference. Are you concerned about these and how these might affect the results?

DR. TROUT: There is always concern about baseline differences, and that was attempted to be accounted for in two mechanisms, one, we looked at change from baseline and we also did a covariate adjustment to try to account for that.

DR. KAWAS: Dr. Katz?

DR. KATZ: I would like to ask Dr. Trout a question also. Dr. Yan mentioned that we didn't believe that the data were normally distributed, and when you transformed the data it didn't really help very much. I don't want to get bogged down in

a hyper-arcane discussion about normally distributed data, but when we did that we got a p value for that comparison -- I guess it was the Epworth, of about 0.01 --

DR. MANI: I am sorry, it wasn't the Epworth. You are talking about the Lammers study where you are talking about the frequency --

DR. KATZ: I thought we were talking about GHB-2.

DR. MANI: Oh, sorry, fine.

DR. KATZ: So, if we are right, it takes the p value which was 0.0001 or something like that

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to 0.01, and then when you get to the multiple comparisons issue it makes it less weak. I agree if you take a p value of 0.001 or 0.0001, no matter what you do to it as far as a multiple comparison, it is still going to be significant. But if it is 0.01 it is a little different story. So, I am just wondering, again without getting into excruciating details, what about this question of the data being normally distributed and not necessarily being improved very much by transforming it? Is there common agreement about that or not?

DR. TROUT: My recollection, and it has been sometime since I have seen the results of the

analysis, is that it suggested that we didn't see a particular problem with the normal distribution as, for example, was the case with cataplexy which was clear. I am not sure if Dr. Yan did a nonparametric covariance analysis or not. I haven't seen those analyses. And, I think the point was made earlier that that would be, I think, an appropriate thing to do in order to account for some potential baseline differences. If she did, then whether it is a reflection of a decreased sensitivity of a nonparametric analysis or whether it is a normal distribution -- I can't answer that without seeing the data. Maybe it was just a standard, nonparametric analysis which might help account for the difference.

[Comment away from microphone; inaudible]

DR. TROUT: No, I know that but Dr. Yan did a nonparametric analysis because she was concerned about the normality, and did look at the log transformation and it didn't have any impact on that, which doesn't surprise me at all.

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DR. KAWAS: I would like to ask the sponsor, I mean, there clearly was a dose relationship in terms of the adverse events. Were any other factors looked at that may be related to

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the adverse event profile, things like age, even previous psychiatric history, other medications? Whether or not they drank alcohol? Anything?

DR. HOUGHTON: No, we didn't go as far as an alcohol history. Certainly for the major psychiatric, a preexisting history of major psychiatric disease emerged. Major psychiatric disease was actually a protocol exclusionary criterion, but in those that, for instance attempted suicide, post-study it was discovered that they had a previous psychiatric history and in actual fact in one of the patients a previous suicide attempt had been made. There was major depressive disease reported in those, but for those who developed psychosis there was definite recorded preexisting psychiatric history.

In terms of age, we haven't done a breakdown of the database, and in most instances there was not a dose relationship. There were just instances that were mentioned in the presentation. Confusion and sleepwalking suggested a dose relationship. In the GHB-2 protocol which was obviously blinded, there was the association with nausea, vomiting, confusion and enuresis that was definite, but that didn't extend across the whole

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study database. So, the relationship with dose is not well defined.

DR. KAWAS: But how about relationship with anything else? For example, were the patients

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who had confusion more likely to be the elder patients? You might be able to tell I am in aging.

DR. HOUGHTON: I can identify well. Do we have a breakdown of confusion by age? A range would be still useful.

[Slide]

Here is a slide that shows that the distribution of age was between 25 and 73 years, with 67 percent over 50 years of age, but the range is still wide. There is the distribution across doses. Four events at 3 g, 10 at 4.5, 12 at 6 g, 8 events at 7.5, and 13 events at 9 g.

DR. KAWAS: Thank you. Do we have any other questions from the committee? If not, we will move on. Dr. Katz?

DR. KATZ: A quick question, if I heard you correctly, there were 14 events reported as convulsions, but when you went back and looked at that, 13 of them were actually cataplexy. So, presumably cataplexy was a verbatim term. How is it that cataplexy got coded as convulsions?

DR. REARDAN: The COSTART dictionary puts cataplexy in as a convulsion. It is a definition. Convulsion has ten different terminologies, verbatim events, and they all code up to convulsion.

DR. WOLINSKY: Along those lines, how come there were only that few number of convulsions when we were studying cataplexy in the trial? I mean, I don't know that it is easy to explain this in both sides of one's mouth.

DR. HOUGHTON: No, and we are not trying to. If there was a cataplexy event that occurred

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of a severity to be seen as unusual for that patient, and the patient volunteered it as an event, then it was recorded as an adverse event. Or, there may have been injury related to the cataplexy events. We do have representation in the database. I can recall absolutely a fractured ankle in the washout study. So, there were traumatic events associated with a major cataplexy event that would have been of sufficient impression on the patient to report as a separate event.

