



IDA
21-754

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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE PATENT OF :
TOSHIRO IWAMOTO ET AL : GROUP ART UNIT: 1811
SERIAL NO: 07/715,961 : EXAMINER: MARSHALL, S. G.
FILED: JUNE 17, 1991 : PATENT NO. 5,376,634
FOR: POLYPEPTIDE COMPOUND AND : ISSUED: DECEMBER 27, 1994
A PROCESS FOR PREPARATION
THEREOF

APPLICATION FOR EXTENSION OF PATENT TERM UNDER

35 U.S.C. § 156 AND 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.750, 1.775 AND
1.785 (b)

MAIL STOP: PATENT TERM EXTENSION

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This is an application for extension of patent term under 35 U.S.C. § 156 and 37 C.F.R. §§ 1.710, 1.720, 1.730, 1.740, 1.741, 1.750, 1.775 and 1.785 (b) for U.S. Patent No. 5,376,634 ("the '634 patent") based on NDA 21-754.

Three additional copies of this application are being submitted herewith (37 C.F.R. § 1.740(b)).

2005E-0252

APP 1

II. Complete Identification of the Federal Statute Under which Regulatory Review Occurred (37 C.F.R. § 1.740(a)(2)).

Regulatory permission to sell Mycamine was granted under 21 U.S.C. § 355(section 505 of the Federal Food, Drug, and Cosmetic Act).

III. Identification of the Date on which the Product Received Approval (37 C.F.R. § 1.740(a)(3)).

Regulatory approval for Mycamine, based on NDA 21-754 was granted on March 16, 2005, and a copy of the approval letter is attached hereto as Exhibit A.

IV. Identification of Each Active Ingredient and Statement that Each Active Ingredient has not been Previously Approved (37 C.F.R. § 1.740(a)(4)).

The sole active ingredient in the approved product is micafungin sodium. Micafungin sodium has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

V. Statement that Application is being Submitted within the Sixty Day Period (37 C.F.R. § 1.740(a)(5)).

This application is being submitted within the sixty day period specified by 35 U.S.C. § 156(1) and 37 C.F.R. § 1.720(f).

VI. Complete Identification of the Patent (37 C.F.R. § 1.740(a)(6)).

The patent for which extension of patent term is sought is U.S. Patent No. 5,376,634 (“the ‘634 patent”), which names Toshiro Iwamoto, Akihiko Fujie, Kumiko Nitta, Yasuhisa Tsurumi, Nobuharu Shigematsu, Chiyoshi Kasahara, Motohiro Hino, Masakuni Okuhara, Kazuo Sakane, Kohji Kawabata, and Hidenori Ohki as inventors, and which issued on

December 27, 1994, from U.S. Patent Application Serial No. 07/715,961, and is currently set to expire on December 27, 2011.

VII. A Copy of the Patent for which Extension of Term is being Sought (37 C.F.R. § 1.740(a)(7)).

A copy of the '634 patent is attached hereto as Exhibit B.

VIII. Copies of any Disclaimers, Certificates of Correction, Receipt of Maintenance Fee Payments, or Reexamination Certificates Issued in the Patent (37 C.F.R. § 1.740(a)(8)).

Applicants state on the record that no disclaimers have been filed in the '634 patent and that no reexamination certificate has been issued in the '634 patent.

Copies of the receipts of maintenance fee payments for the first and second maintenance fees in the '634 patent are attached hereto as Exhibit C.

IX. Statement that the Patent Claims the Approved Product (37 C.F.R. § 1.740(a)(9)).

The approved product, Mycamine, injectable micafungin sodium, is claimed in the '634 patent.

The following chart sets forth the relationship between the claims of the '634 patent and the approved product.

Claim of the '634 Patent

1. A polypeptide compound having antimicrobial activity of the following formula:

[structure omitted]

wherein

R¹ is a hydrogen or acyl group,

R² is hydroxy or acyloxy,

R³ is hydroxysulfonyloxy, and

R⁴ is hydrogen or carbamoyl,

with proviso that

R¹ is not palmitoyl, when R² is hydroxy,

R³ is hydroxysulfonyloxy and

R⁴ is carbamoyl,

and a salt thereof.

11. A pharmaceutical composition having antimicrobial activity which comprises an effective amount of a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier or excipient.

Mycamine

Mycamine contains micafungin sodium, which is the sodium salt of the compound of claim 1, when R¹ is "acyl," R² is "hydroxyl," R³ is "hydroxysulfonyloxy," and R⁴ is "carbamoyl."

Mycamine contains micafungin sodium, which is the sodium salt of the compound of claim 1, when R¹ is "acyl," R² is "hydroxy," R³ is "hydroxysulfonyloxy," and R⁴ is "carbamoyl."

X. Statement of Relevant Dates and Information Pursuant to 35 U.S.C. § 156(g) for a human drug (37 C.F.R. § 1.740(a)(10)(i)).

(A) The Effective Date of the IND and the IND number (37 C.F.R. § 1.740(a)(10)(i)(A)).

The effective date for the IND for the approved product is February 26, 1998, and the IND number for the approved product is IND 55,322. However, the amended protocol, protocol 03-7-005, which is the basis for NDA 21-754, was not filed in IND 55,322 until June 30, 2003. Thus, for the purposes of this application, the regulatory review period did not begin until June 30, 2003.

(B) The Date on which the NDA was Initially Submitted and the NDA Number (37 C.F.R. § 1.740(a)(10)(B)).

The NDA for the approved product was initially submitted on April 23, 2004, and the NDA number for the approved product is 21-754.

(C) The Date on which the NDA was Approved (37 C.F.R. § 1.740(a)(10)(C)).

NDA 21-754 was approved on March 16, 2005.

XI. Brief Description of Significant Activity Undertaken by the Marketing Applicant During the Applicable Regulatory Review Period and the Significant Dates Applicable to Such Activities (37 C.F.R. § 1.740(11)).

A. The IND.

A list of significant activities undertaken by the marketing applicant during IND 55,322 and the significant dates applicable thereto is provided in Table 1 below.

