UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO.	: 8,598,149 B2
APPLICATION NO.	: 12/199114
DATED	: December 3, 2013
INVENTOR(S)	: Belanoff et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page:

The first or sole Notice should read --

Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 990 days.

Signed and Sealed this
Thirtieth Day of December, 2014

Michelle K. Lee

Michelle K. Lee
Deputy Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

KILPATRICK TOWNSEND & STOCKTON
LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO CA 94111-3834

In re Patent No. 8,598,149 :
Joseph K. Belanoff :
Issue Date: 12/03/2013 : ON REDETERMINATION OF
Application No. 12/199114 : PATENT TERM ADJUSTMENT
Filing or 371(c) Date: 08/27/2008 :
Atty. Docket No.: :
85178-756824(004110US) :

This is a response to applicants "REQUEST FOR RECONSIDERATION OF PATENT TERM ADJUSTMENT UNDER 37 CFR 1.705(d)", requesting that the Office adjust the PTA in view of *Exelixis v. Kappos*. The Office has re-determined the PTA to be 990 days.

This redetermination of patent term adjustment is not the Director's decision on the applicant's request for reconsideration within the meaning of 35 U.S.C. 154(b)(4) that triggers a 180-day period for applicant disagreeing with the Office redetermination to commence a civil action in the District Court for the Eastern District of Virginia.

Relevant Procedural History

On December 3, 2013, the above-identified application matured into U.S. Patent No. 8,598,149. The patent issued with a PTA of 866 days. The present request for redetermination of the patent term adjustment was timely filed within two months of the issue date of the patent. Patentee requests recalculation of the Patent Term Adjustment in view of *Exelixis v. Kappos*.

Decision

Patents' arguments have been carefully considered. Upon review, the USPTO finds that patentee is entitled to **990** days of PTA. The Office has revisited the amount of "B" delay under 35 U.S.C. § 154(b)(1)(B) and the amount of overlapping days under 35 U.S.C. § 154(b)(2)(A) pursuant to the Federal Circuit's decision in *Novartis AG v. Lee*, 740 F.3d 593 (Fed. Cir. 2014). Patentee and the Office are in agreement as to the amount of "applicant delay" under 35 U.S.C. § 154(b)(2)(C) and 1.704(b); however, patentee and the Office continue to disagree regarding the amount of "A" delay under 35 U.S.C. § 154(b)(1)(A) and 37 CFR 1.702(a).

As for the amount of "B" delay, the Federal Circuit reviewed the statutory interpretation of 35 U.S.C. § 154(b)(1)(B)(i) and issued a decision regarding the effects of a Request for Continued Examination ("RCE") on "B" delay in *Novartis AG v. Lee*, 740 F.3d 593 (Fed. Cir. 2014). In *Novartis*, the Federal Circuit agreed with the Office that "no ["B" delay] adjustment time is available for any time in continued examination, even if the continued examination was initiated more than three calendar years after the application's filing." *Novartis*, 740 F.3d at 601. However, the *Novartis* court found that if the Office issues a notice of allowance after an RCE is filed, the period after the notice of allowance should not be excluded from the "B" delay period but should be counted as "B" delay. *Id.* at 602. The Federal Circuit issued its mandate in the *Novartis* appeal on March 10, 2014.

Pursuant to the Novartis decision, the USPTO has determined that the patentee is entitled to 519 days of "B" delay. In this case, it was previously determined that the application filing date is August 27, 2008, and the issue date of the patent is December 3, 2013. Accordingly, the total pendency of the application was 1925 days. Thus, the application was pending for 1925 – 1096 = 829 days beyond the three-year anniversary of the application's filing date. This three-year pendency period began on August 28, 2011, and ended on December 3, 2013. During this time, the applicant filed one RCE on September 27, 2012, and the Office mailed a Notice of Allowance on August 2, 2013, for a total of 310 days, which is excluded from the amount of "B" delay. Accordingly, in light of the RCE, the amount of "B" delay amounted to 519 days (1925 – 1096 - 310 = 519).

Regarding patentee delay, Office records confirm that the due date for the reply to the final Office action mailed April 4, 2012, was July 4, 2012, a Federal Holiday, and the due date for the reply was therefore July 5, 2012. Applicant filed a reply to the Office action on September 27, 2012. Accordingly, a period of reduction of 84 days, not 85 days, is properly entered for the reply. *Id.*

The Office finds that there are no overlapping days. In *Wyeth v. Kappos*, 591 F.3d 1364 (Fed. Cir. 2010), the United States Court of Appeals for the Federal Circuit determined that overlap occurs when the calendar days overlap between the "A" and "B" delays. Under this interpretation, the Office finds that no days of "A" delay overlap with the B periods iterated above.

Overall PTA Calculation

Formula:

"A" delay + "B" delay + "C" delay - Overlap - applicant delay = X

USPTO's Calculation:

637 + 519 + 0 – 0 – 166 = 990

Patentee's Calculation

637 + 519 + 0 – 0 – 167 = 989

Conclusion

Patentee is entitled to a PTA of nine hundred ninety (990) days. Using the formula "A" delay + "B" delay + "C" delay - overlap - applicant delay = X, the amount of PTA is calculated as following: 637 + 519 + 0 – 0 – 166 = 990 days.

The Office acknowledges submission of the $200.00 fee set forth in 37 CFR 1.18(e). No additional fees are required.

Patentee is given TWO (2) MONTHS from the mail date of this decision to respond to this redetermination. Extensions of time under 37 CFR 1.136(a) are permitted. This is not final agency action within the meaning of 5 U.S.C. § 704.

The application is being forwarded to the Certificate of Corrections Branch for issuance of a certificate of correction. The Office will issue a certificate of correction indicating that the term of the above-identified patent is extended or adjusted by **nine hundred ninety (990) days**.

Telephone inquiries specific to this matter should be directed to the undersigned at (571) 272-3232.

/DW/

Derek Woods
Attorney Advisor
Office of Petitions

Enclosure: Adjusted PTA calculation
Draft Certificate of Correction

PTA/PTE Information

Application Number*: 12199114 Search Explanation of PTA Calculation Explanation of PTE Calculation

PTA Calculations for Application: 12199114

Application Filing Date	08/27/2008	OverLapping Days Between (A and B) or (A and C)	0
Issue Date of Patent	12/03/2013	Non-Overlapping USPTO Delays:	1033
A Delays	637	PTO Manual Adjustment	124
B Delays	396	Applicant Delay (APPL)	167
C Delays	0	Total PTA (days)	990

* - Sorted Column

File Contents History

Action Number	Action Recorded Date	Action Due Date	Action Code	Action Description	Duration PTO	Duration APPL	Parent Action Number
83	09/02/2014		P028	Adjustment of PTA Calculation by PTO	124	0	
83	09/02/2014		P028	Adjustment of PTA Calculation by PTO	124	0	
77	12/03/2013		PTAC	Patent Issue Date Used in PTA Calculation		0	
76	11/01/2013		EFDC	Export to Final Data Capture		0	
75	10/31/2013		D1935	Dispatch to FDC		0	
74	10/31/2013		PILS	Application Is Considered Ready for Issue		0	
73	10/28/2013		N084	Issue Fee Payment Verified		0	
72	10/28/2013		IFEE	Issue Fee Payment Received		0	
71	08/31/2013		FIDC	Finished Initial Data Capture		0	
67	08/02/2013		MN/=.	Mail Notice of Allowance		0	
66	07/29/2013		OAR	Office Action Review		0	
65	07/29/2013		OAR	Office Action Review		0	
61	07/29/2013		IREV	Issue Revision Completed		0	
60	07/29/2013		DVER	Document Verification		0	
59	07/29/2013		N/=.	Notice of Allowance Data Verification Completed		0	
58	07/29/2013		DOCK	Case Docketed to Examiner in GAU		0	
57	07/29/2013		ACRE	Allowed Case Returned to the Examiner for Clerical Processing		0	
56	07/29/2013		OAR	Office Action Review		0	
55	07/29/2013		OAR	Office Action Review		0	
54	07/23/2013		EX.R	Reasons for Allowance		0	
53	07/23/2013		CNTA	Allowability Notice		0	
52	07/19/2013		FWDX	Date Forwarded to Examiner		0	
51	07/18/2013		A.QU	Response after Ex Parte Quayle Action		0	
50	05/24/2013		ELC_RVW	Electronic Review		0	
49	05/24/2013		EML_NTF	Email Notification		0	
48	05/24/2013	01/27/2013	MCTEQ	Mail Ex Parte Quayle Action (PTOL - 326)	117	43	
47	05/21/2013		OAR	Office Action Review		0	
46	05/20/2013		CTEQ	Quayle action		0	
45	10/01/2012		FWDX	Date Forwarded to Examiner		0	
42	10/01/2012		ABN9	Disposal for a RCE / CPA / R129		0	
44	09/27/2012		AMSB	Amendment Submitted/Entered with Filing of CPA/RCE		0	
43	09/27/2012	07/04/2012	RCEX	Request for Continued Examination (RCE)		85 37	
41	09/27/2012		XT/G	Request for Extension of Time - Granted		0	
40	09/27/2012		BRCE	Workflow - Request for RCE - Begin		0	
77.5	09/26/2012	08/27/2011	PTA36M	PTA 36 Months	396	0.5	
39	04/04/2012		ELC_RVW	Electronic Review		0	
38	04/04/2012		EML_NTF	Email Notification		0	
37	04/04/2012		MCTFR	Mail Final Rejection (PTOL - 326)		0	
36	03/28/2012		OAR	Office Action Review		0	
35	03/27/2012		CTFR	Final Rejection		0	
33	01/26/2012		FWDX	Date Forwarded to Examiner		0	
32	01/24/2012	11/03/2011	A...	Response after Non-Final Action		82 28	
31	01/24/2012		XT/G	Request for Extension of Time - Granted		0	
30	08/03/2011		ELC_RVW	Electronic Review		0	
29	08/03/2011		EML_NTF	Email Notification		0	
28	08/03/2011		MCTNF	Mail Non-Final Rejection		0	
27	07/29/2011		OAR	Office Action Review		0	
26	07/28/2011		CTNF	Non-Final Rejection		0	
24	05/24/2011		FWDX	Date Forwarded to Examiner		0	
23	05/18/2011		ELC.	Response to Election / Restriction Filed		0	
22	05/18/2011		XT/G	Request for Extension of Time - Granted		0	
21	03/31/2011		ELC_RVW	Electronic Review		0	
20	03/31/2011		EML_NTF	Email Notification		0	
19	03/31/2011	10/27/2009	MCTRS	Mail Restriction Requirement	520	0.5	
18	03/28/2011		OAR	Office Action Review		0	

17	03/28/2011	CTRS	Restriction/Election Requirement	0
16	12/05/2009	DOCK	Case Docketed to Examiner in GAU	0
15	10/06/2009	DOCK	Case Docketed to Examiner in GAU	0
14	08/18/2009	DOCK	Case Docketed to Examiner in GAU	0
13	03/05/2009	PG-ISSUE	PG-Pub Issue Notification	0
12	01/31/2009	TSSCOMP	IFW TSS Processing by Tech Center Complete	0
11	12/04/2008	OIPE	Application Dispatched from OIPE	0
10	11/17/2008	PA..	Change in Power of Attorney (May Include Associate POA)	0
9	11/17/2008	PGPC	Sent to Classification Contractor	0
8	11/17/2008	FLRCPT.U	Filing Receipt - Updated	0
7	11/07/2008	ADDFLFEE	Additional Application Filing Fees	0
6	11/07/2008	OATHDECL	A statement by one or more inventors satisfying the requirement under 35 USC 115, Oath of the Applic	0
5	09/11/2008	INCD	Notice Mailed--Application Incomplete--Filing Date Assigned	0
4	09/11/2008	FLRCPT.O	Filing Receipt	0
3	08/27/2008	L194	Cleared by OIPE CSR	0
2	08/27/2008	SCAN	IFW Scan & PACR Auto Security Review	0
1	08/27/2008	IEXX	Initial Exam Team nn	0
0.5	08/27/2008	EFILE	Filing date	0

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UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT : 8,598,149 B2

DATED : **December 3, 2013**

INVENTOR(S) : Belanoff et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the cover page,

[*] Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 USC 154(b) by 866 days.

Delete the phrase "by 866 days" and insert – by 990 days--

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on 2-3-2014.

KILPATRICK TOWNSEND & STOCKTON LLP

By: Jeffrey Lo

PATENT
Docket No.: 85178-756824 (004110US)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Belanoff

Patent No.: 8,598,149

Issued: December 3, 2013

Application No. 12/199,114

For: OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

Customer No. 20350

Confirmation No.: 5376

Examiner: Hui, San Ming R.

Technology Center/Art Unit: 1629

REQUEST FOR RECONSIDERATION OF PATENT TERM ADJUSTMENT UNDER 37 CFR 1.705(b)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Pursuant to 37 C.F.R. § 1.705(b), Applicants respectfully request reconsideration of the patent term adjustment determination. This request is accompanied by the fee set forth in § 1.18(e) and a statement of facts as required under 37 C.F.R. § 1.705(b)(2).

In view of the following, it is respectfully requested that Applicants be granted a corrected patent term adjustment of **989 days**.

Statement of Facts as Required under 37 C.F.R. § 1.705(b)(2)

The correct patent term adjustment is 989 days and not 866 days as stated on the face page of U.S. Patent No. 8,598,149 (*see* **Exhibit A**).

The period of adjustment under § 1.702(a) is 637 days ("A delay").

The period of adjustment under § 1.702(b) is 519 days ("B delay").

The overlap period under § 1.703(a)-(e) is 0 days (overlap).

The period of adjustment under § 1.704(a) is 167 days ("applicant delay").

The period of adjustment under § 1.703(f) is 989 days.

The Relevant Dates as Specified in 37 C.F.R. §§ 1.703(a)-(e) , §§ 1.704 and the Adjustment Specified in 37 C.F.R. § 1.703(f))

1. § 1.703(a)

Applicants are in agreement with the Patent Office's determination of a period of adjustment of 637 days under 37 C.F.R. § 1.703(a). This period of adjustment is comprised of two delay periods of 520 days under § 1.703(a)(1) and 117 days under § 1.703(a)(2).

2. §§ 1.703(b)

The Office failed to issue the above-identified patent within three years from its filing date. The period of adjustment under 37 C.F.R. § 1.702(b) begins on the day after the date that is three years from the filing date of the instant application, August 27, 2011, and is paused with the filing of an RCE or Notice of Appeal. After the filing of an RCE, the period of adjustment under 37 C.F.R. § 1.702(b) resumes upon the mailing of a Notice of Allowance and ends on the day the patent is issued (*see* Novartis AG v. Lee, Nos. 2013-1160, -1179 (Jan. 15, 2014) and Exelixis v. Lee, Nos. 2013-1175, -1198 (Jan. 15, 2014) (*per curiam*)).