DR. WOLINSKY: But then the event would not have been withdrawal from the primary measure of efficacy even though it was also registered as

an adverse event?

DR. HOUGHTON: I am sorry?

DR. WOLINSKY: Was it still counted as an event in the measure of efficacy if it was also shifted to be counted as an adverse event?

DR. REARDAN: Yes, the patient diaries recorded cataplexy. If they record cataplexy as an event itself, that was part of the efficacy outcome. It wasn't necessarily an adverse event. If they had an adverse event -- fall and break an ankle, cataplexy is coded as part of that adverse event. It is the cause of the adverse event and so it shows up in the database.

DR. KAWAS: Dr. Simpson?

DR. SIMPSON: I have two questions. One really was just a clarification of this business about the sleepiness. I think we have all agreed that there has to be some adjustment for multiple comparisons on the sleepiness index, and the GHB-2 study, even if you make an adjustment, there are certainly some of the indices about sleepiness

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which seem to be significant. But coming back to the Lammers study, have we established whether or not, once we have made an adjustment, we have any significance there or not? Because that is the

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pivotal trial, isn't it, because we need two?

DR. REARDAN: Remember that the Lammers study was a very small trial, 24 patients. Daytime sleepiness was a secondary endpoint in that study, and I forget the p value. Maybe Dr. Yan or Dr. Katz could comment. I don't think any formal study of multiple analysis was done, except maybe by Dr. Yan --

DR. YAN: No.

DR. REARDAN: -- and I think she needs to comment on that.

DR. YAN: For Lammers study there was no prespecified analysis, except the Wilcoxon assigned rank test. It was across the study and we considered it not very appropriate, and for a secondary analysis none of the statistical analyses were specified. The problem with this Lammers study is that if you use different statistical analyses which are considered appropriate, you get a very different result. Some could be less than 0.05 and some ranged to something like 0.2. So, the results are not consistent and we don't have a reliable method to see which one we could consider.

DR. REARDAN: We don't disagree with that. I mean, the problem with Lammers is that it was a

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one-sentence statement about how he was going to analyze it, and it was an inappropriate statistical analysis for a crossover study. So, that creates issues about not having a prospective statistical

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plan appropriate for the study. But even in that initial Wilcoxon analysis the daytime sleepiness was statistically significant. It was not corrected for multiple analyses.

DR. KAWAS: Dr. Simpson?

DR. SIMPSON: I just have another question that I wondered if you could clarify. In a lot of these studies you talk about an intent-to-treat analysis, but when I read it I wasn't clear whether or not that meant the patients that were randomized were actually included always in the analysis or not.

DR. REARDAN: Yes, the intent-to-treat would include every patient who received drug. Is that correct?

DR. TROUT: Yes, every patient who received at least one dose.

DR. SIMPSON: So, how did you then deal with the patients who dropped out?

DR. TROUT: In the GHB-2 analysis we selected an endpoint. So, in order for the patient

to be included in that analysis there had to be at least one post-baseline measure of cataplexy or sleepiness, or whichever outcome you want. So, it was an endpoint analysis that was done in order to accommodate that.

DR. KAWAS: It looks like we are completely behind schedule and we will have a very late lunch, I will warn everyone. The FDA's invited speakers on risk management issues is the next component of this discussion. The first speaker is going to be Dr. Carol Falkowski, of the Hazelden Foundation, in Minnesota, who will be

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speaking on the epidemiology of GHB abuse issues.

FDA Invited Speakers on Risk Management Issues

Epidemiology of GHB Abuse Issues

DR. FALKOWSKI: Hello. Good morning, almost afternoon.

[Slide]

This is the title of my talk, GHB Abuse in the United States. I am Director of Research Communications at the Hazelden Foundation. I have been a member of the National Institute on Drug Abuse's Community Epidemiology Work Group since 1986. I am author of a book, called, "Dangerous Drugs: An Easy-to-Use Reference for Parents and

Professionals." What is missing from this overhead is that I served on the Drug Abuse Advisory Committee for the FDA from 1995 through 1999.

[Slide]

In the very short time that I have, I am going to try and just hit the big points about what we know about the abuse of GHB in the United States, starting off with measuring drug abuse. There are a number of things that are thought to bear when we talk about measuring something as complex and multi-dimensional as drug abuse. This includes population surveys. It includes hospital emergency room episodes; medical examiner data; addiction treatment data; law enforcement data, as well as ethnographic studies that look at specific populations of users that are more anthropological and ethnographic in nature.

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I also want to make the point that all data systems have limitations, and this is particularly true in the case of new drugs of

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abuse. For example, if we are talking about GHB and trying to measure the number of patients who have presented to addiction treatment centers across the country with GHB as their primary drug

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of abuse, it is now the case that it is often grouped in a category of drugs called sedative hypnotics. It is not its own line item. So, in preparation for a meeting like this it is very hard to get an accurate count of the extent to which GHB itself is the presenting drug of abuse.