The following abbreviations are used in Table 1:

ANR	Annual Report
BD	Briefing Document (white paper)
CLIN	Clinical Information Amendment
CMC	CMC Information Amendment
GC	General Correspondence (e.g. Cross Reference Letters, Briefing Documents)
PHAS4	Phase 4 Commitment Response
PRO	Protocol (e.g. draft, new, new and revised investigators, revised, amendment)
PT	Pharmacology and Toxicology Information Amendment
SAE	Safety Report (Initial and Follow-up)

Table 1.

DATE	TYPE	DESCRIPTION
3/28/05	GC	Transfer Letter
3/24/05	SAE	IND Safety Reports – Initial and Follow-up
3/15/05	SAE	IND Safety Report – Follow-up
3/2/05	SAE	IND Safety Report – Follow-up
3/1/05	PRO	Protocol Amendment: Revised Protocol 03-0-192 incorporating Amendment 4
2/17/05	SAE	IND Safety Reports – Initial and Follow-up
2/14/05	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192
1/26/05	SAE	IND Safety Reports – Initial and Followup
1/12/05	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192
12/22/04	SAE	IND Safety Report – Initial and Followup
12/7/04	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192 and Revised Transfer of Obligations for -192
10/27/04	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192 and FG-463-21-08
10/20/04	SAE	IND Safety Report - Followup
10/5/01	SAE	IND Safety Report - Initial
10/1/04	CMC	Info Amendment: CMC – notified FDA to cross reference NDA 21-506 and 21-754 for updated CMC information for FK463 drug product
9/30/04	PRO	Protocol Amendment: New and Revised 1572s for Protocol 03-0-192, Transfer of Obligations for -192
9/29/04	GC/PRO	Response to comments from FDA during 7/27/04 T-Con re: proposed closed testing procedure for study 03-0-192.
9/29/04	SAE	IND Safety Reports – F/U
9/17/04	SAE	IND Safety Report – Initial and F/U
9/9/04	SAE	IND Safety Report – Initial and F/U
9/1/04	PRO	Protocol Amendment: New Protocol 03-0-192, Amendments 1-3, Revised Protocol and Investigator Data (Sioson).
8/27/04	SAE	IND Safety Report – Initial

8/20/04	SAE	IND Safety Report – F/U
8/10/04	SAE	IND Safety Report – Initial and F/U
7/29/04	SAE	IND Safety Report – Initial
7/22/04	SAE	IND Safety Report – F/U
7/21/04	PRO	Protocol Amendment: Revised 1572s for Protocols 01-0-124 and FG-463-21-08
7/15/04	SAE	IND Safety Report – Initial and F/U
7/6/04	SAE	IND Safety Report – F/U
7/2/04	PRO	Response to FDA Response re: SPA for Protocol 03-0-192 (Amendment #2 and Revised Protocol)
6/23/04	SAE	IND Safety Report - Initial
6/10/04	ANR	Annual Report for reporting interval 11/27/02 – 11/26/03
6/3/04	SAE	IND Safety Report – F/U
5/28/04	PRO	Protocol Amendment: Revised 1572 for Protocol FG-463-21-08
5/26/04	SAE	IND Safety Report – Initial & F/U
5/24/04	PRO	Request for SPA – Clinical Protocol No. 04-0-199 (BAMSG #2-02) – included list of questions
5/11/04	SAE	IND Safety Report – Initial
4/29/04	SAE	IND Safety Report – Initial & F/U
4/28/04	PRO	Protocol Amendment: New Investigators for Protocol 03-7-005, Revised 1572s for Protocol FG-463-21-08 and 01-0-124
4/14/04	SAE	IND Safety Report – Initial & F/U
4/9/04	PRO	Special Protocol Assessment – Protocol 03-0-192 incorporating Amendment #1
4/8/04	SAE	IND Safety Report – Initial & F/U
4/7/04	SAE	IND Safety Report – F/U
4/7/04	PRO	Protocol Amendment: New Protocol 04-0-193, Admin Change #1, Transfer of Obligations, PI/CV for S. Reilly
3/30/04	SAE	IND Safety Report – Initial and F/U
3/18/04	SAE	IND Safety Report – Initial and F/U
3/16/04	PRO	Protocol Amendment: New Investigators for Protocol 03-7-005 and Revised 1572 for Protocol FG-463-21-08

3/10/04	SAE	IND Safety Report – Initial and F/U
2/19/04	SAE	IND Safety Report – F/U
2/5/04	PRO	Protocol Amendment: New Investigator for Protocol FG-463-21-08
1/30/04	SAE	IND Safety Report – F/U
1/20/04	SAE	IND Safety Report – F/U
1/9/04	PRO	Protocol Amendment: New Investigator for Protocol 98-0-047, Revised 1572s for FG-463-21-08, 01-0-124
1/8/04	SAE	IND Safety Report - Initial
12/23/03	SAE	IND Safety Report – Initial and Followup
12/10/03	SAE	Safety Report: Follow-up
12/5/03	PRO	Protocol Amendment: New Investigators for FG-463-21-08 and Revised Forms for same and 01-0-124
12/3/03	SAE	Safety Report: Initial
11/20/03	SAE	Safety Report: Follow-up
11/20/03	SAE	Safety Report: Initial
11/18/03	SAE	Safety Report: Follow-up
11/12/03	PRO	Submission of Micafungin Candidiasis Clinical Protocols (request of the FDA). 98-0-047, 03-7-005, FG-463-21-08, FG-463-21-09.
11/12/03	GC	Request for Pre-NDA Meeting
11/06/03	SAE	IND Safety Report: Initial
11/06/03	PRO	Protocol Amendment: New Investigators and Revised Forms 1572
11/04/03	SAE	IND Safety Report: Initial
10/30/03	SAE	IND Safety Report: Initial
10/28/03	SAE	IND Safety Report - Followup
10/24/03	BD	Briefing Document for New EC NDA (meeting to be held November 24, 2003)
10/23/03	SAE	IND Safety Report - Followup
10/22/03	CLIN	Addendum to Edition 4 of the IB
10/14/03	SAE	IND Safety Report - Initial