Applicants are not in agreement with the Patent Office's determination of adjustment under 37 C.F.R. § 1.703(b) as 396 days. Applicants submit that an RCE was filed on September 27, 2012, which is after the three-year pendency date of August 27, 2011. In accordance with *Novartis AG v. Lee*, Nos. 2013-1160, -1179 (Jan. 15, 2014) and *Exelixis v. Lee*, Nos. 2013-1175, -1198 (Jan. 15, 2014) (*per curiam*), Applicants have calculated two periods of delay under 37 C.F.R. § 1.703(b): 396 days as the period of time between the date that is three years from the filing date (August 27, 2011) through the filing of an RCE on September 27,

2012; and 123 days as the period of time between the Notice of Allowance mailed on August 2, 2013 through the December 3, 2013 issue date of the instant patent. Thus, the effective period of adjustment under 37 C.F.R. § 1.702(b) is **519** days.

3. 1.703(c)-(e)

There are no relevant dates a specified under §§ 1.703(c)-(e)

4. Overlapping periods under § 1.703(a)-(e)

Applicants have calculated the days of overlap under 35 U.S.C. § 154(b)(1)(A) and 35 U.S.C. § 1.54(b)(1)(B) and submit that there are **0** days of overlap applicable to the subject patent.

5. Adjustment of Patent Term Under 37 C.F.R. §1.704

Applicants do not dispute the calculation by the Office of the period of adjustment under § 1.704(a) as total of 167 days indicated by the attached Patent Term Adjustment History (*see* **Exhibit B**). This period of adjustment is the sum of two delay periods: 82 days and 85 days under § 1.704(b) for a total of 167 days.

6. § 1.703(f)

The period of adjustment under 37 C.F.R. § 1.702(f) is as follows:

Type "A" delay:	637 days
Type "B" delay:	519 days
"A" and "B" overlap:	0 days
Applicant delay	167 days
Adjusted	989 days

Terminal disclaimer

The instant application is not subject to a terminal disclaimer.

Statement under 37 C.F.R. § 1.705(b)

The instant patent issued on December 3, 2013 and Applicants submit that this request for reconsideration of patent term adjustment is being filed within the two-month time frame set forth under 37 CFR §1.705(b).

PATENT TERM ADJUSTMENT DETERMINATION

Pursuant to *Novartis AG* (Nos. 2013-1160, -1179 (Jan. 15, 2014), Applicants are entitled to **989 days** of patent term adjustment, *i.e.*:

[1156 days (A + B delay) minus 0 overlap days] minus [167 days (applicant delay)].

Based on the foregoing, Applicants respectfully request reconsideration of the patent term adjustment determination and issuance of a Certificate of Correction to adjust the patent term awarded to U.S. Patent No. 8,598,149.

The $200.00 fee set forth in 37 C.F.R. § 1.18(e) is being charged concurrently herewith. Please deduct any additional fees from, or credit any overpayments to Deposit Account No. 20-1430, referencing Attorney Docket No. 85178-756824 (004110US).

Respectfully submitted,

Alexander R. Trimble
Reg. No. 52,301

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Two Embarcadero Center, Eighth Floor
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Tel: (415) 576-0200
Fax: (415) 576-0300
ART: jtl
65971883V.1

EXHIBIT A


US008598149B2

(12) **United States Patent**
Belanoff

(10) **Patent No.: US 8,598,149 B2**
(45) **Date of Patent: Dec. 3, 2013**

(54) **OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS**

(75) Inventor: **Joseph K. Belanoff**, Woodside, CA (US)

(73) Assignee: **Corcept Therapeutics, Inc.**, Menlo Park, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 866 days.

(21) Appl. No.: **12/199,114**

(22) Filed: **Aug. 27, 2008**

(65) **Prior Publication Data**

US 2009/0062248 A1 Mar. 5, 2009

Related U.S. Application Data

(60) Provisional application No. 60/969,027, filed on Aug. 30, 2007.

(51) **Int. Cl.**
A61K 31/56 (2006.01)

(52) **U.S. Cl.**
USPC **514/178**; 514/182

(58) **Field of Classification Search**
USPC 514/182, 178
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,964,953 B2 * 11/2005 Belanoff 514/178

OTHER PUBLICATIONS

Sarkar, European Journal of Obstetrics and Gynecology and Reproductive Biology, 2002;101:113-120.*
Medical Encyclopedia of Medline (http:// http://www.nlm.nih.gov/medlineplus/ency/article/003430.htm, Oct. 2005.*

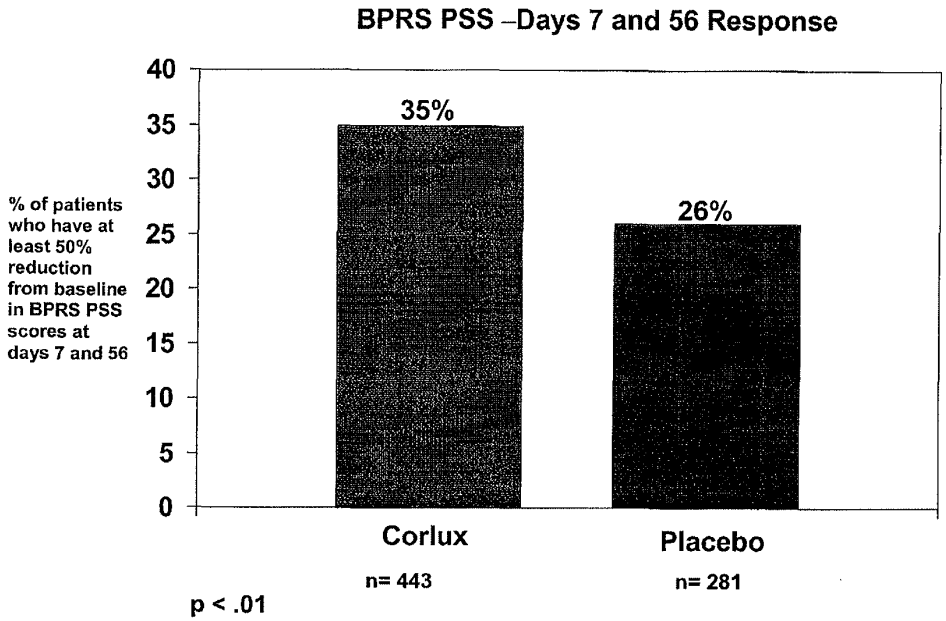
* cited by examiner

Primary Examiner — San-Ming Hui
(74) *Attorney, Agent, or Firm* — Kilpatrick Townsend & Stockton LLP.

(57) **ABSTRACT**

The present invention provides a method for optimizing levels of mifepristone in a patient suffering from a mental disorder amenable to treatment by mifepristone. The method comprises the steps of treating the patient with seven or more daily doses of mifepristone over a period of seven or more days; testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/mL; and adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

7 Claims, 6 Drawing Sheets



12/199,114	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS	85178-756824 (004110US)	02-03-2014::18:42:29

Patent Term Adjustments

Patent Term Adjustment (PTA) for Application Number: 12/199,114

Filing or 371(c) Date:	08-27-2008	Overlapping Days Between {A and B} or {A and C}:	0
Issue Date of Patent:	12-03-2013	Non-Overlapping USPTO Delays:	1033
A Delays:	637	PTO Manual Adjustments:	0
B Delays:	396	Applicant Delays:	167
C Delays:	0	Total PTA Adjustments:	866

Patent Term Adjustment History **Explanation Of Calculations**

Number	Date	Contents Description	PTO (Days)	APPL (Days)	Start
77.5	09-26-2012	PTA 36 Months	396		0.5
77	12-03-2013	Patent Issue Date Used in PTA Calculation			0
76	11-01-2013	Export to Final Data Capture			0
75	10-31-2013	Dispatch to FDC			0
74	10-31-2013	Application Is Considered Ready for Issue			0
73	10-28-2013	Issue Fee Payment Verified			0
72	10-28-2013	Issue Fee Payment Received			0
71	08-31-2013	Finished Initial Data Capture			0
67	08-02-2013	Mail Notice of Allowance			0
66	07-29-2013	Office Action Review			0
65	07-29-2013	Office Action Review			0
61	07-29-2013	Issue Revision Completed			0
60	07-29-2013	Document Verification			0
59	07-29-2013	Notice of Allowance Data Verification Completed			0
58	07-29-2013	Case Docketed to Examiner in GAU			0
57	07-29-2013	Allowed Case Returned to the Examiner for Clerical Processing			0
56	07-29-2013	Office Action Review			0
	07-29-				

EXHIBIT B

55	2013	Office Action Review			0
54	07-23-2013	Reasons for Allowance			0
53	07-23-2013	Allowability Notice			0
52	07-19-2013	Date Forwarded to Examiner			0
51	07-18-2013	Response after Ex Parte Quayle Action			0
50	05-24-2013	Electronic Review			0
49	05-24-2013	Email Notification			0
48	05-24-2013	Mail Ex Parte Quayle Action (PTOL - 326)	117		43
47	05-21-2013	Office Action Review			0
46	05-20-2013	Quayle action			0
45	10-01-2012	Date Forwarded to Examiner			0
44	09-27-2012	Amendment Submitted/Entered with Filing of CPA/RCE			0
43	09-27-2012	Request for Continued Examination (RCE)		85	37
42	10-01-2012	Disposal for a RCE / CPA / R129			0
41	09-27-2012	Request for Extension of Time - Granted			0
40	09-27-2012	Workflow - Request for RCE - Begin			0
39	04-04-2012	Electronic Review			0
38	04-04-2012	Email Notification			0
37	04-04-2012	Mail Final Rejection (PTOL - 326)			0
36	03-28-2012	Office Action Review			0
35	03-27-2012	Final Rejection			0
33	01-26-2012	Date Forwarded to Examiner			0
32	01-24-2012	Response after Non-Final Action		82	28
31	01-24-2012	Request for Extension of Time - Granted			0
30	08-03-2011	Electronic Review			0

EXHIBIT B

29	08-03-2011	Email Notification		0
28	08-03-2011	Mail Non-Final Rejection		0
27	07-29-2011	Office Action Review		0
26	07-28-2011	Non-Final Rejection		0
24	05-24-2011	Date Forwarded to Examiner		0
23	05-18-2011	Response to Election / Restriction Filed		0
22	05-18-2011	Request for Extension of Time - Granted		0
21	03-31-2011	Electronic Review		0
20	03-31-2011	Email Notification		0
19	03-31-2011	Mail Restriction Requirement	520	0.5
18	03-28-2011	Office Action Review		0
17	03-28-2011	Restriction/Election Requirement		0
16	12-05-2009	Case Docketed to Examiner in GAU		0
15	10-06-2009	Case Docketed to Examiner in GAU		0
14	08-18-2009	Case Docketed to Examiner in GAU		0
13	03-05-2009	PG-Pub Issue Notification		0
12	01-31-2009	IFW TSS Processing by Tech Center Complete		0
11	12-04-2008	Application Dispatched from OIPE		0
10	11-17-2008	Change in Power of Attorney (May Include Associate POA)		0
9	11-17-2008	Sent to Classification Contractor		0
8	11-17-2008	Filing Receipt - Updated		0
7	11-07-2008	Additional Application Filing Fees		0
6	11-07-2008	A statement by one or more inventors satisfying the requirement under 35 USC 115, Oath of the Applic		0
5	09-11-2008	Notice Mailed--Application Incomplete--Filing Date Assigned		0
4	09-11-2008	Filing Receipt		0

EXHIBIT B

3	08-27-2008	Cleared by OIPE CSR	0
2	08-27-2008	IFW Scan & PACR Auto Security Review	0
1	08-27-2008	Initial Exam Team nn	0
0.5	08-27-2008	Filing date	0

Close Window

Electronic Patent Application Fee Transmittal

Application Number:	12199114
Filing Date:	27-Aug-2008
Title of Invention:	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Filer:	Alexander Reed Trimble/Jeffrey Luo
Attorney Docket Number:	85178-756824(004110US)

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Application for patent term adjustment	1455	1	200	200
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**200**

Electronic Acknowledgement Receipt	
EFS ID:	18101671
Application Number:	12199114
International Application Number:	
Confirmation Number:	5376
Title of Invention:	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	20350
Filer:	Alexander Reed Trimble/Jeffrey Luo
Filer Authorized By:	Alexander Reed Trimble
Attorney Docket Number:	85178-756824(004110US)
Receipt Date:	03-FEB-2014
Filing Date:	27-AUG-2008
Time Stamp:	19:20:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$200
RAM confirmation Number	6201
Deposit Account	
Authorized User	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Patent Term Adjustment Petition	REQ_RECONSID.pdf	348682 fadcaaf06d6eadc00db2c9c86bfbd35d24e673e7	no	9
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31012 2377ff3939e4fb3cb357153d1fcef2fed6542bf7	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	379694		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/199,114	12/03/2013	8598149	85178-756824(004110US)	5376

20350 7590 11/13/2013

KILPATRICK TOWNSEND & STOCKTON LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 866 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Joseph K. Belanoff, Woodside, CA;

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

20350 7590 08/02/2013
KILPATRICK TOWNSEND & STOCKTON LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

Shemekia N. Brown	(Depositor's name)
/Shemekia N. Brown/	(Signature)
10/28/2013	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/199,114	08/27/2008	Joseph K. Belanoff	85178-756824(004110US)	5376

TITLE OF INVENTION: OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	11/04/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
HUI, SAN MING R	1629	514-178000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Kilpatrick Townsend & Stockton LLP.
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE	(B) RESIDENCE: (CITY and STATE OR COUNTRY)
Corcept Therapeutics, Inc.	Menlo Park, CA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☒ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 20-1430 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
☐ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
☐ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature / Alex Trimble / Date 10/28/2013

Typed or printed name Alex Trimble Registration No. 52,301

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Electronic Patent Application Fee Transmittal

Application Number:	12199114
Filing Date:	27-Aug-2008
Title of Invention:	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Filer:	Alexander Reed Trimble/Shemekia Brown
Attorney Docket Number:	85178-756824(004110US)

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	2501	1	890	890
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**1190**

Electronic Acknowledgement Receipt	
EFS ID:	17242669
Application Number:	12199114
International Application Number:	
Confirmation Number:	5376
Title of Invention:	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	20350
Filer:	Alexander Reed Trimble/Shemekia Brown
Filer Authorized By:	Alexander Reed Trimble
Attorney Docket Number:	85178-756824(004110US)
Receipt Date:	28-OCT-2013
Filing Date:	27-AUG-2008
Time Stamp:	14:58:39
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1190
RAM confirmation Number	1451
Deposit Account	201430
Authorized User	TRIMBLE, ALEXANDER
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	ISSUEFEE.pdf	2089527 b9efc393ba53031af4b9adad85a39781f3feae72	no	2
Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	32681 76cd7e87f3eeec630792ca173838835efb3e6f80	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	2122208		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

20350 7590 08/02/2013

KILPATRICK TOWNSEND & STOCKTON LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER
HUI, SAN MING R

ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 08/02/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/199,114	08/27/2008	Joseph K. Belanoff	85178-756824(004110US)	5376

TITLE OF INVENTION: OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	11/04/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

20350 7590 08/02/2013
KILPATRICK TOWNSEND & STOCKTON LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/199,114	08/27/2008	Joseph K. Belanoff	85178-756824(004110US)	5376

TITLE OF INVENTION: OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	11/04/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
HUI, SAN MING R	1629	514-178000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 _____
2 _____
3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:
- ❑ Issue Fee
- ❑ Publication Fee (No small entity discount permitted)
- ❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ❑ A check is enclosed.
- ❑ Payment by credit card. Form PTO-2038 is attached.
- ❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/199,114	08/27/2008	Joseph K. Belanoff	85178-756824(004110US)	5376

20350 7590 08/02/2013

KILPATRICK TOWNSEND & STOCKTON LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
HUI, SAN MING R	
ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 08/02/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 470 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 470 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 12/199,114	Applicant(s) BELANOFF, JOSEPH K.	
	Examiner SAN-MING HUI	Art Unit 1629	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *7/18/2013*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-7*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☐ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/San-ming Hui/
Primary Examiner, Art Unit 1629

DETAILED ACTION

Applicant's amendments of cancelling claim 8 filed 7/18/2013 have been entered. Claims 1-7 are pending.