Similarly, surveys that are conducted -- we have not added GHB to the National Household Survey or the Monitoring the Future Survey, although to the Monitoring the Future Survey that looks at drug use among 8th, 10th and 12th graders ecstasy, another club drug, has been added.

Also, in terms of law enforcement indicators, there is no field test for GHB so it is hard to also get that indication of it as well.

In addition, new methods of abuse are hard to track. I recall, in 1986, when we started at the national level wanting to track crack cocaine, we knew about how to track cocaine but, all of a sudden, we were looking at it by a different route of administration. So, it was a challenge to all of us to start switching our data systems just to measure crack instead of cocaine, to make that distinction.

Existing data systems are slow to respond,

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and there is a system-wide learning curve when a new drug of abuse appears on the scene. That means it is a learning curve in terms of emergency room personnel, treatment providers, law enforcement, as

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well as prevention agencies, and that is why we rely on a lot of the scientific literature put out, particularly in emergency medicine, to inform the field about emerging drugs of abuse and how people present with those problems.

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My background in this has been as part of the Community Epidemiology Work Group. This is a group of drug abuse researchers from twenty cities in the country that has been convened by the National Institute on Drug Abuse since 1976. This model of drug abuse epidemiology has also been adapted in different parts of the world. There is a similar group in Europe, in Canada, Mexico and Asian cities.

[Slide]

The Community Epidemiology Work Group is an early warning epidemiological surveillance network that detects new drugs of abuse, patterns of use and populations at risk.

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It involves researchers looking at the same data from different geographic areas and in this case, as I mentioned, there are people like me in twenty cities in the country who write quantitative reports on drug abuse twice annually, and we are convened by the National Institute on Drug Abuse twice a year.

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Having done this and written over twenty reports on drug abuse trends in my city and met with my colleagues, it has given me a sort of broad-based perspective on how emerging drugs are

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measured and how we get a handle on them. But everyone looks at medical examiner data. We look at the data from the Drug Abuse Warning Network, which is data from a representative sample of nine federal short-stay hospitals with 24-hour emergency rooms, and that is conducted in 21 cities, as well as some other areas of the country.

We also look at treatment data, law enforcement data and price, purity, trafficking and the sale of drugs, as well as supplemental research data and information from multiple sources.

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I want to start my introduction to GHB by

telling you about the abuse of a group of drugs that are called club drugs. That is really the first time in a long time we have had a name like club drugs applied to drugs because they are used in a particular setting. That is why they came to be called club drugs. It is a mixed category of drugs. It includes stimulant drugs as well as depressant drugs that are used in nightclub settings. GHB is also known in these settings as liquid X, gamma, G, easy lay, Georgia Home Boy or great hormones at bedtime. MDMA or 3,4 methylene dioxide methamphetamine is ecstasy, e or x. Ketamine is known as special K. It is a veterinary anesthetic, a dissociative drug similar in effects to PCP. Flunitrazepam, Rohypnol is a long-acting benzodiazepine, which was dubbed the original date rape drug which is a drug not approved for medical use in this country; methamphetamine and LSD.

If there is one point to make about club drugs as a term, one thing that has emerged is the fact that clearly these drugs are not limited to

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club settings and I will be talking to that in a moment. It is not just clubs where they are used.

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To give you a little slice of the

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progression of GHB and how it came on the CEWG radar screen, it was first mentioned in 1990 through a poison information center from my colleague in Miami. Then, from 1990 to 1994 it appeared in the Miami and the New York city reports. In 1996 it appeared in 6 other cities, and by the year 2000 most cities in this 21-city work group were reporting GHB. It reports 23 deaths in the 20 CEWG cities, and I refer you to a handout that I prepared that sort of gives the chronology of how my colleagues describe the growing abuse of GHB in their cities.

[Slide]

Now, in terms of user typologies, they tend to be young adolescents through adulthood. There is really no age group but when we look at population surveys in this country of who are drug abusers, by and large the biggest bulk of drug abusers are people who are under the age of 35.

The motive for use is multiple. It includes not only intoxication, but also people seeking intoxication effects in the absence of alcohol. I have had people describe it to me as it gives them the effects of alcohol without having to waste that time drinking alcohol. This is by young

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people who haven't developed the taste.

It is also used by weight lifters and body builders for its alleged anabolic effects. It is also marketed in nutritional supplements to promote

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better sex, better sleep and some people take it to counter the effects of other club drugs. One of the characteristics of drug abuse in nightclubs that has come up over the past year is the fact that people seem to have the impression that if you take just a little bit of this and a little bit of that nothing can really hurt you in a club setting. So, you might take a little bit of ecstasy to get you going, with a little bit of cocaine to keep you there, and maybe a little bit of heroin to take the edge off. This sort of mixing and matching is also part of the user typology.