10/14/03	SAE	IND Safety Report - Followup
10/14/03	SAE	IND Safety Report - Initial
10/10/03	PRO	Protocol Amendment: Change in protocol 03-7-005 and draft IAP
9/30/03	SAE	IND Safety Report - Initial
9/29/03	PRO	Protocol Amendment: New Investigators and Revised 1572s
9/26/03	SAE	IND Safety Report - Followup
9/26/03	SAE	IND Safety Report - Followup
9/23/03	SAE	IND Safety Report - Initial
9/16/03	SAE	IND Safety Report - Followup
9/12/03	SAE	IND Safety Report - Followup
9/10/03	SAE	IND Safety Report - Initial
9/9/03	SAE	IND Safety Report - Followups
9/9/03	PRO	Protocol Amendment: New Protocols (03-0-175, 03-0-176, 03-0-177, 03-0-178), Admin Change 01 to all 4 protocols, Investigator Information.
9/5/03	SAE	IND Safety Report - Followup
9/3/03	SAE	IND Safety Report - Followup
08/29/03	PRO	Protocol Amendment: New Protocol (FG-463-21-08) and Investigator Information (McNeil)
08/28/03	SAE	IND Safety Report - Initial
08/27/03	SAE	IND Safety Report - Followup
08/21/03	SAE	IND Safety Report - Initial
08/20/03	SAE	IND Safety Report - Followup
08/14/03	SAE	IND Safety Report - Initial
08/12/03	SAE	IND Safety Report - Initial
08/08/03	SAE	IND Safety Report – Initial and Followup
08/07/03	SAE	IND Safety Report - Initial
08/01/03	SAE	IND Safety Report - Initial

07/30/03	SAE	IND Safety Report - Initial
07/24/03	SAE	IND Safety Report - Initial
07/18/03	SAE	IND Safety Report - Followup
07/09/03	SAE	IND Safety Reports: Initial and Followup.
07/03/03	GC	Proposal for New NDA Esophageal Candidiasis (Fujisawa's Proposal to Address Issues Raised in the Division's May 23, 2003 Letter concerning the Minimum 300 subjects receiving FK463 at a dose of 150 mg/day for 10 days).
06/30/03	PRO	Protocol Amendment: New Protocol 03-7-005
06/27/03	SAE	IND Safety Reports - Initial
06/25/03	PRO	Protocol Amendment: New Investigators for Protocol 01-0-124 and Revised Forms FDA 1572 for Protocols 98-0-046 and 01-0-124
6/17/03	SAE	IND Safety Reports - Initial
6/10/03	SAE	IND Safety Reports - Initial and Followup
6/3/03	SAE	IND Safety Reports - Followups
5/21/03	SAE	IND Safety Reports - Followups
5/16/03	PRO	Protocol Amendment: New Investigators and Revised Form FDA 1572 for 046, 124
5/6/03	SAE	IND Safety Reports - Initial
5/5/03	ANR	Annual Report 11/27/01-11/26/02
4/29/03	SAE	IND Safety Reports - Initial and Followup
4/18/03	SAE	IND Safety Reports - Initial and Followup
4/9/03	PRO	Protocol Amendment: New Investigators and Revised Form FDA 1572 for 046, 124, and 125
4/4/03	SAE	IND Safety Reports - Followup
3/26/03	PRO	Protocol Amendment: Amendment 02 to Protocol 01-0-124
3/21/03	SAE	IND Safety Report - Initial
3/14/03	SAE	IND Safety Reports - Followup
3/13/03	SAE	IND Safety Reports-Followup (FAX) Same as Serial 158 Hard-copy)
3/7/03	PRO	Protocol Amendment: New Investigators for 01-0-124

2/27/03	SAE	IND Safety Reports– Initial and Followup
2/18/03	SAE	IND Safety Reports- Initial
2/17/03	PRO	Protocol Amendment: New Investigators and Revised 1572 for 01-0-124
1/3/03	PRO	Protocol Amendment: New Investigator for 01-0-124 & revised 1572 for 98-0-047
12/13/02	PRO	Protocol Amendment: Revised Transfer of Obligations for -124 and -125
12/10/02	SAE	IND Safety Report - Followup
11/25/02	PRO	Protocol Amendment: Revised 1572s for 98-0-046 & 98-0-047
11/5/02	PRO	Protocol Amendment: New Protocol 01-0-125 & Investigator Information for N. Seibel
10/23/02	PRO	Protocol Amendment 1 to Protocol 01-0-124 and Investigator Information
10/3/02	PRO	Protocol Amendment: New Investigators for 98-0-046, 98-0-047 & 99-0-063; Revised 1572s for 98-0-046 & 98-0-047
9/27/02	ANR	Annual Report 11/27/00-11/26/01
9/26/02	SAE	IND Safety Report (15-day)
08/30/02	PRO	Protocol Amendment: Revised 1572s for 98-0-046 & 98-0-047
08/9/02	SAE	IND Safety Report (15-day)
07/31/02	PRO	Pre-emptive White Paper/Protocol 01-0-124 (received acknowledgement letter from FDA dated 10/8/02)
07/26/02	SAE	Follow-up IND Safety Report (15-day)
07/18/02	PRO	Protocol Amendment: Revised 1572s for 98-0-046, 98-0-047, and 99-0-063
06/14/02	SAE	Initial IND Safety Report (15 day)
5/10/02	PRO	Protocol Amendment – Revised 1572s for 98-0-046, 98-0-047, and 98-0-050
4/8/02	GEN	General Correspondence: Response to FDA’s Fax dated 4/3/02 re: FHI’s submission of proposed SAS datasets and data def files (Serial No. 132)
04/03/02	SAE	Follow-up IND Safety Report (15-day)
03/15/02	PRO	Protocol Amendment – New Investigator (Myint) for 98-0-046; Revised 1572s for 98-0-046, 98-0-047, and 99-0-063
03/13/02	SAE	Initial IND Safety Report (15-day)
03/08/02	GEN	Submission of Proposed Archival SAS datasets and data definition files (–050 Study) and proposed SAS datasets (SHAM) for Reviewer Aids