REASONS FOR ALLOWANCE

The following is an examiner's statement of reasons for allowance: The method of using mifepristone level for adjusting the treatment of mental disorder is not taught or fairly suggested by the prior art. Although effective dosages of mifepristone for treating mental disorders are known, the correlation of the level of mifepristone to the therapeutic effectiveness of mifepristone in treating such disorders is not known.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAN-MING HUI whose telephone number is (571)272-0626. The examiner can normally be reached on Mon - Fri from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Melenie McCormick can be reached on (571) 272-8037. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

San-ming Hui
Primary Examiner
Art Unit 1629

/San-ming Hui/
Primary Examiner, Art Unit 1629

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12199114	BELANOFF, JOSEPH K.
	Examiner	Art Unit
	SAN-MING HUI	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/28/2011	07/28/2011	03/27/2012	05/20/2013	07/23/2013				
	1	÷	✓	✓	=	=				
	2	÷	✓	✓	=	=				
	3	÷	✓	✓	=	=				
	4	÷	✓	✓	=	=				
	5	÷	✓	✓	=	=				
	6	÷	✓	✓	=	=				
	7	÷	✓	✓	=	=				
	8	÷	N	N	N					

UNITED STATES PATENT AND TRADEMARK OFFICE

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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

BIB DATA SHEET

CONFIRMATION NO. 5376

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
12/199,114	08/27/2008 RULE	514	1629	85178-756824(004110US)

APPLICANTS
Joseph K. Belanoff, Woodside, CA;

**** CONTINUING DATA ***************************
This appln claims benefit of 60/969,027 08/30/2007

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
09/08/2008

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /SAN-MING R HUI/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		CA	6	8	2

ADDRESS

KILPATRICK TOWNSEND & STOCKTON LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834
UNITED STATES

TITLE

OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

FILING FEE RECEIVED		
500	FEES: Authority has been given in Paper No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____ ☐ Credit

BIB (Rev. 05/07).

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	5140	mifepristone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/07/23 13:58
L2	15281	post adj traumatic	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/07/23 13:58
L3	507	L1 and L2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/07/23 13:58
L4	4	L1 same L2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/07/23 13:58
L5	503	L1 and L2 and dosage	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/07/23 13:58
L6	8353	post adj traumatic adj stress	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/07/23 13:58
L7	112	L1 and L6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/07/23 13:58
L8	1763	514/178.ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/07/23 13:58

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L9	1520	514/178.ccls.	US-PGPUB; USPAT	OR	OFF	2013/07/23 14:05

7/23/2013 2:06:31 PM
C:\Users\shui\Documents\EAST\Workspaces\12-199114.wsp

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12199114	BELANOFF, JOSEPH K.
	Examiner	**Art Unit**
	SAN-MING HUI	1629

CPC		
Symbol	**Type**	**Version**

CPC Combination Sets				
Symbol	**Type**	**Set**	**Ranking**	**Version**

NONE (Assistant Examiner) (Date)		**Total Claims Allowed:** 7	
/SAN-MING HUI/ Primary Examiner.Art Unit 1629 (Primary Examiner)	07/23/2013 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 1

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12199114	BELANOFF, JOSEPH K.
	Examiner	**Art Unit**
	SAN-MING HUI	1629

US ORIGINAL CLASSIFICATION		INTERNATIONAL CLASSIFICATION										
CLASS	SUBCLASS	CLAIMED					NON-CLAIMED					
514	178	A	6	1	K	31 / 56 (2006.0)						
CROSS REFERENCE(S)												
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)											
514	182											

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 7	
/SAN-MING HUI/ Primary Examiner.Art Unit 1629 (Primary Examiner)	07/23/2013 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 1

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12199114	BELANOFF, JOSEPH K.
	Examiner	**Art Unit**
	SAN-MING HUI	1629

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE (Assistant Examiner)	(Date)	**Total Claims Allowed:** 7	
/SAN-MING HUI/ Primary Examiner.Art Unit 1629 (Primary Examiner)	07/23/2013 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 1

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12199114	BELANOFF, JOSEPH K.
	Examiner	Art Unit
	SAN-MING HUI	1628

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	182, 178	7/27/11	SH
514	178, 182	3/27/12	SH
514	178, 182	5/20/13	SH
514	178,182	7/23/13	SH

SEARCH NOTES		
Search Notes	Date	Examiner
EAST adn inventor search in PALM	7/27/11	SH
EAST and inventor search in PALM	3/27/12	SH
EAST and inventor search in PALM	5/20/13	SH
EAST and inventor search in PALM	7/23/13	SH

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
514	178,182	7/23/13	SH

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on 7/18/2013.

KILPATRICK TOWNSEND & STOCKTON LLP

By: _____

PATENT
Attorney Docket No.: 85178-756824
Family ID No.: 004110US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 5376
Joseph K. Belanoff	Examiner: San Ming R Hui
Application No.: 12/199,114	Technology Center/Art Unit: 1628
Filed: August 27, 2008	
For: OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS	
Customer No.: 20350	AMENDMENT D

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Ex Parte Quayle action mailed May 24, 2013, please enter the following amendments and remarks.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 4 of this paper.

Amendments to the Claims:

The following is a complete list of claims indicating the changes incorporated by the present amendment and replacing all prior versions of the claims. Any claims canceled herein and all deletions made in claims that are not canceled herein are done so without prejudice to being re-instituted at a later date in this or a related application.

Listing of Claims:

1. (Original) A method for optimizing levels of mifepristone in a patient suffering from a mental disorder amenable to treatment by mifepristone, the method comprising:

treating the patient with seven or more daily doses of mifepristone over a period of seven or more days;

testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/mL; and

adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

2. (Original) The method of claim 1, wherein the mental disorder is a member selected from the group consisting of a stress disorder, delirium, mild cognitive impairment (MCI), dementia, psychosis and psychotic major depression.

3. (Original) The method of claim 2, wherein the stress disorder is a member selected from the group consisting of Acute Stress Disorder, Post-Traumatic Stress Disorder and Brief Psychotic Disorder with Marked Stressor(s).

4. (Original) The method of claim 1, wherein each of the seven or more daily doses of mifepristone are administered orally.

5. (Original) The method of claim 1, wherein the patient is treated with 28 or more daily doses over a period of 28 or more days.

6. (Original) The method of claim 1, wherein the testing is performed by a plasma sampling collection device suitable for detecting mifepristone serum levels.

7. (Original) The method of claim 1, wherein the adjusting step comprises increasing the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

8. (Canceled)

REMARKS

Upon entry of the present amendment, claims 1-7 are pending in the above-referenced patent application and are currently allowed. Claim 8 is canceled. Reconsideration of the application is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Alexander R. Trimble
Reg. No. 52,301

KILPATRICK TOWNSEND & STOCKTON LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
65567507v1

Electronic Acknowledgement Receipt

EFS ID:	16357442
Application Number:	12199114
International Application Number:	
Confirmation Number:	5376
Title of Invention:	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	20350
Filer:	Alexander Reed Trimble/Shemekia Brown
Filer Authorized By:	Alexander Reed Trimble
Attorney Docket Number:	85178-756824(004110US)
Receipt Date:	18-JUL-2013
Filing Date:	27-AUG-2008
Time Stamp:	17:43:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response after Ex Parte Quayle Action	AMEND.pdf	116308 d25de9a2a30d945f2a13197058a1e648cf82e52f	no	4

Warnings:

Information:

Total Files Size (in bytes):	116308

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/199,114	Filing Date 08/27/2008	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	07/18/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 7	Minus	** 20	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/SHOWANE SMITH/

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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/199,114	08/27/2008	Joseph K. Belanoff	85178-756824(004110US)	5376

20350 7590 05/24/2013

KILPATRICK TOWNSEND & STOCKTON LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
HUI, SAN MING R	
ART UNIT	**PAPER NUMBER**
1629	

NOTIFICATION DATE	DELIVERY MODE
05/24/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ipefiling@kilpatricktownsend.com
jlhice@kilpatrick.foundationip.com
mcollins@kilpatricktownsend.com

Office Action Summary	Application No. 12/199,114	Applicant(s) BELANOFF, JOSEPH K.	
	Examiner SAN-MING HUI	Art Unit 1629	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 2 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☒ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) 1-8 is/are pending in the application.

5a) Of the above claim(s) 8 is/are withdrawn from consideration.

6)☒ Claim(s) 1-7 is/are allowed.

7)☐ Claim(s) _____ is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some * c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Interim copies:

a)☐ All b)☐ Some c)☐ None of the: Interim copies of the priority documents have been received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/27/2012 has been entered.

Claims 1-8 are pending. Claim 8 is withdrawn from consideration as the claim is drawn to non-elected invention.

Applicant's remarks and arguments filed 9/27/2012 have been considered and are found persuasive to withdraw the outstanding rejection under 35 USC 103(a).

The method of using the mifepristone level for adjusting the treatment of mental disorder is not taught or fairly suggested by the prior art. Although the effective dosages of mifepristone for treating mental disorders are known, the correlation of the level of mifepristone to the therapeutic effectiveness of mifepristone is not known.

This application is in condition for allowance except for the following formal matters:

Since claim 8 is directed to non-elected invention, the applicant is required to cancel the claim.

Prosecution on the merits is closed in accordance with the practice under *Ex parte Quayle*, 25 USPQ 74, 453 O.G. 213, (Comm'r Pat. 1935).

A shortened statutory period for reply to this action is set to expire **TWO MONTHS** from the mailing date of this letter.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAN-MING HUI whose telephone number is (571)272-0626. The examiner can normally be reached on Mon - Fri from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Melenie McCormick can be reached on (571) 272-8037. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

San-ming Hui
Primary Examiner
Art Unit 1629

/San-ming Hui/
Primary Examiner, Art Unit 1629

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12199114	BELANOFF, JOSEPH K.
	Examiner	**Art Unit**
	SAN-MING HUI	1628

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/28/2011	07/28/2011	03/27/2012	05/20/2013					
	1	÷	✓	✓	=					
	2	÷	✓	✓	=					
	3	÷	✓	✓	=					
	4	÷	✓	✓	=					
	5	÷	✓	✓	=					
	6	÷	✓	✓	=					
	7	÷	✓	✓	=					
	8	÷	N	N	N					

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S17	4999	mifepristone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/05/20 10:24
S18	14956	post adj traumatic	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/05/20 10:24
S19	498	S17 and S18	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/05/20 10:24
S20	2	S17 same S18	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/05/20 10:24
S21	495	S17 and S18 and dosage	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/05/20 10:24
S22	8142	post adj traumatic adj stress	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/05/20 10:24
S23	108	S17 and S22	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/05/20 10:24
S24	1629	514/178.ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/05/20 10:24

EAST Search History (Interference)

<This search history is empty>

5/20/2013 11:48:53 AM
C:\Users\shui\Documents\EAST\Workspaces\12-199114.wsp

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12199114	BELANOFF, JOSEPH K.
	Examiner	Art Unit
	SAN-MING HUI	1628

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
514	182, 178	7/27/11	SH
514	178, 182	3/27/12	SH
514	178, 182	5/20/13	SH

SEARCH NOTES		
Search Notes	Date	Examiner
EAST adn inventor search in PALM	7/27/11	SH
EAST and inventor search in PALM	3/27/12	SH
EAST and inventor search in PALM	5/20/13	SH

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner

PTO/SB/30 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Request For Continued Examination (RCE) Transmittal

Address to:
Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Application Number	12/199,114
Filing Date	August 27, 2008
First Named Inventor	Joseph Belanoff
Art Unit	1628
Examiner Name	San Ming R Hui
Attorney Docket Number	85178-756824

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. See Instruction Sheet for RCEs (not to be submitted to the USPTO) on page 2.

1. Submission required under 37 C.F.R. 1.114 Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

a. ☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

i. ☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____
ii. ☐ Other _____

b. . ☒ Enclosed

i. ☒ Amendment/Reply
ii ☐ Affidavit(s)/Declaration(s)
iii. ☐ Information Disclosure Statement (IDS)
iv. ☐ Other _____

2. Miscellaneous

a. ☐ Suspension of action on the above-identified application is requested under 37 C.F.R. 1.103(c) for a period of _____ months. (Period of suspension shall not exceed 3 months; Fee under 37 C.F.R. 1.17(i) required)

b. ☐ Other _____

3. **Fees** The RCE fee under 37 C.F.R. 1.17(e) is required by 37 C.F.R. 1.114 when the RCE is filed.

a. ☒ The Director is hereby authorized to charge the following fees, any underpayment of fees, or credit any overpayments, to Deposit Account No. 20-1430.

i. ☒ RCE fee required under 37 C.F.R. 1.17(e)
ii. ☒ Extension of time fee (37 C.F.R. 1.136 and 1.17)
iii. ☐ Other _____

b. ☐ Check in the amount of $ _____ enclosed

c. ☒ Payment by credit card (Form PTO-2038 enclosed)

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

Signature	/Alexander R. Trimble/	Date	09/27/12
Name (Print /Type)	Alexander R. Trimble	Registration No.	52,301

CERTIFICATE OF MAILING OR TRANSMISSION

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P. O. Box 1450, Alexandria, VA 22313-1450 or facsimile transmitted to the U.S. Patent and Trademark Office on the date shown below.