The settings it is used in are nightclubs, raves, parties, but also in homes, in health clubs, gyms and other settings. The sources of it come from health food stores, mail order kits, the Internet or at these clubs where it is being used by the capful. Sometimes at these clubs, because ecstasy dehydrates you, people have a lot of water bottles and it is not unusual to have a water bottle that may have GHB mixed in it, and for ten

bucks someone can get a swig of it. This makes it very imprecise dosing, as you can imagine.

[Slide]

In terms of deaths, in terms of the consequences of use -- there is a huge bullet missing from this slide, which I will get to. So, if everybody wants to find their slides and write a bullet in it, I would appreciate it. Deaths -- there have been 71 documented deaths, according to the Drug Enforcement Administration, through November of last year. Again, the problem is that because it is a new drug of abuse people don't

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know. You know, you have to know what you are looking for to be able to find something and this has clearly been the case in trying to document GHB deaths. It is a huge issue and I hope we get enlightened on that this afternoon.

Also, there have been adverse medical reactions, not only people who come into emergency rooms, but the countless people, which is quite hard to quantify, who have episodes but never get emergency room treatment for it. But there have been medical reactions, adverse ones.

Dependence -- there has been a reported increase in people presenting to addiction

treatment centers with GHB as their primary substance of abuse, and an increase in the reported addiction to GHB by those who may not make it to treatment programs.

I work at the Hazelden Foundation. We are based in Center City, Minnesota, with campuses in Chicago, New York City and West Palm Beach. There were 5 patients in 1999 who had a history of GHB abuse, and that had grown to 39 in the year 2000 and we are just one treatment center.

Finally, the missing bullet on here is drug rape. One thing we have seen in this country since the early 1990's is the use of drugs, this predatory use of drugs where you administer drugs to people without their knowledge for the purpose of disabling them to commit crime on them. The first drug that came to this sort of notoriety was Rohypnol, but now we are in a situation where GHB is often used in drug-induced rape. In fact, several years ago when President Clinton signed the federal date-rape law, the Samantha Reid and Hilary

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Farris Date Rape Act, that was in response to two cases of drug rape that were not related to Rohypnol but to GHB. So, that bullet should be up there, drug rape.

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Also, another bullet would include the trafficking, sale and manufacture, the law enforcement consequences.

[Slide]

Let's look at hospital emergency room episodes of GHB. This looks at them from 1994 through 1999. You can see the increase in hospital emergency department mentions of GHB. Mentions is sort of unusual term for people who aren't familiar with the Drug Abuse Warning Network, and it quite literally means, in a retrospective review of patient records, that they find a mention of GHB. Sometimes it is the sole drug that precipitated the medical emergency and sometimes it is used in combination with other drugs. For every drug abuse episode in the Drug Abuse Warning Network there can be the mention of 4 drugs and alcohol, but when alcohol is used in combination with other drugs; it is not an alcohol tracking system.

[Slide]

So, this is what it looks like through 1999. This looks at it by half year increments. You can see this takes us into the year 2000 and we have the first half of the year 2000.

I want to go back to just my opening

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remarks about club drug abuse. I think in the general population when we think of club drugs, you know, what we hear about, what everybody is talking about, what seems to be in U.S. News and World

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Report, in Newsweek and Time Magazine is ecstasy.

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This is from exactly one year ago. This is Time Magazine from June 5, 2000. It talks about ecstasy. For many folks, club drugs -- you think ecstasy.

[Slide]

This was, I believe, from Time magazine as well. You see the water bottle there. If you didn't see Time magazine, you may have seen The New York Times Sunday magazine insert. This is from January of this year, talking again about ecstasy. This is from January 2001.

So, since it is in the same category of drug, I think it is relevant to look at how GHB emergency room episodes compare with those of ecstasy.

[Slide]

Ecstasy, or MDMA, is in the pink and GHB is in blue. You can see in the first half of the year 2000 that GHB hospital emergency episodes have

surpassed those of ecstasy.

[Slide]

Efforts to control GHB -- a number of states have done things to try to control GHB abuse in their states. This is sort of a listing of the scheduling of it in various different states. It was added, as you know from the materials the committee received, to the Federal Control Substance Act.

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Finally in conclusion, GHB is a significant, growing drug of abuse. We have seen

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rapid growth in the adverse medical consequences related to GHB since 1999 and, in fact, hospital emergency mentions of GHB now surpass those of ecstasy or MDMA. We have seen rapid growth in adverse medical reactions despite not only federal scheduling but the scheduling in numerous states. We have multiple user typologies. This is not a substance that is sought after simply by people at parties and raves. These products that contain GHB as well as its precursor drugs, GBL and 1,4-BD, are sought after by people who believe the claims on these nutritional supplements and take them for promoting muscle growth, for sleep; and take them

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for better sex, as well, and as I said, use it in sort of predatory way. Dependence is clearly possible.