02/28/02	SAE	Follow-up IND Safety Report (15-day)
02/15/02	PRO	Protocol Amendment – New Investigators/CVs and Revised 1572s for 98-0-046, 98-0-047, 98-0-050. Revised 1572s for 01-0-110 and 01-0-111.
02/12/02	SAE	Initial IND Safety Report (15-day)
01/16/02	PRO	Protocol Amendment – New Investigators and Revised 1572s for 98-0-046, 98-0-047
11/09/01	PRO	Protocol Amendment – New Investigators for 98-0-046, 98-0-047, 01-0-110, 01-0-111
11/8/01	GC	Request for Meeting with Stat and Medical Reviewers to discuss proposed SAS datasets and proposed format of data definition files (submitted on CD-ROM)
10/26/01	GC	Summary of micafungin dosing
10/12/01	PRO	Protocol Amendment: New Investigators to 98-0-046 98-0-057, 98-0-050 , 99-0-063 and revised 1572s
9/20/01	PRO	Protocol Amendment: New Protocols (01-0-105, 110, 111) and 1572/CV Information for each protocol
8/29/01	PRO	Protocol Amendment: New Protocol (01-0-104) and 1572/CV for S. Austin
8/28/01	SAE	Follow-up IND Safety Report (15-day)
8/3/01	SAE	Initial IND Safety Report (15-day)
7/13/01	SAE	Initial IND Safety Report (15-day)
7/5/01	GEN	Submission of e-mail correspondence between R. Reed (FHI) and L. Chan (FDA). Communications dated 6/29/01 and 7/03/01
6/29/01	GEN	Submission of 4 Draft Protocol Synopses
6/14/01	PRO/IB	Submission of Revised IB and Amendment 2 to Protocol 99-0-063
6/13/01	SAE	IND F/U Safety Report
6/1/01	PRO	Protocol Amendment-New Investigators and Revised 1572s
5/29/01	SAE	IND Safety Alert Report
5/18/01	SAE	IND Safety Alert Report
4/19/01	BRFDOC	Submission of Pre-NDA Briefing Document
4/6/01	GC	Request for a teleconference
4/3/01	PRO	Protocol Amendment: New and revised 1572s
4/3/01	ANR	Annual Report
2/20/01	PRO	Protocol Amendment: New and revised 1572s

12/27/00	PRO	Protocol Amendment: New and revised 1572s
12/12/00	SAE	15-day Alert Report
11/16/00	PRO	New protocol (99-0-063) and investigator to it.
11/15/00	SAE	15-day Alert Report
11/6/00	PRO	Protocol Amendment: new and revised 1572s
10/27/00	SAE	15-day Alert Report
9/21/00	PRO	Protocol amendment: new and revised 1572s.
8/22/00	SAE	15-day Alert Report
8/4/00	SAE	15-day Alert Report
7/31/00	PRO	Protocol Amendment: New and revised 1572s.
7/7/00	PRO	Protocol Amendment: New Investigators
6/9/00	SAE	15-day Alert Report
6/6/00	AMEND	Information Amendment: Clinical pK study for 98-0-040
5/30/00	PRO	Protocol Amendment: New Investigators
5/9/00	SAE	15-day Alert Report
5/5/00	PRO	Protocol Amendment: New Investigators and revised information to 98-0-046, 98-0-047, and 98-0-050
5/3/00	PRO	Protocol Amendments: Change in protocol 98-0-046 and 98-0-047 (Amendments 4)
04/12/00	PRO	Protocol Amendment: New Investigators and revised 1572s to 98-0-050, 98-0-046 and 98-0-047
03/22/00	PRO	Protocol Amendment: New Investigators
03/07/00	AMEND	Amendment to Annual Report; submitted two stability reports RAR000097 and RAR000098
03/01/00	SAE	15-day Alert Report
03/01/00	ANR	Annual Report 11/27/98 to 11/26/99
02/28/00	PRO	Protocol Amendment: New Investigators to 98-0-050, 98-0-046 and 98-0-047
02/25/00	SAE	15-day Alert Report
02/15/00	PRO	Protocol Amendment: New Investigators to 98-0-050 and revised 1572s
02/11/00	SAE	15-day Alert Report

02/10/00	SAE	15 day alert report
02/02/00	SAE	Follow-up safety report
01/26/00	AMEND	Information Amendment: Clinical pK study L1999000044 for Protocol 97-0-041
01/20/00	SAE	Initial safety report
01/19/00	PRO	Protocol Amendment: New Investigators to 98-0-050
01/05/00	PAE	15-day Alert report
12/20/99	PRO	Protocol Amendment: New investigators to 98-0-050
12/15/99	AMEND	CMC Amendment to the drug product
12/9/99	SAE	IND Safety report submitted to FDA for one initial report
12/9/99	PRO	Protocol Amendment: New Investigators to 98-0-046, 98-0-047 and 98-0-050
12/8/99	AMEND	Information Amendment: Clinical. Final report for Protocol 97-0-041 entitled "A phase I/II study to determine the maximum tolerated dose and pharmacokinetics of FK463 in combination with fluconazole for prophylaxis of fungal infections in adult patients undergoing a bone marrow or peripheral stem cell transplant."
12/3/99	SAE	15-day Follow-up Safety Report
11/30/99	LTR	General Correspondence : Request to FDA to review Drug Master File
11/10/99	PRO	Protocol Amendment: New investigators to 98-0-046 and 98-0-047
11/04/99	SAE	Two IND initial safety reports submitted to FDA
11/03/99	PRO	Protocol Amendment: Change in Protocol 98-0-043: to increase dose to be evaluated to include 3.0 and 4.0 mg/kg/day and administrative changes
10/28/99	PRO	Protocol Amendment: New Protocol (98-0-050), Amendment 01 and first investigator
10/26/99	LTR	Response to FDA EOP2 Meeting minutes from 9/10 meeting
10/22/99	SAE	1 initial report
10/19/99	PRO	Protocol Amendment: New Investigators to 97-0-047
10/05/99	SAE	IND Safety Report: 1 follow-up safety report submitted to FDA
09/14/99	PRO	Protocol Amendment: New Investigators to 98-0-043, 98-0-046 and 98-0-047
09/17/99	SAE	IND Safety Reports – 2 initial reports submitted to FDA
09/02/99	LTR	Additional Information for EOP2 Meeting: Revision to question