Signature	/Shemekia N. Brown/		
Name (Print /Type)	Shemekia N. Brown	Date	9/27/12

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/22 (09-11)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)	Docket Number (Optional) 85178-756824
Application Number 12/199,114	Filed August 27, 2008
For OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS	
Art Unit 1628	Examiner San Ming R Hui

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$150	$75	$_____
☐	Two months (37 CFR 1.17(a)(2))	$560	$280	$_____
☒	Three months (37 CFR 1.17(a)(3))	$1270	$635	$635
☐	Four months (37 CFR 1.17(a)(4))	$1980	$990	$_____
☐	Five months (37 CFR 1.17(a)(5))	$2690	$1345	$_____

☒ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☒ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 20-1430 .

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 52,301

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34. _____ .

/Alexander R. Trimble/	09/27/2012
Signature	Date
Alexander R. Trimble	415-273-4718
Typed or printed name	Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☐ Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.136(a). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on 9/27/12

KILPATRICK TOWNSEND & STOCKTON LLP

By: _____

PATENT
Attorney Docket No.: 85178-756824
Family ID No.: 004110US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 5376
Joseph K. Belanoff	Examiner: San Ming R Hui
Application No.: 12/199,114	Technology Center/Art Unit: 1628
Filed: August 27, 2008	
For: OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS	
Customer No.: 20350	AMENDMENT C UNDER 37 CFR 1.116 EXPEDITED PROCEDURE EXAMINING GROUP 1639

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Office Action mailed April 4, 2012, please enter the following amendments and remarks. A petition for a **three-month extension of time** is filed concurrently herewith. A **request for continued examination (RCE)** is filed concurrently herewith.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 4 of this paper.

Amendments to the Claims:

The following is a complete list of claims indicating the changes incorporated by the present amendment and replacing all prior versions of the claims. Any claims canceled herein and all deletions made in claims that are not canceled herein are done so without prejudice to being re-instituted at a later date in this or a related application.

Listing of Claims:

1. (Original) A method for optimizing levels of mifepristone in a patient suffering from a mental disorder amenable to treatment by mifepristone, the method comprising:

treating the patient with seven or more daily doses of mifepristone over a period of seven or more days;

testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/mL; and

adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

2. (Original) The method of claim 1, wherein the mental disorder is a member selected from the group consisting of a stress disorder, delirium, mild cognitive impairment (MCI), dementia, psychosis and psychotic major depression.

3. (Original) The method of claim 2, wherein the stress disorder is a member selected from the group consisting of Acute Stress Disorder, Post-Traumatic Stress Disorder and Brief Psychotic Disorder with Marked Stressor(s).

4. (Original) The method of claim 1, wherein each of the seven or more daily doses of mifepristone are administered orally.

5. (Original) The method of claim 1, wherein the patient is treated with 28 or more daily doses over a period of 28 or more days.

6. (Original) The method of claim 1, wherein the testing is performed by a plasma sampling collection device suitable for detecting mifepristone serum levels.

7. (Original) The method of claim 1, wherein the adjusting step comprises increasing the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

8. (Withdrawn) A kit for treating a mental disorder amenable to treatment by mifepristone, the kit comprising:

seven daily doses of mifepristone; and

a plasma sampling collection device suitable for detecting mifepristone serum levels.

REMARKS

Upon entry of the present amendment, claims 1- 8 are pending in the above-referenced patent application and are currently under examination. Claim 8 is withdrawn. Reconsideration of the application is respectfully requested.

I. OBVIOUSNESS OVER MEDICAL ENCYCLOPEDIA OF MEDLINE, THE '953 PATENT AND SARKAR

Claims 1-7 are rejected under 35 USC § 103(a) as allegedly being obvious over Medical Encyclopedia of Medline (http://www.nlm.nih.gov/medlineplus/ency/article/003430.htm, October 2005, "Medical Encyclopedia") in view of U.S. Patent No. 6,964,953 and Sarkar, European Journal of Obstetrics and Gynecology and Reproductive Biology 2002, 101, 113-120. Applicants respectfully traverse the rejection in view of the comments below.

The Office maintains the obviousness rejection and the position that one of ordinary skill would have been motivated to optimize the serum level of mifepristone in Acute Stress Disorder patients because adjusting the serum level of mifepristone would be seen as equivalent to adjusting the dosage of mifepristone to treat Acute Stress Disorder and would be reasonably expected to be successful. Applicants disagree because there is no description in the combination of references regarding the criticality of mifepristone serum levels of 1300 ng/ml of mifepristone for treatment of a mental disorder amenable to treatment by mifepristone. Moreover, historical measurements of mifepristone serum levels are not accurate measurements of mifepristone serum levels due to the inability of the radioimmunoassay (RIA) to distinguish mifepristone from its metabolites, and the rapid metabolism of mifepristone leads to metabolite concentrations higher than mifepristone itself. Applicants discuss in detail below.

Historical mifepristone serum levels are not comparable to the claimed mifepristone serum level because radioimmunoassay detection methods cannot distinguish mifepristone from its metabolites

Applicants note the Office does not point to a single description in any of the cited references regarding the criticality of 1300 ng/ml of mifepristone for the treatment of a mental disorder amenable to treatment by mifepristone. Instead, the Office points to the '953 patent describing use of mifepristone for the treatment of acute stress disorder where mifepristone can be

administered at 1 to 10 mg/kg, corresponding to 75 to 750 mg for an adult of 75 kg, for 30 days. The Office then relies on the teachings of Sarkar to allege that the doses used in the '953 patent would produce serum concentrations of at least the claimed 1300 ng/ml.

The data in Sarkar that the Office relies on, however, was obtained using a radioimmunoassay, which is unable to distinguish between mifepristone and mifepristone's metabolites, thus providing serum levels that overestimate the mifepristone serum level. For example, the Office points to the teachings of Sarkar of a medium dose (100-200 mg) of mifepristone achieving a serum concentration of 4.5-5.4 μmol/l (1933.2 ng/ml to 2276.88 ng/ml), with higher doses (400-600 mg) achieving higher serum concentrations (page 3 of the Final Office Action, pointing to pages 114-115 of Sarkar).

The serum levels cited in Sarkar and relied on by the Office come from reference [6] of Sarkar, *Contraception* 1986, 34(5), 469-481, 479 (Exhibit A). *Contraception* 1986 describes use of RIA for detection of mifepristone (page 471-473). Moreover, *Contraception* 1986 states the presence of two metabolites of mifepristone could not be excluded from the assay (Abstract):

> The levels of RU 486 were measured by a radioimmunoassay method which uses chromatography on Sephadex LH 20 columns. The identity of the compound assayed as RU 486 was confirmed, but **the presence of small amounts of two highly cross-reacting metabolites (monodemethyl and didemethyl RU 486) in the analyzed fractions could not be excluded**. (Emphasis added.)

Contraception 1986 goes further, stating that in separating mifepristone from the plasma samples by chromatographic methods, two of the metabolites were not completely removed, such that "small but significant amounts of both metabolites were present." (*Contraception* 1986, pp.472-473.)

Accordingly, mifepristone serum values from *Contraception* 1986 obtained using RIA, reported in Sarkar and relied upon by the Office, do not accurately reflect *mifepristone* serum levels, but, instead, reflect the combined serum level of mifepristone *and its metabolites*. Moreover, the "small amounts" of mifepristone metabolites referred to in *Contraception* 1986 can actually be similar to, and in some cases greater than, the serum levels of mifepristone, depending on when the serum levels are measured (see below for more detail).

The claimed mifepristone serum levels are determined using High Pressure Liquid Chromatography (HPLC) methods capable of separating mifepristone from its metabolites and accurately measuring mifepristone serum levels

In contrast to *Contraception* 1986, mifepristone serum levels of the present invention were detected using High Pressure Liquid Chromatography (HPLC) methods capable of separating mifepristone from its metabolites and accurately measuring mifepristone serum levels. As described in Example 1 of the instant application, the serum samples were analyzed by reverse-phase high pressure liquid chromatography and mass spectrometry (see paragraph 0079):

> The sample was then analyzed by reverse-phase high pressure liquid chromatography using a water:acetonitrile:formic acid (60:40:0.1) mobile phase (isocratic) at a flow rate of 0.3 mL/min. The column was a phenyl column maintained at 50°C. Mifepristone elutes at 4.2 minutes. Following elution, the mobile phase was nebulized using heated nitrogen in a Z-spray source/interface and the ionized compounds detected using a tandem quadrupole mass spectrometer. Mifepristone (molecular weight of 430 g/mol) was detected at m/z 372.30. The internal standard mifepristone-d4 was detected at m/z 376.30. The ratio of the mifepristone peak height to the mifepristone-d4 peak height was calculated.

The benefits of using HPLC detection methods, especially compared to the historical RIA or RRA methods for determining mifepristone serum levels, are well known in the art:

- *European Journal of Endocrinology* 2007, 157, 561 (Exhibit B) describes plasma half-life of mifepristone as being higher when calculated via radioimmunoassay (RIA) or radio receptor assays (RRA) as compared to HPLC detection methods (page 562):

  > The plasma half-life of mifepristone has been reported to vary between 24 and 48 h when analysed by high performance liquid chromatography (HPLC), and between 55 and 90 h when RIA or radioreceptor assays are used.

- *Contraception* 2003, 68, 421 (Exhibit C) describes the inability of RIA & RRA to distinguish between mifepristone and the metabolites (page 422):

  > Various assay methods such as radioimmunoassay (RIA) [9], radioreceptorassay (RRA) [10,11] and assays based on high-performance liquid chromatography (HPLC) have been used to measure serum mifepristone levels [12–14]. It soon became apparent that mifepristone is extensively metabolized, and due to the cross-reacting metabolites, **direct RIA and RRA failed to distinguish the parent mifepristone from its metabolites** [15]. (Emphasis added.)

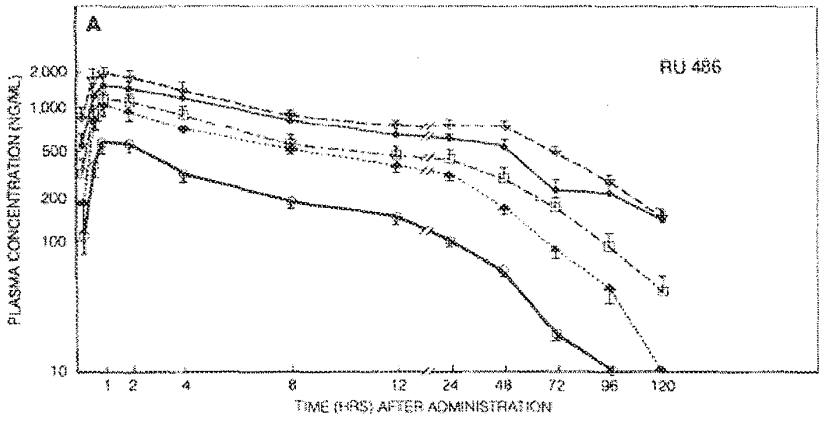
- *Journal of Steroid Biochemistry* 1989, 32(1A), 21 (Exhibit D, reference [8] of Sarkar) describes RIA as giving higher serum levels than HPLC detection methods (page 23):

> There was a good correlation between the serum levels of RU 486 measured by HPLC and RIA (Fig. 4). The correlation coefficient was 0.92 (n = 80), but at the serum concentrations exceeding 0.64 µmol/l RIA gave higher values than HPLC.

Accordingly, mifepristone serum levels determined using RIA or RRA reflect the concentration of *mifepristone and its metabolites*, not mifepristone alone, while the HPLC method used in the claimed invention provides values for mifepristone only.

Mifepristone metabolizes quickly, leading to serum levels of the metabolites similar to, or even greater than, mifepristone itself

The inability of the RIA and RRA assays to distinguish between mifepristone and its metabolites is compounded by the rapid metabolism of mifepristone leading to high serum levels of the metabolites. Moreover, at least one metabolite has higher serum levels than mifepristone itself soon after administration. For example, *Contraception* 1993, 48, 133 (Exhibit E, reference [5] of Sarkar) shows serum levels of mifepristone and its metabolites over 5 days following a single 600 mg dose (Figures 3A-3D), as determined using HPLC detection methods:



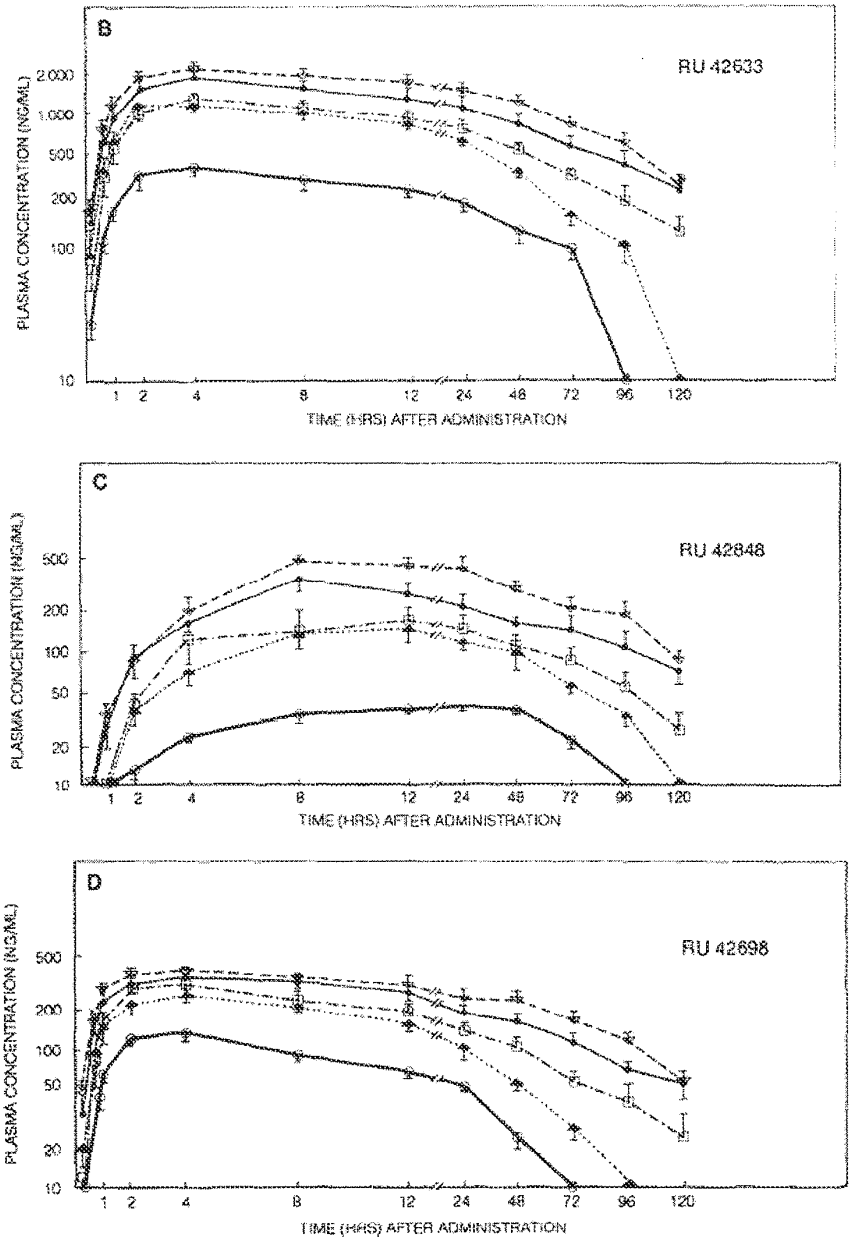


FIGURE 3A-D: Mean (SEM) concentrations of RU 486 (A) and its metabolites (RU 42633: B; RU 42848: C; RU 42698: D) after oral administration of various doses of RU 486 to non-pregnant women.
(●—●: 25 mg; ▲—▲: 100 mg; □—□: 200 mg; ◆—◆: 400 mg; ▽—▽: 600 mg)

As shown in the table below, the serum levels of the metabolites rise very quickly, even surpassing mifepristone within several hours for at least one metabolite. Moreover, the mifepristone plasma level drops below the claimed value of 1300 ng/ml within 8 hours following administration.

Time	Mifepristone (ng/ml)	RU 42633 (ng/ml)	RU 42848 (ng/ml)	RU 42698 (ng/ml)
1 hr.	~1900	~800	~35	~300
4 hr.	~1300	~2200	~200	~400
8 hr.	~900	~2000	~500	~400
24 hr.	~800	~1900	~450	~350

See also Figure 2 of *Journal of Steroid Biochemistry* 1987, 26(2), 279 (Exhibit F, reference [14] of Sarkar), showing metabolite RU 42633 as having higher serum levels than mifepristone beginning about 1 hour after a 100 mg dose, as determined using HPLC detection methods:

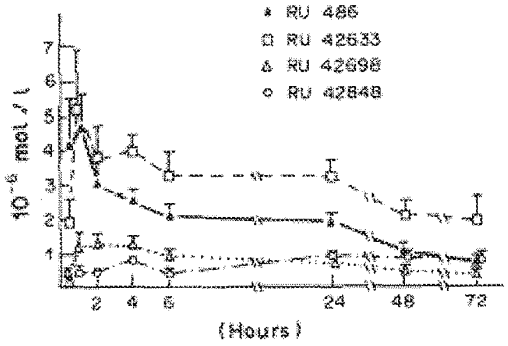


Fig. 2. Plasma concentrations (mean + SEM) of RU 486, RU 42633, RU 42848 and RU 42698, after oral ingestion of 100 mg of RU 486 by five female volunteers.

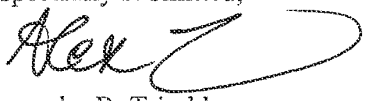
In view of the inability of RIA and RRA detection methods to distinguish mifepristone from its metabolites, especially in view of the rapid mifepristone metabolism and high serum levels of mifepristone metabolites, there is no reasonable expectation of success for identifying 1300 ng/ml as the serum level of *mifepristone* only necessary to treat a patient suffering from a mental disorder amenable to treatment by mifepristone. Thus, the present invention is not obvious under 35 USC § 103(a) over the combination of Medical Encyclopedia, the '953 patent and Sarkar. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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PLASMA CONCENTRATIONS AND RECEPTOR BINDING OF RU 486 AND ITS METABOLITES IN HUMANS

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Summary—Using Chromosorb® chromatography and HPLC, we measured the plasma concentrations of RU 486, and its monodemethylated (RU 42633), didemethylated (RU 42848) and alcoholic nondemethylated (RU 42698) metabolites up to 72 h following oral ingestion of 100 mg of RU 486 by five female volunteers. The peak plasma level of RU 486 (4.5 μmol/l) occurred within 1 h after ingestion of the compound; at this point significant amounts of the metabolites were also present in the plasma. After the initial redistribution within 6 h the plasma concentrations of RU 486 and three of its metabolites measured remained stable for 24 h. Concentrations of the monodemethylated metabolite exceeded those of the parent steroid during the time period measured, whereas the concentrations of the didemethylated and alcoholic metabolites were lower than those of RU 486, but still notable. At 72 h the concentrations of all the four steroids were still in the micromolar range. The relative binding affinities of these metabolites to human endometrial and myometrial progesterone receptors as well as to human placental glucocorticoid receptors were determined *in vitro*. The affinity of RU 486 for the human uterine progesterone receptor ($K_d = 1.3 \times 10^{-9}$ M for RU 486) was higher than that of progesterone but lower than that of ORG-2058, a potent synthetic progestin. The relative binding affinities of the monodemethylated, alcoholic and didemethylated metabolites to the progesterone receptor were 21, 15 and 9%, respectively, compared with the parent compound RU 486; each was lower than that of progesterone (43%). RU 486 had an approx. 4-fold higher relative binding affinity to the glucocorticoid receptor than dexamethasone. Interestingly, the relative binding affinities of the metabolites studied to the human glucocorticoid receptor exceeded those of dexamethasone or cortisol. Compared with the parent compound RU 486, they were 61, 48 and 45% for the monodemethylated, alcoholic and didemethylated metabolites, respectively; each was higher than that of dexamethasone (23%). The affinity of dexamethasone to the human glucocorticoid receptor was 1.6×10^{-9} M. These data indicate that the pool of certain metabolites of RU 486 may contribute to a significant extent to the antiprogestagenic (23–33%) and even greater extent to the antiglucocorticoid (47–61%) effects of RU 486.

INTRODUCTION

RU 486 is a recently described 19-nor-steroid derivative with considerable antiprogestagenic and antiglucocorticoidal properties [1, 2]. When given during the luteal phase of the menstrual cycle, RU 486 is able to induce uterine bleeding [1]. In preliminary clinical studies RU 486 induced abortion in approx. 80% of the subjects when given between weeks 5–8 of pregnancy, at a daily dose of 200 mg for 4 days [3, 4]. Recently, using RU 486, Nieman *et al.* reported successful symptomatic treatment of Cushing's syndrome [5].

The dimethylaminophenyl side-chain at carbon 11 of RU 486 is important for antiprogestagenic action [6]. For all mammalian progesterone receptors investigated, RU 486 has a higher affinity than progesterone [4, 7, 8]. The relative binding affinity of RU 486 for the glucocorticoid receptor is either equal to [7] or greater than [4] that of dexamethasone. Synthetic steroids may have biologically active metabolites. Recently, Deraedt *et al.*[9] identified micromolar plasma concentrations of a monodemethylated metabolite after oral ingestion of RU 486. Our earlier studies indicate the presence of additional immunoreactive metabolites [10].

Deraedt *et al.* studied the metabolism of RU 486 in rats and found that the monodemethylated, didemethylated and alcoholic metabolites all retain antiglucocorticoidal and antiprogestagenic activity that correlated with the binding affinity to both progesterone and glucocorticoid receptors [9].

Since RU 486 has a high potential for clinical use, the biological activity of its major metabolites is of

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interest. Hence, plasma concentrations of RU 486 and its monodemethylated (RU 42633), didemethylated (RU 42848) and alcoholic non-demethylated (RU 42698) metabolites were measured specifically by high pressure liquid chromatography (HPLC) up to 72 h following oral ingestion of 100 mg of RU 486. Furthermore, their relative binding affinities for human placental glucocorticoid and uterine (myometrial and endometrial) progesterone receptors *in vitro* were compared with those of reference steroids.

EXPERIMENTAL

Chemicals

RU 486 (17β-hydroxy-11β-(4-dimethylaminophenyl)-17α-(1-propynyl)-estra-4,9-dien-3-one), the monodemethylated metabolite RU 42633 (17β-hydroxy-11β-(4-monomethylaminophenyl)-17α-(1-propynyl)-estra-4,9-dien-3-one), the didemethylated metabolite RU 42848 (17β-hydroxy-11β-(4-aminophenyl)-17α-(1-propynyl)-estra-4,9-dien-3-one), the alcoholic metabolite RU 42698 (17β-hydroxy-11β-(4-dimethylaminophenyl)-17α-(1-propynol)-estra-4,9-dien-3-one) and [6,7-^{3}H]RU 486 (sp. act. 37 Ci/mmol) were kindly donated by the Roussel-Uclaf Research Center, Romainville, France. The molecular structures of the compounds are presented in Fig. 1.

Progesterone (4-pregnene-3,20-dione), dexamethasone (9-fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione) and cortisol (11β,17,21-trihydroxy-4-pregnene-3,20-dione) were purchased from Steraloids Inc., Wilton, NH, U.S.A. ORG-2058 (16α-ethyl-21-hydroxy-19-nor-4-pregnene-3,20-dione) was obtained from Organon Int., Oss, The Netherlands. [6,7-^{3}H] dexamethasone [DXM] (sp. act. 45.8 Ci/mmol) was from New England Nuclear, Boston, MA, U.S.A., and [6,7-^{3}H]ORG-2058 (sp.act. 54 Ci/mmol) from Amersham Int, Ltd, Amersham, U.K.

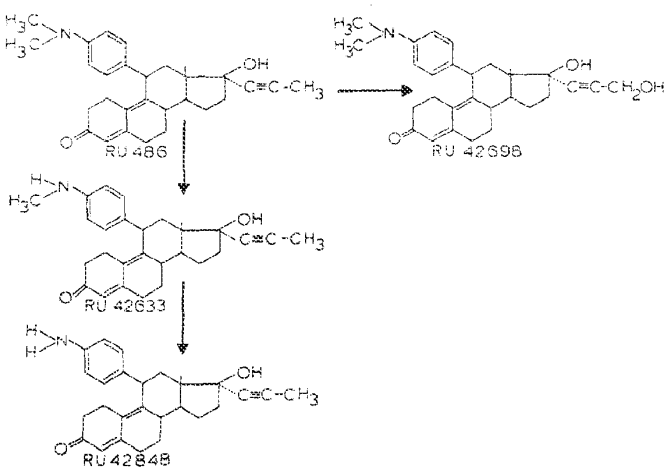
Acetic acid, diethyl ether, ethyl acetate, ethylene glycol, *n*-hexane, gelatin, glycerol, methanol, triethanolamine, titriplex III (EDTA), and HPLC column Hibar LiChrosorb RP-18 (250 × 4 mm int. dia) were purchased from Merck, Darmstadt, West Germany. Tris–HCl, dithiothreitol and Chromosorb® W-NAW 60/80 Mesh were from Sigma, St Louis, MI, U.S.A. Norit A was purchased from Amend, Irvington, NJ, U.S.A., and dextran T70 from Pharmacia, Uppsala, Sweden. Ammonium sulfate was purchased from Schwartz/Mann and scintillation fluid YA-riatuike (70% pseudochumene) was obtained from Yliopiston Apteekki, Helsinki, Finland.

Human samples

Plasma samples were collected from five healthy female volunteers after oral ingestion of 100 mg RU 486 in mid-luteal phase of their cycle. Uteri were obtained from patients undergoing hysterectomy for uterine fibroids. The last menstrual period of the patients had occurred approx. 2 weeks prior to operation. Only non-myomatous uterine tissue was used for the experiments described below. Placentas were obtained from women undergoing elective Caesarean section.

HPLC studies

The Chromosorb® column—HPLC-method described before [10] was modified. Disposable Pasteur pipettes were packed with 3 ml of Chromosorb® W-NAW 60/80 Mesh/20% ethylene glycol. A plasma sample was applied to the column, left for 30 min



MOLECULAR STRUCTURES OF RU 486, RU 42633, RU 42848 AND RU 42698

Fig. 1. Molecular structures of RU 486 and its monodemethylated (RU 42633), didemethylated (RU 42848) and alcoholic non-demethylated (RU 42698) metabolites.

and then eluted as follows: (I) 5 ml of ethyl acetate–*n*-hexane 5:95, and (II) 5 ml of ethyl acetate–*n*-hexane 60:40. The eluates were evaporated to dryness, redissolved in the HPLC-eluent used and vortex-mixed. A sample (100 μl) was injected into the HPLC system. The eluent used in HPLC for the assay of RU 486 was methanol–water–triethanolamine, 90:10:0.05, pumped at a rate of 1.5 ml/min; and for the assay of the three metabolites, methanol–water–acetic acid–diethyl ether–triethanolamine, 75:45:30:7.5:0.05, pumped at a rate of 2.2 ml/min.

Preparation of tissue samples

The uterine samples were processed as described by Haukkamaa [11] and placental tissues as described by Kontula *et al.* for adrenal cortical tissue [12]. Cytosol samples were prepared by high-speed centrifugation of tissue homogenates. To remove endogenous steroids from the cytosol samples a Dextran-coated charcoal (DCC) suspension containing 0.5% Norit A, 0.005% Dextran T70 and 0.1% gelatin in 50 mM Tris–HCl-buffer, pH 7.4, was prepared. An aliquot of DCC suspension (the volume corresponding to the cytosolic preparation to be stripped) was centrifuged at 3000 *g* for 10 min. The supernatant was discarded and the cytosol preparation was added to the charcoal pellet. The tubes were vortex-mixed and incubated for 10 min at +4°C. After centrifugation at 3000 *g* for 10 min, the stripped cytosol samples were used for the competitive protein binding assays.