So in closing, here we have a drug with an established widespread abuse record. With GHB we needn't talk about abuse potential. With GHB we have abuse reality. We have a decade of GHB abuse in this country; a decade of deaths and hospital emergency room episodes and dependence. We have escalating abuse of GHB in spite of recent efforts to control it and, yes, people acquire this drug and its precursors in many ways. But make no mistake, the effects being sought are the GHB effects. The chemical agent in the body that is producing these effects is GHB, and this undisputable fact is entirely relevant to our discussions today.

I have to take issue with the statement from the sponsor that says Xyrem is not the problem. If Xyrem equals GHB, then I believe it is a problem. This drug, if approved, will exist

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outside the confines of this room. Patients will use it outside the confines of clinical trials. In America, in 2001 we have a serious, significant and growing problem with GHB abuse in this country, and

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it just so happens that this coincides with Orphan Medical seeking approval for this drug.

This drug already has avid followers, and there is no reason to assume that another source of GHB would not be sought after by these folks, and I think we need to bear that in mind throughout our discussions. Thank you.

DR. KAWAS: Dr. Falkowski, can I ask you one question? With regards to the emergency department data for GHB, I recognize the difficulties of all of this kind of data but, for example, MDMA is not infrequently the only drug and when they go to the emergency room that is clearly because of the MDMA. Can you give us any kind of quantification or semi-quantification? You mentioned that sometimes GHB is the only drug.

DR. FALKOWSKI: The question was how often is GHB used in combination, and let me find that.

DR. KAWAS: For the emergency room data.

DR. FALKOWSKI: Yes, that is what I am looking for. I have it right here. It is 70 percent of the time. Like many other drugs, GHB episodes involve drugs other than GHB as well.

I would also like to add that I believe these hospital emergency room episodes

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underestimate GHB because drugs that are used in a predatory way, that are administered to people without their knowledge are not DAWN reportable. So, if someone comes to the emergency room and says

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I believe somebody gave me something and it is making me sick, that is not a DAWN reportable thing. That is being addressed by the Substance Abuse and Mental Health Services Administration. But what that means is that people who are drugged with any sort of drug are not picked up by this particular reporting system.

DR. KAWAS: And, what are the most common drugs or classes of drugs that go along with GHB when people take them in combination? What are the favorites?

DR. FALKOWSKI: It is probably ecstasy, MDMA, and to a lesser extent ketamine and also alcohol.

DR. SANNERUD: I have some data on the DAWN statistics too. When drugs are used in combination, 50 percent alcohol, 11 percent stimulants, 8 percent marijuana, poly drugs, hallucinogens and sedatives and all these are at least at 3 and 2 percent each.

DR. KAWAS: Dr. Dyer, I believe you are

our next speaker.

DR. KATZ: Claudia, if I could just ask a question, and I don't know who best to direct it, but you said 70 percent of the time the reports are of GHB in association with something else. So, presumably 30 percent of the time it is the sole drug. I have a sort of methadologic question. How reliable would you say that information is, just in general? What is sort of the nature of the information that is recorded and from whom that allows us to conclude that, in fact, GHB is the only drug that was taken? Who reports that, and

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how reliable are those reports, just as a general rule? Number one.

Number two, how many of the deaths and very serious adverse events were associated with GHB use alone?

DR. FALKOWSKI: I believe you could address the reliability of DAWN. You are a DAWN reporter. Again, regarding the deaths, you know, the Drug Abuse Warning Network also collects data from medical examiners, but the people in the 20-city work group of mine rely more often on getting data directly from the medical examiners, first because it is more timely and also because it

casts a better net. It captures situations that are not only due to drug-related toxicity but also ones where the use of drugs were considered by the medical examiner to be significant contributing factors to the death. So, that is what I can say about deaths.

Also, I have a table, if you are interested, that I could make available that shows exactly DAWN emergency room data for 1999 and what were the co-ingestants.

DR. KAWAS: Our next speaker is Dr. Jo Ellen Dyer, from the California Poison Control System at UCSF, speaking on adverse medical effects with GHB.

Adverse Medical Effects with GHB

DR. DYER: Thank you and good afternoon.

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In 1990 I identified and made the first reports on GHB abuse from over-the-counter sales of GHB. Over the next 11 years I have been following GHB. I have an interest in it and I have been

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reporting on the progress, the adverse effects and the trends in use.

[Slide]

This is a description of the California

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Poison Control System data of GHB reports to our center. We logged these reports over 10 years. The first years are when the San Francisco center stood alone so it is a population base of 7 or 8 million. We became a system in '97 so we have 4 years of data for the entire state.

We are a medical toxicology consult service, so we are not a required or mandatory reporting center. So, this reflects just the tip of the iceberg of use and abuse and adverse effects that are out there.