		#5
08/25/99	LTR	End of Phase 2 Meeting Agenda and List of Attendees for FHI
08/24/99	SAE	IND Safety Report – 1 follow up report
08/11/99	PRO	Protocol Amendment: New Investigators.
08/05/99	LTR	End of phase 2 Briefing Document
08/05/99	SAE	15 day /alert report
07/20/99	AMEND	Information Amendment: Pharm./Tox Report GLR980160
07/13/99	PRO	Protocol Amendment: New Investigators to: 98-0-046 and 98-0-47
07/01/99	PRO	Protocol Amendment: New Investigators New investigators to 98-0-046 and 98-0-047.
06/30/99	AMEND	Information Amendment: Pharm./Tox. Reports CRD980156, CRD980083, GLR980003, CRD980043 and GLR980004.
06/29/99	SAE	IND Safety Report – follow-up report submitted to FDA
06/23/99	SAE	IND Safety Reports – follow-up reports submitted to FDA
06/09/99	PRO	Protocol Amendment: Change in Protocol Change in protocol 98-0-042 (to increase dose to 2.0 mg/kg/day, the rationale for doing so and administrative changes.
06/09/99	PRO	Protocol Amendment: Change in Protocol Change in European protocols FG463-21-01 and FG463-21-02
06/09/99	PRO	Protocol Amendment: New Investigators New investigators added to Protocol 98-0-046 and 98-0-047
05/20/99	SAE	IND Safety Report
05/06/99	PRO	Protocol Amendment: New Investigators New investigators added to Protocol 98-0-046 and 98-0-047.
05/05/99	SAE	IND Safety Report – initial report submitted to FDA
04/30/99	PRO	Protocol Amendment: Change in Protocols Change in Protocol 98-0-046, increase initial dose to 75 mg/day, etc. To 98-0-047, dose adjustments to 150 mg/day, etc.
04/14/99	PRO	Protocol Amendment: New Investigators Protocol 98-0-046 and Protocol 98-0-047

04/02/99	PRO	Protocol Amendment: New Investigators New Investigators added to protocol 98-0-047
03/30/99	AMEND	Information Amendment: Pharmacology/ Toxicology: FK463 and an amendment to the final report, 4 week IV toxicity study of FR179463 in rats with recovery study (GLR970116); a copy of report GLR980020 re: Single dose IV toxicity study of photo-degraded FK463 product in rats.
03/26/99	LTR	Response to FDA fax dated 1/19/99 Response to the FDA fax of 1/1/9/99 re: 4 attachments, agency's comments and FHI responses, QC sample data for studies CLR980023 and CLR980025; report titled PK of FK463 in Phase I repeated dose study; survival data that support ED50 values in reports CRR980116 and CRR980117.
03/24/99	PRO	Protocol Amendment: Change in Protocol Letter sent to FDA on 3/24/99 re: Change in Protocols 98-0-046 and 98-0-047 for exclusion of de novo patients at Canadian sites.
03/23/99	PRO	Protocol Amendment: New Investigator 98-0-046 and 98-0-047 .
03/16/99	LTR	FHI Meeting Minutes Minutes of 2/5/99 teleconference with FDA
03/16/99	PRO	Protocol Amendment: New Investigator Protocol 98-0-046 and 98-0-047
03/15/99	ANR	Annual Report Reporting interval 03/26/98 to 11/26/98
03/11/99	PRO	Protocol Amendment: New Investigator Protocol 98-0-043
03/03/99	SAE	IND Safety Report One initial safety report submitted on 3/3/99
03/02/99	PRO	Protocol Amendment: New Investigators Protocols 98-0-046 and 98-0-047;
02/23/99	PRO	Protocol Amendment: New Protocols, Protocol Amendment and New Investigator Protocol 98-0-047 "An Open-Label, Non-comparative Study of FK463 in the Treatment of Candidemia or Invasive Candidiasis", Amendment 01 to adjust the initial dose, to update the reconstitution procedures and to include regulatory agencies in addition to FDA; Protocol FG463-21-02 (European of same name as 98-0-047); and new investigator
02/23/99	GC	Response to FDA Letter FHI response to 12/4/98 letter regarding Serial numbers 014 and 015

02/12/99	PRO	Protocol Amendment: Change in protocol Amendment #4 Increase dose to be evaluated to 200 mg (protocol 97-0-041)
02/03/99	PRO	Protocol Amendment: New Protocol, amendment and New Investigator: Protocols 98-0-046 (US) and FG463-21-01 (European) "An Open-Label Non-Comparative Study of FK463 for the Treatment of Invasive Aspergillosis:, Amendment 01 to 98-0-046 and New Investigator.
01/20/99	GC	General Correspondence End-of-Phase 2 Meeting Request for mid-April
01/07/99	PRO	Protocol Amendment: New Investigator Protocol 97-0-041, Dr. Pranatharthi Chandrasekar
12/28/98	PRO	Protocol Amendment: New DRAFT Protocol Protocol 98-0-050 "A Phase III Randomized Double Blind Comparative Trial of FK463 versus Fluconazole for Prophylaxis of Fungal Infections in Patients Undergoing Bone Marrow or Peripheral Stem Cell Transplantation
12/07/98	PRO	Protocol Amendment: New Investigator N. Chao to 97-0-041
11/20/98	PRO	Protocol Amendment: New Investigator P. Flynn to 98-0-043
11/19/98	AMEND	Information Amendment: CMC Labeling change to clinical trial labels
11/13/98	PRO	Protocol Amendment: New Investigator T. Walsh to Protocol 98-0-043
11/4/98	PRO	Protocol Amendment: Change in protocol Change to 97-0-041; Amendment 03 increase dose from 100 mg/day to 150 mg/day
10/28/98	PRO	Protocol Amendment: New Protocol 98-0-043, Amendment 01 to this protocol and new investigator (Nita Seibel).
10/26/98	SAE	IND Safety Report
10/8/98	PRO	Protocol Amendment: New Investigators S. Devine and D. Simpson to 97-0-041
10/6/98	AMEND	Information Amendment: Clinical 2 non-IND clinical trial reports CLR980023 (R98-0224-463-C1-E) Phase 1 Single-Dose Intravenous Administration Study of FK463; CLR980025 (R98-0223-463-C1-E) Phase 1 Repeated Dose Intravenous Administration Study of FK463.
10/6/98	AMEND	Information Amendment - Pharm/Tox Three Non-clinical Reports: CRR980115 (R98-0200-463-P1-E) Prophylactic effect of FK463 against Pneumocystis carinii infection in mice. CRR980116 (R98-0201-463-P1-E) Efficacy of intravenous injection of