Competitive receptor binding assays

All assays were performed in duplicate or triplicate in disposable glass test tubes and were repeated at least 3 times. For progesterone receptor studies, varying amounts (final concentrations, 10^{-10} to 10^{-5} M) of the steroids investigated (RU 486, RU 42633, RU 42848, RU 42698, ORG-2058 and progesterone) together with 10^{-7} M cortisol (to block binding to corticosteroid-binding globulin and to the glucocorticoid receptor), were pipetted into the tubes and evaporated to dryness. One-hundred microliters of cytosol (diluted to such an extent that approx 50% of the tritiated ligand was bound in the absence of any competitor) and 0.03 μCi of [^{3}H]ORG-2058 (pipetted in 100 μl of 50 mM Tris containing 1% ethanol; final concentration 2.8 nM) were added, the tubes were vortexed-mixed and then incubated overnight at +4°C. After incubation, 200 μl of DCC suspension was added to each tube and the contents vortex-mixed. After 10 min at +4°C, The tubes were centrifuged for 5 min at 3000 *g*. The supernatants (containing the bound fraction of the tritiated ligand) were transferred to polyethylene counting vials together with 3 ml of scintillation fluid and were counted for 5 min in a liquid scintillation 1212 Minibeta counter (Wallac, Turku, Finland). The relative binding affinities of the different compounds to the progesterone receptor were calculated at the 50% competition level according to Korenman [13].

For glucocorticoid receptor studies, similar incubations were carried out, with the following modifications: undiluted placental cytosol was used instead of uterine cytosol; no cortisol was added to the tubes; and [^{3}H]DXM (0.03 μCi/tube; final concentration 3.3 nM) served as tracer instead of [^{3}H]ORG-2058.

Scatchard-plot analysis

To verify the glucocorticoid receptor-nature of the steroid-binding component in placental cytosol, the dissociation constant (K_d) of its interaction with [^{3}H]DXM was measured. Aliquots (0.1 ml) of charcoal-stripped placental cytosol were incubated, in a total volume of 0.2 ml, with varying concentrations (0.3–300 nM) of [^{3}H]DXM dissolved in 50 mM Tris-buffer. The extent of non-specific binding of [^{3}H]DXM was estimated from a parallel set of tubes also containing 10^{-5} M non-radioactive DXM. The tubes were incubated overnight at +4°C. 0.25 ml of DCC was added to separate bound and unbound steroids. Further steps were carried out as described above for the competitive receptor binding assays. The binding data (corrected for non-specific binding) were analyzed according to Scatchard [14].

To measure the K_d of RU 486 for the human uterine progesterone receptor, a partially purified progesterone receptor preparation from human myometrial cytosol was first prepared as described by Kontula *et al.*[15]. Before use, [^{3}H]RU 486 was purified using the Chromosorb® technique [10]. The rest of the analysis was essentially as described above, except that partially purified progesterone receptor preparation and [^{3}H]RU 486 were used instead of placental cytosol and [^{3}H]DXM, respectively, and non-radioactive RU 486 was used instead of DXM for the correction for non-specific binding. No excess of cortisol was used.

RESULTS

The u.v.-absorption spectra of the synthetic metabolites and their behavior in our HPLC system were analyzed. All the synthetic metabolites shared a common u.v.-absorption maximum at 304 nm. Each also had a characteristic u.v.-absorption maximum: RU 42633 at 250 nm, RU 42848 at 240 nm and RU 42698 at 258 nm. Their retention times in our HPLC system were 4 min 36 s, 3 min 56 s and 2 min 49 s, respectively.

Plasma concentrations (mean + SEM) of RU 486 and of its monodemethylated (RU 42633), didemethylated (RU 42848) and non-demethylated alcoholic (RU 42698) metabolites, after oral ingestion of 100 mg of RU 486 by five female volunteers, are depicted in Fig. 2. Peak plasma concentrations of RU 486 (4.5 μmol/l) were reached within 1 h after ingestion of the drug. The concentrations of the monodemethylated metabolite (RU 42633) and hydroxylated alcoholic metabolite (RU 42698) also reached

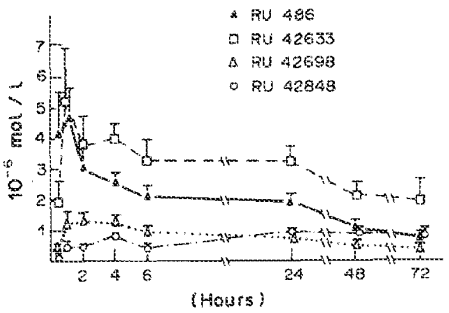


Fig. 2. Plasma concentrations (mean + SEM) of RU 486, RU 42633, RU 42848 and RU 42698, after oral ingestion of 100 mg of RU 486 by five female volunteers.

peak concentrations within 1–2 h suggesting rapid first pass metabolism of RU 486. Plasma concentrations of the didemethylated metabolite (RU 42848) increased slowly between 6 and 24 h, maximum concentrations were measured 24 h after ingestion of RU 486. After initial redistribution of 6 h the plasma concentrations of RU 486 and three of the metabolites assayed plateaued for 24 h or more. Concentrations of the monodemethylated metabolite exceeded those of the parent RU 486. Plasma concentrations of the didemethylated and the alcoholic metabolite were lower than those of RU 486 but still notable. Importantly, both RU 486 and the three metabolites were still present in micromolar concentrations at 72 h.

The binding of RU 486 and its metabolites to human progesterone receptor *in vitro* was studied

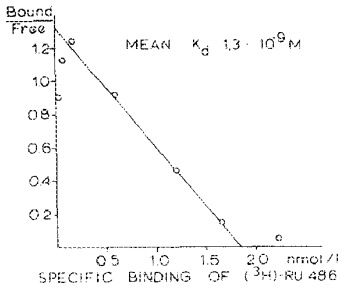


Fig. 3. [^{3}H]RU 486 Scatchard plot analysis of human myometrial progesterone receptor. Mean K_d 1.3×10^{-9} M.

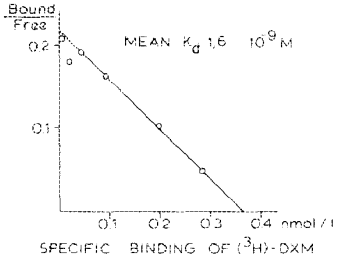


Fig. 4. [^{3}H]dexamethasone Scatchard plot analysis of human placental glucocorticoid receptor. Mean K_d 1.6×10^{-9} M.

Table 1. The relative binding affinities of the steroids investigated for human myometrial and endometrial progesterone receptor

Compound*	Relative† affinity %
ORG-2058	373
RU 486	100
Progesterone	43
RU 42633	21
RU 42698	15
RU 42848	9

*For systematic names see Experimental.
†Relative to RU 486 (= 100%).

using both human endometrial and myometrical cytosol. The relative binding affinities were identical and therefore combined. The K_d (mean of three separate experiments) of the binding of RU 486 to the human myometrial progesterone receptor was 1.3×10^{-9} M (Fig. 3). The relative binding affinity of RU 486 to the human progesterone receptor was higher than that of progesterone but lower than that of the potent synthetic progestin ORG-2058. All the metabolites of RU 486 studied had a lower affinity to the progesterone receptor than progesterone itself. The relative binding affinities of ORG-2058, progesterone and the three metabolites of RU 486 to the progesterone receptor are given in Table 1.

The binding of RU 486 and its metabolites to the human glucocorticoid receptor *in vitro* was studied using human placental cytosol. Figure 4 shows a representative Scatchard-plot of the interaction between the placental glucocorticoid receptor and tritiated DXM. The mean K_d in four experiments was 1.6×10^{-9} M. Competition studies revealed that all three major metabolites of RU 486, along with the parent compound, had higher affinities for the glucocorticoid receptor than the potent glucocorticoids dexamethasone and cortisol. Table 2 gives the relative affinities of the steroids tested for the human placental glucocorticoid receptor (mean values of 5 separate experiments).

DISCUSSION

Synthetic steroid derivatives may have biologically active metabolites. Radioimmunoassays often lack

Table 2. The relative binding affinities of the steroids investigated for human glucocorticoid receptor

Compound*	Relative affinity %
RU 486	100
RU 42633	61
RU 42698	48
RU 42848	45
Dexamethasone	23
Cortisol	9

*For systematic names, see Experimental.
†Relative to RU 486 (= 100%).

the specificity to discriminate between the parent compounds and their metabolites. Furthermore, a metabolite cross-reacting in the radioimmunoassay may lack biological activity.

Earlier studies on plasma RU 486 concentrations were carried out using direct radioimmunoassay [16, 17]. We have developed methods to specifically measure plasma concentrations of RU 486 and its three most proximal metabolic products using Chromosorb®-column chromatography and HPLC. The HPLC method described previously [9] had to be improved since it did not separate the monodemethylated metabolite from the alcoholic metabolite. Our results show that after ingestion of 100 mg of RU 486 by human female volunteers, at least three metabolites of RU 486, the monodemethylated (RU 42633), didemethylated (RU 42848) and alcoholic non-demethylated (RU 42698) forms, are circulating in micromolar concentrations, i.e. close to that of the parent compound for 72 h. When measured by a specific Chromosorb®-HPLC-method the plasma concentrations of RU 486 did not differ significantly when the single oral dose of RU 486 was increased from 100 to 800 mg [10]. This suggests rapid distribution of RU 486 into the tissues, and rapid first-pass metabolism of RU 486. Oral administration of [^{3}H]RU 486 resulted in remarkable extravascular diffusion in rats as reported by Deraedt *et al.*[9]. Studies employing specific HPLC method will reveal whether there is a change in the ratios between RU 486 and its metabolites after the administration of different oral and parenteral doses of RU 486. In general the receptor binding ability of a steroid gives an indication, although not proof, of its biological activity. Deraedt *et al.* determined the relative binding affinities of RU 486, RU 42633, RU 42848 and RU 42698 to cytosolic progesterone and glucocorticoid receptors. Oral administration of RU 486, RU 42633, RU 42848 or RU 42698 in rats resulted in abortion or inhibited the thymolytic effect of dexamethasone thus demonstrating their antiprogestational and antiglucocorticoidal nature, respectively [9]. Their results indicate that the alcoholic metabolite might have a higher biological activity in relation to receptor binding as compared with the monodemethylated metabolite. The relative binding affinities of RU 486 and its three metabolites to the human glucocorticoid and progesterone receptors were determined, using dexamethasone and ORG-2058, respectively, as reference steroids. Before accepting the previously characterized progesterone [11] and glucocorticoid receptor [12] systems as models, the saturability and high affinity of the binding was confirmed in each case (Figs 3 and 4). In previous studies, RU 486 has been shown to display a binding affinity greater than that of progesterone in all the mammalian progesterone receptors investigated [4, 7]. Variations in the reported affinities [4, 7, 8] may be explained by species differences in the characteristics of steroid receptors [15]. The lower binding affinity of progesterone to the human progesterone receptor, as compared to RU 486 (43%, Table 1), is in accord with the value of 67%, which was reported previously by Gravanis *et al.*[8].

The hydrophobic molecular structure of RU 486 reveals features suggesting high affinity binding to progesterone receptor [18]. The antiprogestagenic properties of RU 486 are thought to be due to the dimethylaminophenyl side chain at carbon 11 [6]. Demethylation of this side chain decreases its hydrophobicity, and also decreases the binding affinity of mono- and didemethylated metabolites to 21 and 9%, respectively (Table 1). Hydroxylation of the side chain at carbon 17 decreases the binding affinity of the compound from 100% (RU 486) to 15% [RU 42698) (Table 1).

Based on the relative receptor binding affinities of the metabolites (Table 1) and their plasma concentrations (Fig. 2), it is possible to estimate the contribution of the metabolite pool in the antiprogestational action of RU 486. The theoretical contribution of the prevailing metabolite pool to the antiprogestational activity of RU 486 after ingestion of 100 mg of RU 486 amounts to about 23% at 1 h but as high as 33% at 24 h.

Comparatively little is known about the relative affinity of RU 486 for human glucocorticoid receptors. However, in comparison with published clinical and experimental studies [2, 4, 7], the high affinities of RU 486 and of its metabolites to the human glucocorticoid receptor (Table 2) are not surprising. However, it must be kept in mind that competition studies performed at 0–+4°C in cell-free conditions do not necessarily correctly reflect the situation at +37°C and in the whole organism [19]. The theoretical contribution of the metabolites of RU 486 to the antiglucocorticoidal action of RU 486 was calculated. This was based on the relative receptor binding affinities (Table 2) and plasma concentrations (Fig. 2) of the metabolites. These results suggests that 1 and 24 h after the intake of 100 mg of RU 486, the three metabolites would represent 47 and 61%, respectively, of the total antiglucocorticoid activity of RU 486.

Despite the high affinity binding of RU 486 and its metabolites to the human glucocorticoid receptor *in vitro*, previous clinical experience suggests that large single doses of RU 486 ($\geq$400 mg) are needed to promote antiglucocorticoid effects *in vivo* [2, 20]. Chronic treatment with 25–200 mg/day of RU 486, doses sufficient to produce uterine bleeding in 80% or more cases, did not result in any apparent antiglucocorticoidal effects [1, 3]. This may be partly explained by the fact that the concentrations of plasma cortisol are at least one order of magnitude higher than that of plasma progesterone, even during the luteal phase of the menstrual cycle. The commonly used clinical parameters of antiglucocorticoid activity, i.e. plasma ACTH and cortisol concentrations,

necessitate transport of the antiglucocorticoid molecule to the hypothalamus or the pituitary in order to affect ACTH secretion. Thus, the fact that up to 400 mg of RU 486 was needed to equal the suppressive effects of 1 mg of dexamethasone on ACTH and cortisol *in vivo* [2], might be explained by the higher bioavailability of DXM (32% non-protein bound in plasma, ref. 21) or higher hypothalamic/pituitary uptake of DMX compared to RU 486. In view of the fact that plasma concentrations of RU 486 are not elevated by increasing the oral dose of RU 486 from 100 to 800 mg, all associated with micromolar concentrations of antiglucocorticoid steroids (Fig. 2, ref.10), it still remains an enigma why systemic antiglucocorticoidal effects are virtually never seen at RU 486 doses below 400 mg.

In conclusion, the remarkable binding affinities of the metabolites of RU 486 to human progesterone and glucocorticoid receptors suggest an important role of these metabolites, along with the parent compound, as regards the antisteroidal action of RU 486. This also justifies further metabolic studies after administration of varying oral or parenteral doses of RU 486.

Acknowledgements—This work was undertaken as part of the contraceptive development program sponsored by the International Committee for Contraception Research of the Population Council, Inc., New York. The financial support provided by the Ford Foundation, the Mellon Foundation and the Pehr Oscar Klingendahl Foundation is gratefully acknowledged. The content does not necessarily reflect the policy of any of the funding sources. We thank Ms Marjatta Tevilin for her expert technical help and Ms Tellervo Hiljanen for her kind assistance.