[Slide]

In our experience GHB produces a profound coma. This has been known for over 40 years, starting out in surgical anesthetic studies where it was evaluated as an anesthetic and now through numerous occurrences of coma in users through this widespread public use, where accidental overdoses are occurring because of the narrow and variable therapeutic index for this drug.

[Slide]

Looking at 5 studies, anesthetic studies that cover over 700 patients -- there are many other studies; I just picked a small set of them -- you see the effects of GHB in a controlled

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situation. GHB causes unconsciousness and a profound coma. This is what is intended with an anesthetic. The respiratory effects that are seen are Cheyne-stokes respiration. There were

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aspirations. There was a case of unexplained pulmonary edema. In many of these cases the patients are intubated and the airway is attended to. If their airway was left to chance in these situations, it would be compromised. They lose their airway protective reflexes. They have no gag. So, with the high incidence of vomiting, about 30 percent in these studies, combined with the loss of gag, it is not difficult to see how aspiration is going to occur.

There are cardiovascular effects, like bradycardia, and then there are isolated incidences where blood pressure rose up to 30-60 mmHg for unexplained reasons really. There is myoclonus that we see. There is an emergence delirium, confusion. There are also secretions like salivation, vomiting, incontinence and diaphoresis.

[Slide]

If I look at 16 reports that cover 175 cases of adverse events where GHB was in public use, you see these same physiologic responses to

GHB. You have profound coma. They develop a mild respiratory acidosis; bradycardia; myoclonus; confusion; emergence delirium; and then the secretions. This raises doubts for safety of use among a generalized public population.

[Slide]

If we look at a closer group where we did a study in our emergency department, and this is the San Francisco County emergency room that sees over 200 patients a day -- we looked at GHB overdoses that we had over 3 years. This is just a retrospective descriptive study where we were

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trying to get a handle on what is going on. We found that of those cases, about 33 percent had no co-ingestion. This was documented by either toxicology or patient report. Those patients came in, a quarter of them, with Glasgow Coma Score of 3. So, they were profoundly comatose and 33 percent of them had coma scores between 4-8. The coma lasted 15 minutes to 6 hours.

Again, a third of the patients had these same symptoms, bradycardia, respiratory acidosis, hypothermia, vomiting. We saw hypotension in about 11 percent. Those cases were primarily cases where alcohol was co-ingested. Then, on emergence these

patients are difficult to manage. They can have an emergence delirium which includes combative, agitated behavior.

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Because of that evidence and wanting to focus in closer and get some GHB levels to find out if that is truly what we were looking at, we did a prospective study over 6 months, looking at 15 cases of GHB overdose, and 73 percent of those came in with a Glasgow Coma Score of 3. Our intent was to document the presence of GHB, to detect the co-ingestants and what they were or if there were none, and then to verify that our ability to predict an overdose is truly GHB by the toxidrome that we are using, whether or not that was effective.

So, all of these 15 cases did have GHB that was measurable. They were young, ages 20-39; 73 percent were male. The study inclusion criteria were patients presenting with Glasgow Coma Scores less than 8 and 73 percent of these patients had a

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Glasgow Coma Score less than 3.

In 5 of the cases there were no other drugs or alcohol detected. The GCS was 3 in 80 percent of those cases. So, profound coma from

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accidental overdose; no other obvious cause.

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It is clear to us that there is really substantial evidence that GHB causes coma. Coma is life-threatening, and these deaths are occurring from accident or injury and from respiratory compromise. We are seeing that through aspiration; through apnea; through positional asphyxia -- these are profoundly comatose people, they can't even move to open their airway -- and through pulmonary edema.

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So, I have reviewed 20 GHB related fatalities where I had autopsy reports. I just sent letters to medical examiners asking for their reports. In these cases, the ages ranged from 15 to 46 years. Three-quarters of them were male; 20 percent of them had no concurrent ingestions. If we look at those that had co-ingestants, the 80 percent. We will see that many of these substances are legal commonly ingested things. Tylenol was one of them; caffeine; alcohol. The levels of alcohol went up to 0.17 percent. The legal limit for driving ranges from 0.08 to 0.1. So, most of these cases were in the lower range, right around

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the legal limit of driving, saying that they had maybe one or two drinks and none of these would reach an alcohol level that would cause coma.

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The societal costs that were seen from GHB abuse, there are many driving under the influence arrests that have occurred with GHB. There were a whole lot that were not recognized until GHB testing became available and now they are being recognized. I don't go out really and collect this data but there are two vehicular manslaughter, I guess they would call it, cases where a person driving under the influence of GHB has hit and killed another individual. One of those was in '96 and one was in 2000.

Another societal cost is the assaults where the victim is under the influence of GHB given to them or slipped to them by the assailant. It is common enough that they have a term for it. It is called being "scooped" by GHB. The assailant then attacks the victim while they are unconscious or amnestic to the effects of the drug, making prosecution and even reporting of these very, very difficult.