		FK463 in mouse models of pulmonary candidiasis and aspergillosis. CRR980117 (R98-0202-463-P1-E) Efficacy of intravenous injection of FK463 in mouse models of disseminated candidiasis and aspergillosis
8/4/98	PRO	Protocol Amendment: Change in Protocol 97-0-041 Amendment 2: Enrollment of allogeneic bone marrow or peripheral stem cell transplant patients.
7/6/98	AMEND	Information Amendment Response to May 1 letter of request and recommendations
6/15/98	PRO	Protocol Amendment – New Investigator New 1572s to 97-0-041 P. Cagnoni and J. Hiemenz
6/8/98	PRO	Protocol Amendment Change in Protocol 97-0-040 and an addendum to the Informed Consent Form.
6/3/98	LTR	Change in Corporate Name to FHI
5/14/98	PRO	Protocol Amendment – New Investigator To protocol 97-0-040 J. Kisicki
5/15/98	AMEND	Information Amendment - Pharm./Tox. 6 reports for as pharmacological and metabolic support: CRD980078, CRD980079, CRD980084, GLR980047, GLR980049 and GLR980048
4/13/98	PRO	Protocol Amendment Submission of requested information - 14-C Study, Informed Consent and amount of radiation per patient. (4/21/98 - This was returned by FDA as it was sent to the Fishers Lane address via Fed. Ex. By direction of A. Chun. Fishers Lane does not accept Fed. Ex. Packages. Was resubmitted to the Division via Fed. Ex
4/1/98	PRO	Protocol Amendment Revised protocol 97-0-041 to clarify the collection and processing of blood samples for pharmacokinetics analysis
02/26/98	IND	Original IND

B. The NDA.

A list of significant activities undertaken by the marketing applicant during the review of NDA 21-754 and the significant dates applicable thereto is provided in Table 2 below.

The following abbreviations are used in Table 2:

AMEND	Amendment to NDA or sNDA
ANR	Annual Report
FIELD	District Office Copy of CMC Supplement
GC	General Correspondence (e.g. Cross Reference Letters, Briefing Documents)
PHAS4	Phase 4 Commitments
PSUR	Periodic Safety Update Report
SUPL	Supplement

Table 2.

DATE	TYPE	DESCRIPTION
4/15/05A	GC	Forms FDA 3542 – Patent Information for Mycamine desk copies sent to Christina Chi (faxed to division on 4/15/2005)
4/15/05	SUPL	Changes Being Effected – Supplement (CBE-30 Alternative-Closure Configuration)
4/4/05	GC	Acceptance Letter
3/31/05	GC/LABEL	Submission of FPL (FHI) as required in approval letter (submitted electronically to both NDA 21-506 and 21-754). This represents the last submission to NDA 21-754 – all future submissions will be submitted to NDA 21-506 only
	GC	Transfer Letter

DATE	TYPE	DESCRIPTION
3/10/05A	GC	Submission of proposed press release for review and comment (including current draft PI dated 3/7/05). Note document was also submitted to DDMAC for their review and comment as well.
3/10/05	AMEND	Submitted latest versions of draft labeling - PI dated 3/7/05 and Vial/Carton dated 3/10/05 as submitted via e-mail (Submitted electronically to both NDA 21-754 and 21-506)
3/9/05	AMEND	Submitted latest versions of draft labeling - PI dated 3/7/05 and Vial/Carton dated 2/24/05 as submitted via e-mail (Submitted electronically to both NDA 21-754 and 21-506)
3/8/05	AMEND	Response to 3/4/05 e-mail request – Prophylaxis Efficacy Results (Submitted electronically to both NDA 21-754 and 21-506)
2/22/05	AMEND	Response to FDA Request for Information dated 2/21/05 (item-by-item response to comments raised by Microbiologist in a 3/23/03 e-mail). Also included in submission were the draft carton and container labeling for Mycamine (50 mg strength), which incorporated comments from the Division during 2/18/05 discussion.
2/18/05	AMEND	Response to FDA Request for Information dated 2/17/05 regarding reevaluation of Serious Hepatic Adverse Events and Hepatic Laboratory Changes.
2/11/05	AMEND	Response to Info Request Dated 2/4/05 (Division re-defined request on 2/10) and Response to Item 2 in 2/7/05 e-mail request. Submitted electronically to both NDA 21-754 and 21-506.