REFERENCES

1. Schaison G., George M., Lestrat N., Reinberg A. and Baulieu E. E.: Effects of the antiprogesterone steroid RU 486 during midluteal phase in normal women. *J. clin. Endocr. Metab.* **61** (1985) 484–489.
2. Bertagna X., Bertagna C., Luton J-P., Husson J-M. and Girard F.: The new steroid analog RU 486 inhibits glucocorticoid action in man. *J. clin. Endocr. Metab.* **59** (1984) 25–28.
3. Haspels A. A.: Interruption of early pregnancy by an anti-progestional compound, RU 486. *Eur. J. Obstet. Gynec. reprod. Biol.* **20** (1985) 169–175.
4. Herrmann W., Wyss R., Riondel A., Philibert D., Teutsch G., Sakiz E. and Baulieu E. E.: 1982 Effet d'un stéroide antiprogestérone chez la femme. Interruption du cycle menstruel et de la grossesse au début. *C. r. hebd. Acad. seanc. Sci. Paris* **294** (1982) 933–938.
5. Nieman L., Chrousos G., Kellner C., Spitz I., Nisula B., Cutler G., Merriam G., Bardin W. and Loriaux L.: Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *J. clin. Endocr. Metab.* **61** (1985) 536–540.
6. Teutsch G.: Analogues of RU 486 for the mapping of the progestin receptor: synthetic and structural aspects. In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Edited by E. E. Baulieu and S. Segal). Plenum Press, New York (1985) pp. 27–47.
7. Schreiber J., Hsueh A. and Baulieu E. E.: Binding of the antiprogestin RU 486 to rat ovary steroid receptors. *Contraception* **28** (1983) 77–85.
8. Gravanis A., Schaison G., George M., de Brux J., Satyaswaroop P. G., Baulieu E. E. and Robel P.: Endometrial and pituitary responses to the steroidal antiprogestin RU 486 in postmenopausal women. *J. clin. Endocr. Metab.* **60** (1985) 156–163.
9. Deraedt R., Bonnat C., Busigny M., Chatelet P., Cousty C., Mouren M., Philibert D., Pottier J. and Salmon J.: Pharmacokinetics of RU 486. In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Edited by E. E. Baulieu and S. Segal). Plenum Press, New York (1985) pp. 103–122.
10. Heikinheimo O., Tevilin M., Shoupe D., Croxatto H. and Lähteenmäki P.: Quantitation of RU 486 in human plasma by HPLC and RIA after column chromatogrpahy. *Contraception* **34** (1986) 613–624.
11. Haukkamaa M.: Binding of progesterone by rat myometrium during pregnancy and by human myometrium in late pregnancy. *J. steroid Biochem.* **5** (1974) 73–79.
12. Kontula K., Pomoell U-M., Gunsalus G. and Pelkonen R.: Glucocorticoid receptors and responsiveness of normal and neoplastic human adrenal cortex. *J. clin. Endocr. Metab.* **60** (1985) 283–289.
13. Korenman S. G.: Relation between estrogen inhibitory activity and binding to cytosol of rabbit and human uterus. *Endocrinology* **87** (1970) 1119–1123.
14. Scatchard G.: The attaction of proteins for small molecules and ions. *Ann. N.Y. Acad. Sci.* **51** (1949) 660–672.
15. Kontula K., Jänne O., Rajakoski E., Tanhuanpää E. and Vihko R.: Ligand specificity of progesterone-binding proteins in guinea pig and sheep. *J. steroid Biochem.* **5** (1974) 39–44.
16. Shoupe D., Spitz I., Lacarra M., Gutierrez E., Lähteenmäki P. and Mishell D. Jr: Endocrinologic effects of the antiprogesterone, RU 486, in normal women in the luteal phase. In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Edited by E. E. Baulieu and S. Segal). Plenum Press, New York (1985) pp. 285–293.
17. Salmon J. and Mouren M.: Radioimmunoassay of RU 486. In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Edited by E. E. Baulieu and S. Segal). Plenum Press, New York (1985) pp. 99–101.
18. Jänne O., Kontula K., Luukkainen T. and Vihko R.: Oestrogen-induced progesterone receptor in human uterus. *J. steroid Biochem.* **6** (1974) 501–506.
19. Raynaud J. P., Bouton M. M., Moguilewsky M., Ojasoo T., Philibert D., Beck G., Labrie F. and Mornon J. P.: Steroid hormone receptors and pharmacology. *J. steroid Biochem.* **12** (1980) 143–158.
20. Gaillard R., Riondel A., Muller A., Herrmann W. and Baulieu E. E.: RU 486: A steroid with antiglucocorticosteroid activity that disinhibits the human pituitary-adrenal system at a specific time of day. *Proc. nain. Acad. Sci. U.S.A.* **81** (1984) 3879–3882.
21. Benet L. and Sheiner L.: Design and optimization of dosage regimens; pharmacokinetic data. In *The Pharmacological Basis of Therapeutics* (Edited by A. G. Gilman, L. S. Goodman, T. W. Rall and F. Murad). Macmillan, New York (1985) pp. 1663–1733.

Clinical Article

Pharmacokinetic study of RU 486 and its metabolites after oral administration of single doses to pregnant and non-pregnant women

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RU 486 and three of its metabolites (RU 42633 - monodemethyl, RU 42848 - didemethyl, and RU 42698 - hydroxymetabolite) were determined by HPLC in plasma from nine non-pregnant and 36 pregnant women. Each non-pregnant subject took an oral dose of RU 486 (25, 100, 400 and 600 mg consecutively) once per menstrual cycle. Six of the nine women also received a dose of 200 mg. The 36 pregnant women were randomized into four groups which were given a single dose of 25, 100, 400 or 600 mg RU 486. Blood samples were taken up to 120 h after dosing. Peak concentrations of RU 486 occurred on most occasions within 2 h. Plasma concentrations at 1 h and at 24 h increased in proportion to log dose. There was a wide variability (up to ten-fold) in the pharmacokinetic parameters within each dose group. Plasma concentra- tions of RU 42633 were similar to those of RU 486 but concentrations of RU 42848 and RU 42698 were much lower. As with RU 486, the plasma concentrations of the metabolites were maintained at high levels for

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up to 48-72 h after dosing. The findings were consistent with a rapid metabolism of RU 486 to RU 42633; removal of the second methyl group leading to RU 42698 occurred much more slowly and to a much less extent than removal of the first. There appeared to be no significant differences between the non-pregnant and pregnant women in either the plasma concentrations or pharmacokinetic parameters of RU 486 and its metabolites.

Keywords: Mifepristone (RU 486), RU 486 metabolites, human pharmacokinetics

Introduction

RU 486 [mifepristone; 17β-hydroxy-11β-(4-dimethylaminophenyl)-17α-(1-propynyl)-estra-4,9-dien-3-one] is a potent antiprogestational steroid (1) which has been shown to be effective in terminating early pregnancy, especially in combination with a prostaglandin (2-5). Three metabolites of RU 486 have been identified (Fig. 1). The compound undergoes demethylation to give the mono- (RU 42633) and di- (RU 42848) demethylated derivatives as well as hydroxylation of the propynyl group (RU 42698). RU 486 and its metabolites can be readily assayed in blood by HPLC (6),

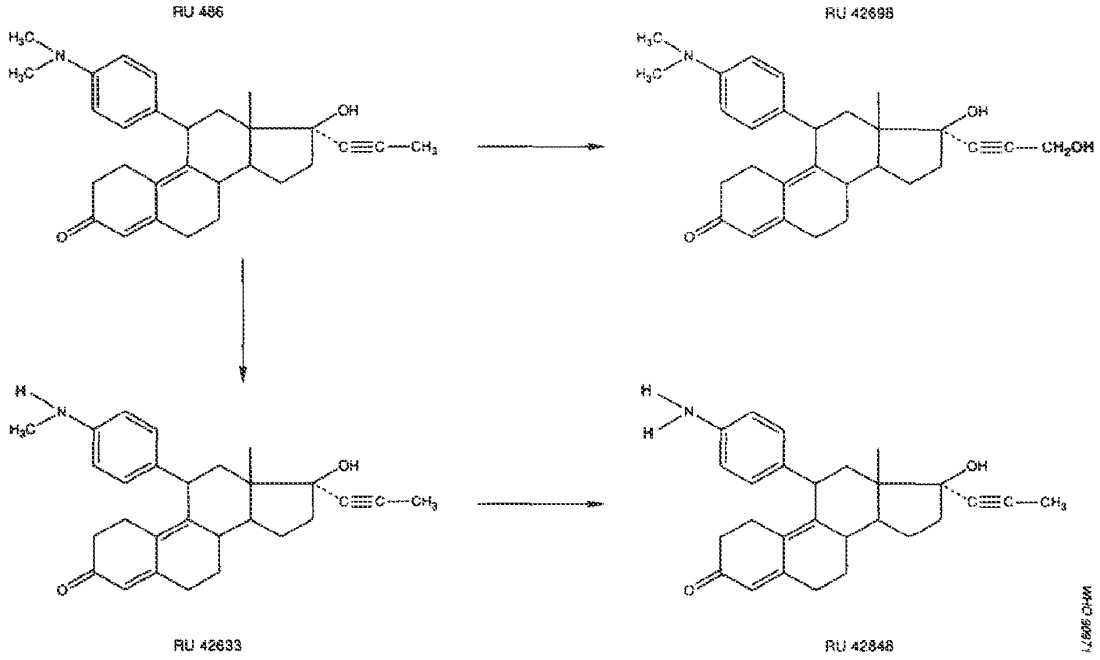

FIGURE 1. RU 486 and its three metabolites assayed in the present study.

and information is available regarding the blood concentrations of the three metabolites in non-pregnant women (7-9). The results of these studies suggest that the pharmacokinetics of RU 486 vary depending on the dose given, probably because the compound binds to a high affinity-limited capacity binding protein in serum (8). The absence of a proportional increase in the plasma concentrations of RU 486 following ingestion of larger doses may explain the lack of a dose-response relationship when the drug is used alone for the termination of early pregnancy (10).

In order to further examine the pharmacokinetics of RU 486, the blood levels of the parent compound and its three main metabolites were measured by HPLC after administration of various doses to the same group of non-pregnant women, and the derived pharmacokinetic parameters compared to those found in pregnant women taking similar doses of the antiprogestin.

Subjects and Methods

Permission for the study had been granted by the Ethics Committees of the Shanghai Institute for Planned Parenthood Research and of the World Health Organization, and informed consent was obtained from the volunteers after the purpose of the study and the procedures involved had been explained.

Nine non-pregnant and 36 pregnant women were recruited. All subjects were healthy with no history of liver, renal, cardiovascular or endocrine disease and none had taken any steroid-containing drugs for at least three months. The non-pregnant subjects had had normal menstrual cycles (25-35 days) for at least three months prior to admission to the study. The pregnant subjects also had had regular menstrual cycles (25-35 days) for at least three months prior to conception and, at the time of study, had been amenorrhoeic for up to 49 days with an ultrasonographically confirmed, normal intrauterine pregnancy.

Each non-pregnant subject received a dose of RU 486 once per menstrual cycle, three days before the expected time of menses. The doses, administered consecutively, were 25, 100, 400 and 600 mg. In six of the nine women, a dose of 200 mg was also given. The pregnant subjects were randomized into four groups which were given a single dose of 25, 100, 400 or 600 mg RU 486. The pregnancies were terminated by vacuum aspiration after collection of the last blood sample.

In both pregnant and non-pregnant women, blood samples were taken from an antecubital vein immediately before and 20 min, 40 min, 1, 2, 4, 8, 12, 48, 72, 96 and 120 h after administration of RU 486. Heparin was used as anticoagulant and the plasma obtained after centrifugation was stored at -20°C until analysed.

RU 486 and its three metabolites were determined in the plasma sam-

ples by HPLC as described previously (6) with minor modifications. An ODS reversed phase column (200mm x 3.5mm ID) was used with a mobile phase of methanol: methylcyanide: water (42: 28: 30 by vol) at a flow rate of 1 ml/min. Recoveries of RU 486 and its three metabolites RU 42633, RU 42698 and RU 42848 were 92%, 93%, 94% and 64%, respectively, the sensitivity of detection for the four steroids in plasma was 10 ng/ml, and the intra- and interassay coefficients of variation were < 10%. Adequate separation of the four steroids was achieved as illustrated in Fig. 2.

Plasma RU 486 concentration-time curves were analysed by the iterative method. With doses of 200 mg or less, the curves were in agreement with a two-compartment open model, whereas with higher doses, zero-order kinetics applied for a period of about 48 h after completion of the absorption and distribution phases. Accordingly, the values were computed according to a non-compartment model (11,12). Clearance (Cl) was calculated from dose/AUC (area under the plasma concentration-time curves obtained by the trapezoid rule). Volume of distribution (Vd) was calculated from Cl/kel.

Statistical analysis was done by t-test and differences were considered significant if $P < 0.05$. Because of the size of the dose groups (nine women),

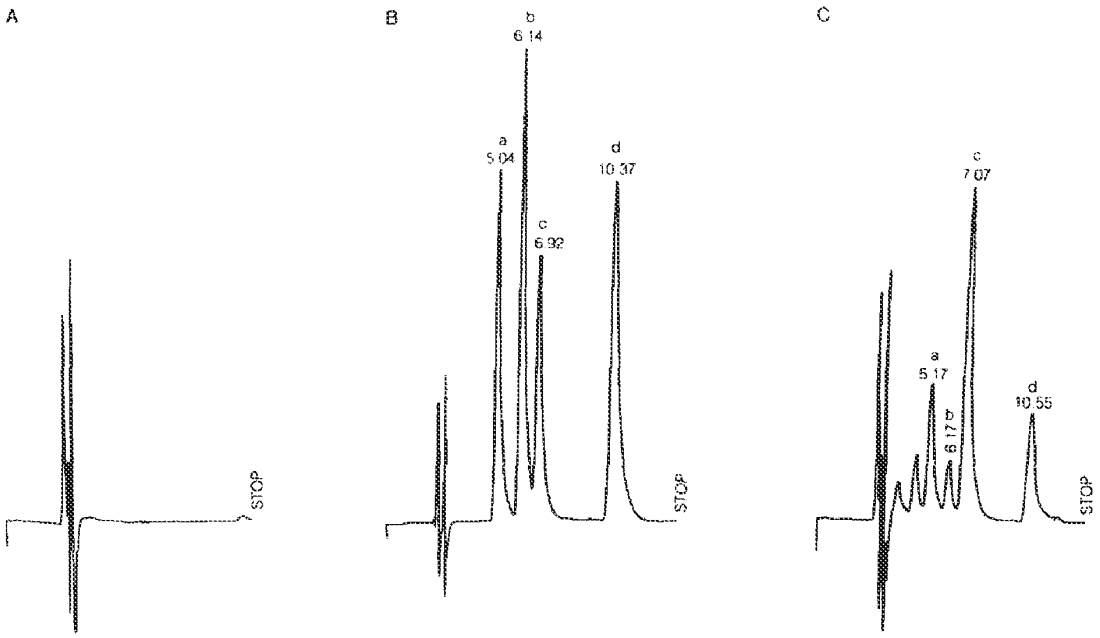

FIGURE 2. HPLC of RU 486 and its metabolites (a: RU 42848; b: RU 42698; c: RU 42633; d: RU 486); A: blank plasma; B: blank plasma with standards added; C: plasma obtained eight hours after a single dose of 100 mg RU 486.

the study could be expected to demonstrate differences between groups of about 1 SD (95% level two-tailed test; 90% power). Based on our previous work (6), this discriminatory power would be sufficient to demon- strate differences in pharmacokinetic parameters of biological relevance.