These are 4 cases. There are others. But

in these GHB was clearly documented as the cause. The first was a woman who was drugged and assaulted by her boss as they went out with a group of colleagues after work. She had GHB in her urine. There were 10 victims of some DJs in Los Angeles that were slipping GHB into drinks and then assaulting them. There was a 24-year old that was eventually prosecuted more for trafficking drugs after a woman had reported an assault to them and, in kind of the bargaining, he admitted, yes, he had drugged her twice with GHB and she has no memory of the first event at all. Nothing. The last is two

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15-year old females who were unconscious at a party. One was hospitalized and one of these girls died.

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We also see addiction as another burden from GHB abuse. We are currently seeing one to two cases a month at our poison center, and this is eight cases that I collected. The age range is young, 22-38, again three-quarters male. The pattern just continues through all these of the demographics of who is using. Of these, 63 percent started taking GHB for body building. They had what they thought was kind of a legitimate use of

this dietary supplement. In this group, 88 percent of them were employed or students. These were functional members of society that have had trouble now because of this drug. These are not people that really had drug-seeking behavior. The onset of symptoms we see within 1-6 hours. It progresses over a couple of days. The duration is 5-15 days.

Now, these are often unrecognized by healthcare professionals when they present for treatment. GHB abuse addiction is not really very well known out there. These are severe neuropsychiatric symptoms with autonomic instability that we see. I have had physicians who have treated many, many cases of severe alcohol withdrawal that have called me up and said, my gosh, I am impressed; I am so impressed by this withdrawal symptom. The patients become agitated, combative, delirious. They are hallucinating. They require sedation, a milligram a minute of IV Ativan has been used over a few hours to gain control. They require four-point leather

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restraints and intensive care. One of the patients in this series died while being hospitalized for GHB withdrawal.

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Substantial and compelling evidence from case reports of accidental poisoning and from toxicology supported adverse events really shows us that these effects are due to GHB. It is not some contaminant or something else that is causing these. And, there is an insufficient or no safety margin between the effective level of the therapeutic dose of these drugs that these people are taking and the dose that causes these effects. As you can see from the sponsor's study, the adverse effects that they are reporting are very similar. The confusion, the nausea, the vomiting are very similar to the things that we are seeing.

One physician, Dr. Gallamberti from Italy, who is doing therapeutic use of GHB withdrawal states talks about a 15 percent problematic GHB use among his population. This can be dose escalation. This can be GHB overdoses up to 10 times a year, or GHB dependence.

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This slide just looks at the kinetics to illustrate that there is really a very narrow therapeutic index with this drug and there is a lot of variability. The pharmacokinetics of GHB are capacity-limited absorption, capacity-limited

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elimination. The coefficient of variation of some of these parameters is 50 percent. There is a lot of variation and we don't really know what the consequence in different populations and different

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people of these really variable kinetics is going to be, or why they are so variable. You are used to using phenytoin. It has capacity-limited elimination. We know that when you are bumping the dose of a patient on phenytoin you have to be really careful because they can exponentially increase their level. Well, the same thing happens with GHB and we don't know where that is yet. There is not enough experience. And, with phenytoin the absorption is pretty good. We know the bioavailability of IV phenytoin and oral phenytoin. Here, I don't think it is so constant. It really changes with food and there is a capacity-limited absorption that is going to vary between patients. So, this is a really difficult drug to control, particularly orally on an outpatient basis.

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So, what is the current level of GHB abuse that is out there? We really don't know. If we wanted to project from one survey that was done,

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Dr. Miotto, a UCLA physician that works addiction medicine did a 45-minute structured interview with 42 GHB users. Among that group, 69 percent had admitted that they had lost consciousness, had periods of consciousness laps from minutes to hours. There was variability in the amnesia dependent upon how often people used. Twenty-eight percent admitted having an overdose; 9 percent had been to the emergency department for an overdose.

Now, there is an interesting misconception here where they don't consider the loss of consciousness to be an overdose, and people

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overdose and when they are in a profound coma are not taken to the emergency department. So, there are really some problems there, and this gives us an example of the kind of under-reporting that is out there.

If we try and extrapolate from the amount of drug that we are seeing marketed illicitly, this is just one arrest in Marin County, a small county north of San Francisco, where they had 207 L of butanediol. The average street dose varies around 2 g. If you look at that, that is 103,500 doses in one capture at one house, and there are many, many of these. There are lists of different amounts

that have been busted all over.

Then there is the problem that Carol has already talked about, surveying and policing the issues of this type of new drug abuse. There is no systematic method in place for data collection on this.

There is rapid metabolism of the drug. It clears from the blood in within about 6 hours; it clears from the urine within about 12 hours. We can't test these people and find it. When we are trying to get evidence in a drug assault case, it is gone. It is really difficult to detect. And, should we increase our level of detection to the very, very minute nanogram kind of range, then we are going to start running into the biological background so we aren't even going to be able to do that if we increase our ability to detect. There are also very poor assays currently out there. None of the hospitals have an assay for this, and none of the law enforcement has a field kit for it. So, it has to be taken into a lab and specifically

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run through a complicated GC mass spec procedure to get a level out, which is expensive.