DATE	TYPE	DESCRIPTION
2/4/05A	AMEND	Response to FDA E-Mail request dated 2/3/05 (info re: Study -050). Complete response with exception requested SAS dataset
2/4/05	AMEND	Response to FDA E-Mail request dated 2/2/05 (clinical). Also included patient narratives requested in 2/1/05 request. Submitted electronically to both NDA 21-754 and 21-506
2/3/05	AMEND	Submission of FDA Form 3542a (Patent Certification) for new patent for Mycamine and statement to FDA that Fujisawa does NOT wish to pursue commercialization of the 25 mg product formulation at this time. Submitted electronically to both NDA 21-754 and 21-506
2/2/05	AMEND	Response to FDA E-mail request dated 2/1/05 – Response submitted electronically to both NDA 21-754 and 21-506
1/27/05	AMEND	Response to FDA Request for Information Dated 1/26/05 (E-mail from Dr. Singer). Also included was final compatibility report requested on 1/14/05, official submission of Medwatch forms requested 1/24/05 and proposed vial/carton labeling requested 1/25/05
1/26/05	AMEND	Final Response to FDA Info Request Dated 12/14/04 (Clinical) – completes the response to this request (submitted to both NDA 21-754 and 21-506)
1/10/05B	AMEND	Response to FDA Request for Information Dated 1/6/05 from Biostats Reviewer – Datasets submitted in SAS format (as requested) to NDA 21-754
1/10/05A	AMEND	Response to FDA Request for Information Dated 1/5/05 from Clinical Reviewer – Response submitted in full (electronically) to both NDA 21-754 and 21-506
1/10/05	AMEND	Response to FDA Request for Information Dated 1/3/05 from Clinical Reviewer – Response submitted in full (electronically) to both NDA 21-754 and 21-506
1/6/05	AMEND	Response to FDA Request for Information dated 12/22/05 from Clinical Reviewer (additional safety information and datasets for patients across several studies). Sent to both NDA 21-506 and 21-754
12/23/04	AMEND	Partial response to FDA Request for Information Dated 12/21/04 (Fax from Clinical Reviewer) – response submitted in full (electronically) to both NDA 21-506 and 21-754 (submission of requested datasets were NOT included)
12/22/04	AMEND	Response to FDA Request for Information Dated 12/14/04 (Fax from Clinical Reviewer) – response submitted in full (electronically) to both NDA 21-506 and 21-754. It was noted that several items would be submitted under separate cover when available.
12/1/04	AMEND	Response to FDA Request for Information Dated 10/27/04 from Clinical Reviewer (Item #2 – Expert Hematologist

DATE	TYPE	DESCRIPTION
		Panel Review)
11/18/04	AMEND	Response to FDA Request for Information Dated 11/15/04 from Clinical Reviewer
11/12/04	AMEND	Response to FDA Request for Information Dated 10/27/04 from Clinical Reviewer (except for Item #2)
10/20/04	AMEND	Response to FDA Request for Information Dated 10/19/04 from Chemistry & Microbiology Reviewers
10/1/04	GC	Submitted copy of IND Serial submission (Serial No. 262) submitted to provide for cross reference information to NDAs 21-506 and 21-754 for drug product
9/22/04	AMEND	Response to FDA's September 10, 2004 Request for Additional Clinical Information (full response).
8/24/04	AMEND	Submission of Section 9: 120-day Safety Update and Updated Labeling (package insert) – FSR for 03-7-005 and FG14 were also included
5/11/04	AMEND	Updated Patent Certification/Information on Forms 3542a (3 patents were submitted) submitted to NDA
4/23/04	ORIGINAL	Submission of Original NDA (electronic DLT Tape submitted to FDA) – no hard copies provided

XII. Statement that in the Opinion of the Applicant the Patent is Eligible for Extension of Patent Term and Statement as to the Length of extension and how the Length was Determined (37 C.F.R. § 1.740(a)(12)).

In the opinion of the applicant, the '634 patent is eligible for extension. In the opinion of the applicant, the '634 patent is entitled to an extension of 476 days, *i.e.*, the '634 patent is entitled to an extended expiration date of March 16, 2013. The extension of 476 days was calculated by the method described in 37 C.F.R. § 1.775.

The number of days by which the '634 patent should be extended was calculated as follows:

- A. The number of days in the regulatory review period was calculated according to 37 C.F.R. § 1.775(c) and reduced as appropriate pursuant to 37 C.F.R. §§ 1.775(d)(1)-(6).
- B. The number of days in the regulatory review was calculated by adding the number of days pursuant to (37 C.F.R. § 1.775(c)(1)) and the number of days pursuant to (37 C.F.R. § 1.775(c)(2)).
- C. The number of days pursuant to (37 C.F.R. § 1.775(c)(1)) was calculated as the number of days in the period starting from the date on which IND 55,322 was amended to include the protocol on which NDA 21-754 was based, June 30, 2003, and ending on the date NDA 21-754 was submitted, April 23, 2004, and determined to be 298 days.
- D. The number of days pursuant to (37 C.F.R. § 1.775(c)(2)) was calculated as the number of days in the period starting from the date NDA 21-754 was submitted, April 23, 2004, and ending on the date of approval of NDA 21-754, March 16, 2005, and determined to be 327 days.
- E. Thus, the number of days in the regulatory review was calculated by adding 298 days to 327 days and determined to be 625 days

- F. The number of days to be subtracted from the regulatory review period under 37 C.F.R. § 1.775(d)(1) was calculated by determining the number of days pursuant to each of C.F.R. §§ 1.775(d)(1)(i)-(iii).
- G. Since the regulatory review period began on February 26, 1998, and since the '634 patent issued on December 27, 1994, 0 days in the regulatory review period were on or before the date on which the '634 patent issued. Thus, the number of days pursuant to C.F.R. § 1.775(d)(1)(i) was determined to be 0.
- H. As set forth above, applicants have acted with due diligence during the entire regulatory review period. Thus, the number of days pursuant to C.F.R. § 1.775(d)(1)(ii) was determined to be 0.
- I. The number of days pursuant to C.F.R. § 1.775(d)(1)(iii) was calculated by dividing the number of days pursuant to 37 C.F.R. § 1.775(c)(1), 298 days, in half and determined to be 149 days.
- J. The number of days pursuant to C.F.R. § 1.775(d)(1) was calculated by subtracting the number of days calculated pursuant to C.F.R. § 1.775(d)(1)(iii), 149 days, from the number of days calculated pursuant to C.F.R. § 1.775(c), 625 days, and determined to be 476 days.
- K. The term of the '634 patent as extended as determined by C.F.R. § 1.775(d)(2) was calculated by adding the number of days calculated pursuant to C.F.R. § 1.775(d)(1), 476 days, to the original term of the '634 patent (current expiration date December 27, 2011) and determined to be March 16, 2013.
- L. The term of the '634 patent as extended as determined by C.F.R. § 1.775(d)(3) was calculated by adding 14 years to the date of approval, March 16, 2005, and determined to be March 16, 2019.

- M. The term of the '634 patent as extended as determined by C.F.R. § 1.775(d)(4) was calculated by comparing the dates calculated pursuant to C.F.R. § 1.775(d)(3) and C.F.R. § 1.775(d)(4) and selecting the earlier date and determined to be March 16, 2013.
- N. The term of the '634 patent as extended as determined by C.F.R. § 1.775(d)(5)(i) was calculated by adding five years to the original expiration date of the '634 patent (December 27, 2011) and determined to be December 27, 2016.
- O. The term of the '634 patent as extended as determined by C.F.R. § 1.775(d)(5)(ii) was calculated by selecting the earlier date pursuant to C.F.R. § 1.775(d)(4) and C.F.R. § 1.775(d)(5)(i) and determined to be March 16, 2013.
- P. Since the '634 patent issued after September 24, 1984, no adjustment was made under C.F.R. § 1.775(d)(6).

XIII. Statement that Applicant Acknowledges a Duty to Disclose any Information which is Material to the Determination of the Entitlement to the Extension Sought (37 C.F.R. §§ 1.740(a)(13) and 1.765).

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.

It is understood that the duty of candor and good faith toward the Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture rests on the patent owner or its agent, on each attorney or agent who represents the patent owner and on every other individual who is substantively involved on behalf of the patent owner in a patent term extension proceeding. All such individuals who are aware, or become aware, of material information adverse to a determination of entitlement to the extension sought, which has not been previously made of record in the patent term extension proceeding must bring such information to the attention of the Office or the Secretary, as appropriate, as soon as it is practical to do so after the individual becomes aware of the information. Information is material where there is a substantial likelihood that the Office or the Secretary would consider it important in determinations to be made in the patent term extension proceeding. 37 C.F.R. § 1.765(a).

It is also understood that disclosures pursuant to this section must be accompanied by a copy of each written document which is being disclosed. The disclosure must be made to the Office or the Secretary, as appropriate, unless the disclosure is material to determinations to be made by both the Office and the Secretary, in which case duplicate copies, certified as such, must be filed in the Office and with the Secretary. Disclosures pursuant to this section may be made to the Office or the Secretary, as appropriate, through an attorney or agent having responsibility on behalf of the patent owner or its agent for the patent term extension

proceeding or through a patent owner acting on his or her own behalf. Disclosure to such an attorney, agent or patent owner shall satisfy the duty of any other individual. Such an attorney, agent or patent owner has no duty to transmit information which is not material to the determination of entitlement to the extension sought. 37 C.F.R. § 1.765(b).

It is further understood that no patent will be determined eligible for extension and no extension will be issued if it is determined that fraud on the Office or the Secretary was practiced or attempted or the duty of disclosure was violated through bad faith or gross negligence in connection with the patent term extension proceeding. If it is established by clear and convincing evidence that any fraud was practiced or attempted on the Office or the Secretary in connection with the patent term extension proceeding or that there was any violation of the duty of disclosure through bad faith or gross negligence in connection with the patent term extension proceeding, a final determination will be made that the patent is not eligible for extension. 37 C.F.R. § 1.765(c).

In compliance of the duty of disclosure, it is acknowledged that two additional applications for term extension for two additional patents based on the same regulatory review are also being filed. Specifically:

1. An application for term extension based on the regulatory review of Mycamine under NDA 21-506 was filed for U.S. Patent No. 6,107,458 (attorney docket no. 271987US0SD) on May 12, 2005;
2. An application for term extension based on the regulatory review of Mycamine under NDA 21-506 is also being filed for U.S. Patent No. 5,376,634 (attorney docket no. 270677US0SD);
3. An application for term extension based on the regulatory review of Mycamine under NDA 21-506 is also being filed for U.S. Patent No. 6,265,536 (attorney docket no. 271988US0SD);

4. An application for term extension based on the regulatory review of Mycamine under NDA 21-754 is also being filed for U.S. Patent No. 6,107,458 (attorney docket no. 272499US0SD); and

5. An application for term extension based on the regulatory review of Mycamine under NDA 21-754 is also being filed for U.S. Patent No. 6,265,536 (attorney docket no. 272500US0SD).

XIV. Prescribed Fee (37 C.F.R. § 1.740(a)(14)).

The fee as prescribed in 37 C.F.R. § 1.20(j)(2) is attached hereto in the form of a credit card form for the amount of \$1120.00.

XV. Correspondence Information (37 C.F.R. § 1.740(a)(15)).

All inquiries and correspondence should be sent to:

Customer Number: 22850

Which corresponds to:

Oblon, Spivak, McClelland, Maier & Neustadt, P.C.
1940 Duke Street
Alexandria, VA 22314

Telephone: 703-413-3000
Facsimile: 703-413-2220

XVI. Power of Attorney (37 C.F.R. §§ 1.730(a)(2) and (d)).

As can be seen from the face of the '634 patent itself, the '634 patent was originally assigned to Fujisawa Pharmaceutical Co., Ltd., of Osaka, Japan ("Fujisawa"), and Oblon, Spivak, McClelland, Maier & Neustadt is the attorney of record. Effective April 1, 2005,

Fujiswa became part of Astellas Pharma Inc., of Tokyo, Japan. A formal notice of the change of name has already been filed in the USPTO, and copies of the papers filed are attached hereto as Exhibit D. Oblon, Spivak, McClelland, Maier & Neustadt, P.C., remains the attorney of record for the '634 patent.

In view of the foregoing, Applicants submit that the present patent is entitled to the requested extension of patent term, and early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Stephen G. Baxter
Attorney of Record
Registration No. 32,884

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22850

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(OSMMN 08/03)