The current documentation clearly grossly underestimates the amount of use that is out there.

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And, it is very clear that there is a little, if any, safety margin with GHB use in the therapeutic doses that are proposed. GHB is a very potent new drug of abuse. It has been around 10 years. We thought it was going to come and go as a fad, it hasn't and it is not going to. The use is still increasing.

There is a very high acute toxicity in accidental overdose -- coma, bradycardia, myoclonus, vomiting, aspiration -- we are seeing a lot of it, and it has very high abuse and addiction potential. So, I think that we have to be very careful and it is very difficult to try and minimize these potential risks, the risks of having it get out into the drug abusing population but also among patients that we are going to be giving this drug to take at home. At the poison center, every night at bedtime, 9 to 11 o'clock I am called by people that say, oh, I'm sorry, I accidentally took a double dose of my medication. What should I do? In this case, they are all going to go to the emergency room. There is really not a margin of safety with this drug. Thanks.

DR. KAWAS: Thank you, Dr. Dyer. The next presentation is from the sponsor, presentation on

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risk management and abuse liability, Dr. Bob Balster, from the Medical College of Virginia.

DR. REARDAN: Yes, I would like to now introduce Dr. Balster who will present his views

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with respect to abuse liability of Xyrem and GHB. Dr. Balster is a previous chair of the FDA Drug Abuse Advisory Committee and a widely published abuse pharmacologist from the Medical College of Virginia. He is editor and chief of a leading addiction journal, Drug and Alcohol Dependence, and a past president of the College on Problems of Drug Abuse.

Sponsor Presentation on Risk Management and Abuse Liability

DR. BALSTER: Thank you very much, Dayton. Good morning or good afternoon, I guess it is now.

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Well, as you have just heard, the development of Xyrem as a medication has taken place in a context of a national epidemic of the abuse of its constituent GHB, and also the abuse of a number of GHB-related drugs that I will tell you about.

As Dr. Houghton told you, Orphan is very well aware of this problem and has consulted many

drug abuse experts to try to understand the problem better. My own analysis of this situation is that Xyrem has certainly not contributed to the problem that exists today with the abuse of this class of compounds. I guess where I may disagree a bit is that I am pretty convinced that Xyrem is not going to be a player in this over the long term.

I think in order to understand and make an appropriate public health response to this situation, you need to know a little bit about what some of the causes are of this GHB abuse problem.

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So, I hope to make two points in this presentation. The first point is that I believe that the recent abuse of GHB-like substances probably reflects a ready availability more than their inherent pharmacological propensity for abuse.

I think I will make this point by first off reviewing for you the incredible availability of these compounds, and then also review very quickly scientific studies that have been done on the abuse liability of GHB as it is compared to other drugs of abuse you might be familiar with. Secondly, I believe that Xyrem, if approved for

medical use, will not contribute to the public health problem of the abuse of these GHB-like substances in any significant way.

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Before we continue, it is very important to know the cast of characters here. I think next to the federal government, the next worst developer of abbreviations is a drug abuse research community, with MDMA, and PCP, and GHB, and BD -- it must be hard to kind of keep track of the players but, of course, the drug we are talking about here is GHB, gamma hydroxybutyrate. But there are a bunch of other drugs that are basically part of this national drug abuse problem.

You have heard a little bit about them, but these precursors, gamma butyrolactone or GBL, 1,4 butanediol or 1,4-BD are precursor compounds that, if obtained, can be easily and readily converted into GHB. They also can be consumed directly because they are metabolized by the body into GHB. So, they themselves are drugs of abuse

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like GHB. Then there are others that are also available.

Now, of all these chemicals only GHB is actually a scheduled drug. It is Schedule I under

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the Controlled Substances Act for the abusable versions, GHB; Schedule III for an approved medical product. So, only GHB is scheduled. Now, GBL is what is called listed so its availability is diminished. These others are still freely available without any drug abuse controls.

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You have heard a lot about GHB abuse but I am pretty convinced that what we are seeing here is something that has resulted from an amazing situation of the availability of these compounds. To remind you, GHB was available legally and legitimately through health food stores up through 1990 when you could buy it anywhere, and the abuse problem with this drug began during that period of time.

Then through that time and afterwards GHB could be obtained through the Internet. There was an amazing number of sites set up to sell GHB. Then, as GHB became less easy to get because Internet sources dried up, the Internet sources were selling the precursors, etc., etc. I will show you some data a little bit more, but these precursors are not going to disappear any time soon from public availability. Now that the

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availability of GHB has been restricted by the federal scheduling actions and actions by the FDA, people can now purchase the precursors and make their own GHB. Essentially anyone can do that. It

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