Results

Characteristics of subjects

There were no significant differences in physical characteristics between the groups studied (Table 1).

Plasma levels of RU 486 and its metabolites

Mean plasma concentrations of RU 486 and its three metabolites at various times after oral administration of single doses of RU 486 to the nonpregnant women are shown in Fig. 3A. Absorption of RU 486 was rapid, as illustrated by the presence of detectable amounts of the steroid in all 20 min samples of all subjects except one who received a 25 mg dose. The rapidity of absorption was also shown by the finding that peak plasma concentrations were achieved at 1 h or less for 21 of the 42 administrations of RU 486, between 1 and 2 h for 15 administrations and after 2 h in only six. There was a very marked between-subject variation in the plasma concentrations after the same dose of RU 486, and examples of the size of this variation are given for some sample times in Table 2. Detectable levels of RU 486 were found in the 96 h samples of all women receiving 200 mg or more, in seven of the nine samples after 100 mg, but in none of the samples after the 25 mg dose.

The ratio of the lh:24h concentrations for the five doses of RU 486 decreased with increase in dose (25 mg, 5.8; 100 mg, 3.5; 200 mg, 2.9; 400 mg, 2.6; 600 mg, 2.4) suggesting that the rate of metabolism decreased with increase in dose. This is also suggested by the data in Fig. 3A where

TABLE 1. Physical characteristics of subjects (X ± SE)

	Non-pregnant	Pregnant			
Dose (mg)	25–600	25	100	400	600
Age (yrs)	28.9 ± 5.1	29.1 ± 3.9	26.1 ± 5.5	28.7 ± 4.6	30.2 ± 4.8
Height (cm)	159.6 ± 4.7	161.7 ± 1.5	162.4 ± 3.8	161.4 ± 3.8	161.0 ± 2.7
Weight (kg)	55.4 ± 7.0	54.6 ± 4.4	52.3 ± 4.2	51.7 ± 5.3	53.5 ± 4.4
Body mass index	21.7 ± 2.1	20.7 ± 1.7	19.8 ± 1.7	19.8 ± 1.5	20.6 ± 1.8

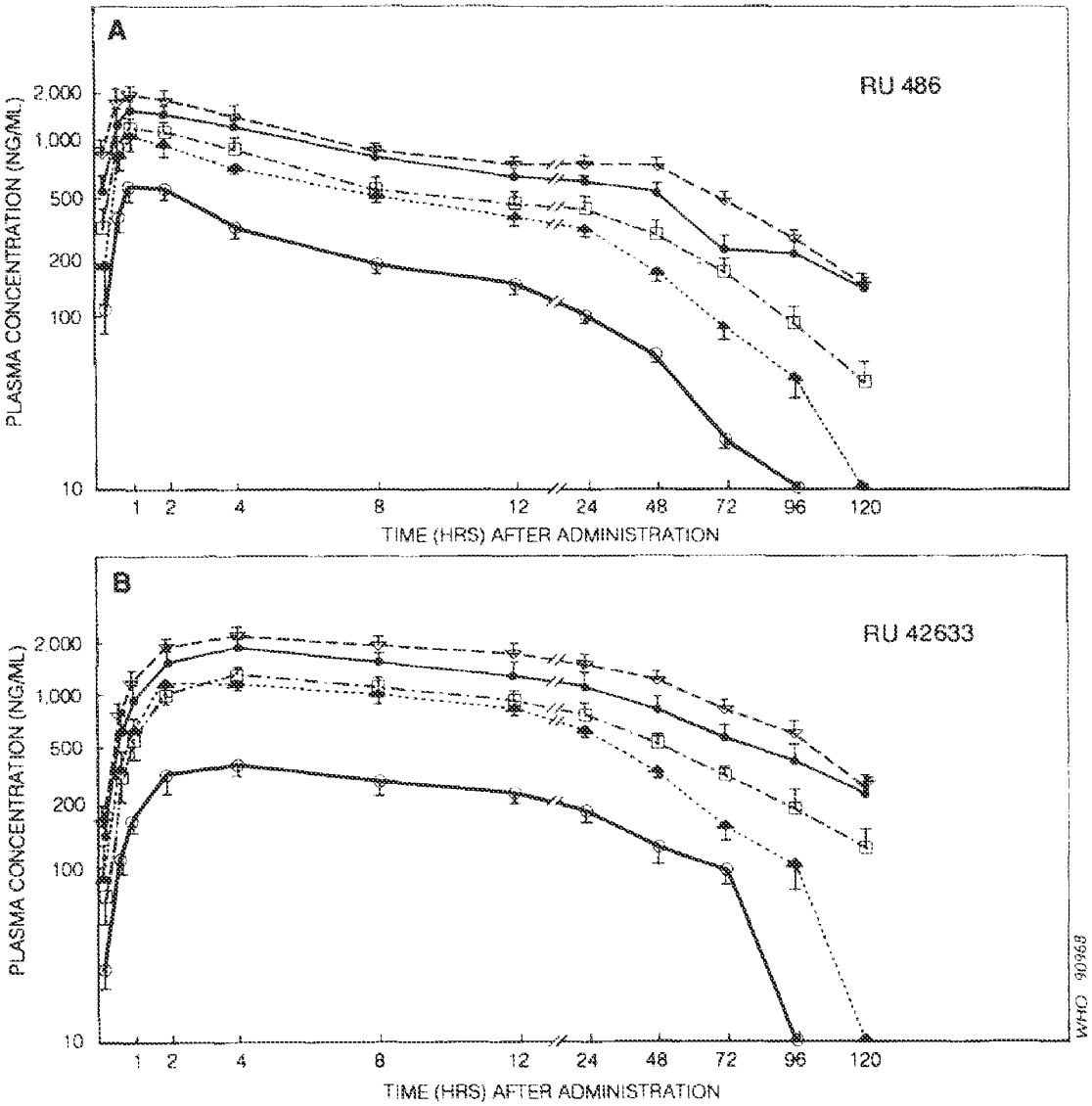

FIGURE 3A-D: Mean (SEM) concentrations of RU 486 (A) and its metabolites (RU 42633: B; RU 42848: C; RU 42698: D) after oral administration of various doses of RU 486 to non-pregnant women.
(○—○: 25 mg; ▲----▲: 100 mg; □–□: 200 mg; •—•: 400 mg; ▽---▽: 600 mg)

for the higher doses, in contrast with the lower doses, the steady decrease in plasma levels continues up to 96 - 120 h. Although increasing the dose of RU 486 led to an increase in its mean plasma concentrations, this increase appeared unrelated to dose. Thus, the ratios of plasma concentrations at 1 h for the 25, 100, 200, 400 and 600 mg doses were 1: 1.9: 2.1:

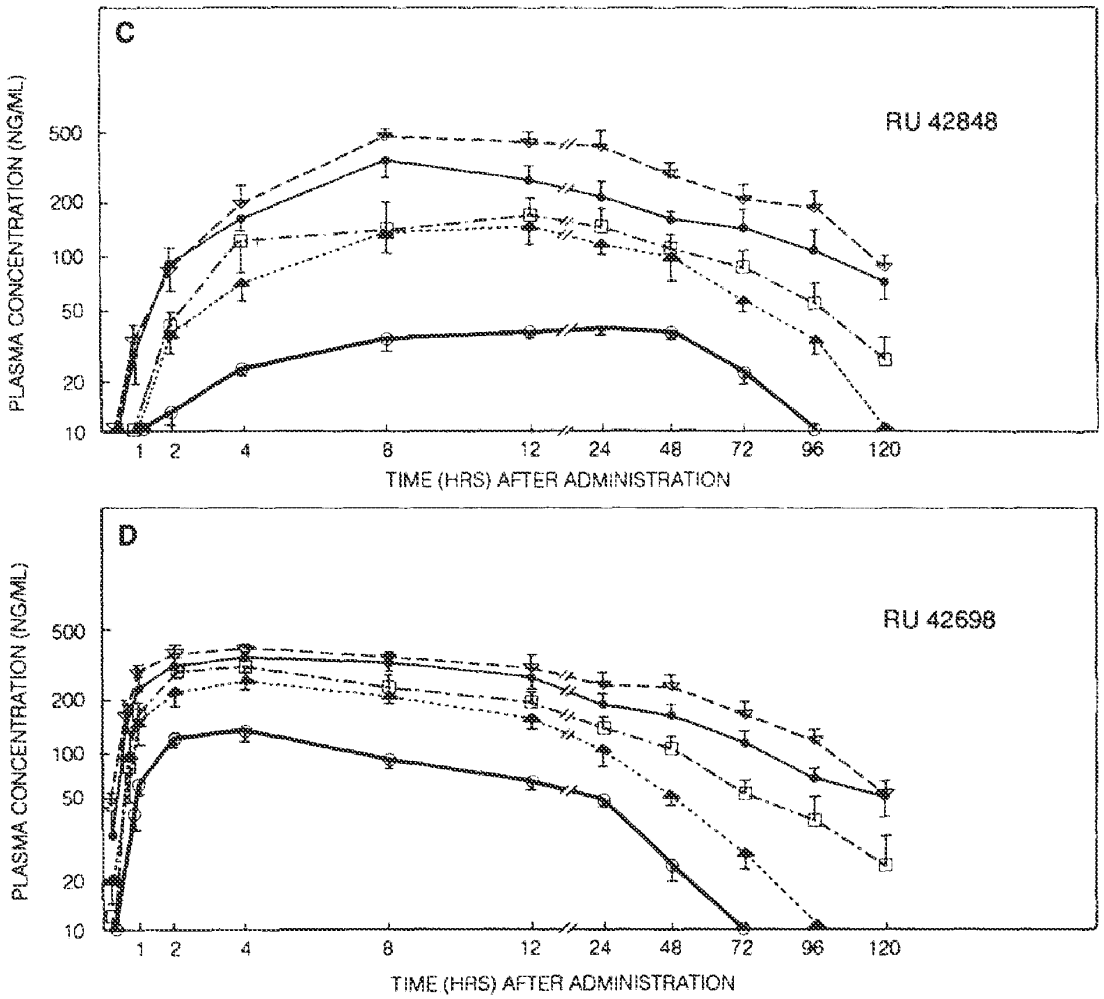

FIGURE 3 (contd).

TABLE 2. Between-subject variation in plasma RU 486 concentrations. Values are minimum and maximum concentrations (ng/ml) at four selected times after administration of the various doses of RU 486 to non-pregnant women

Dose (mg)	25	100	200	400	600
Time 20 min	0–301	15–787	113–859	73–1098	37–1469
1 h	59–1296	123–2080	770–1840	417–2943	1280–2966
8 h	116–319	368–716	318–1077	503–1249	548–1328
48 h	31–103	89–291	97–520	241–788	452–1083

2.6: 3.2 compared to dose ratios of 1: 4: 8: 16: 24. However, there were significant correlations between log dose and 1 h plasma concentrations ($R = 0.98$), and between dose and the ratio of plasma concentrations at 1 h ($R = 0.95$). Similarly, there were significant correlations between log dose and 24 h plasma concentrations ($R = 0.98$), and between dose and the ratio of the plasma concentrations at 24 h ($R = 0.97$).

Fig. 3B shows the plasma concentrations of the monodemethylated metabolite. RU 42633 reached peak levels that were similar to those of RU 486, but the peak was attained more slowly. Thus, in contrast with RU 486, peak concentrations of RU 42633 were reached in less than 2 h for only two of the 42 administrations of RU 486, from 2 to 4 h for 19 administrations, and after 4 h for 21. From 4 h after dosing, mean plasma concentrations of RU 42633 were greater than those of RU 486. Detectable levels of RU 42633 were present in the 96 h samples after administration of 100 mg or more of RU 486 and in three of the nine samples after the 25 mg dose.

Peak concentrations of RU 42848 (Fig. 3C) and RU 42698 (Fig. 3D) were only about 25% of those of RU 486 and RU 42633 and occurred much later. Thus, for 42 administrations of RU 486, peak concentrations of RU 42848 occurred in less than 12 h on 18 occasions, between 12 and 24 h in 20, and between 24 and 48 h in four. In spite of the lower peak concentrations of RU 42848, detectable levels were found at 96 h in all samples except one, when the dose of RU 486 was 100 mg or more. The times to reach peak concentrations of RU 42698 were similar to those for RU 42633, occurring on six occasions in less than 2 h, between 2 and 4 h for 18 administrations, and after 4 h for 18. Plasma concentrations of RU 42698 declined more quickly than those of RU 42848; detectable levels were present at 96 h in all samples except one after 200 mg or more of RU 486, in only one of the samples after 100 mg, and in none of the samples after 25 mg.

Plasma concentrations of RU 486 after a single oral dose of the compound to pregnant women are shown in Fig. 4A and were not significantly different from the corresponding values in the non-pregnant subjects. Plasma concentrations of the metabolites are not presented in detail since they too did not differ significantly between the pregnant and non-pregnant women. The values for the subjects receiving the 600 mg dose of RU 486 are compared in Fig. 4B.

Pharmacokinetic parameters

The calculated parameters for various doses of RU 486 in pregnant and non-pregnant women are summarized in Table 3. For women in any particular dose group, there was a wide variability (up to ten-fold) in most of the parameters. For Cmax, some of the women in the 25-mg dose group had values

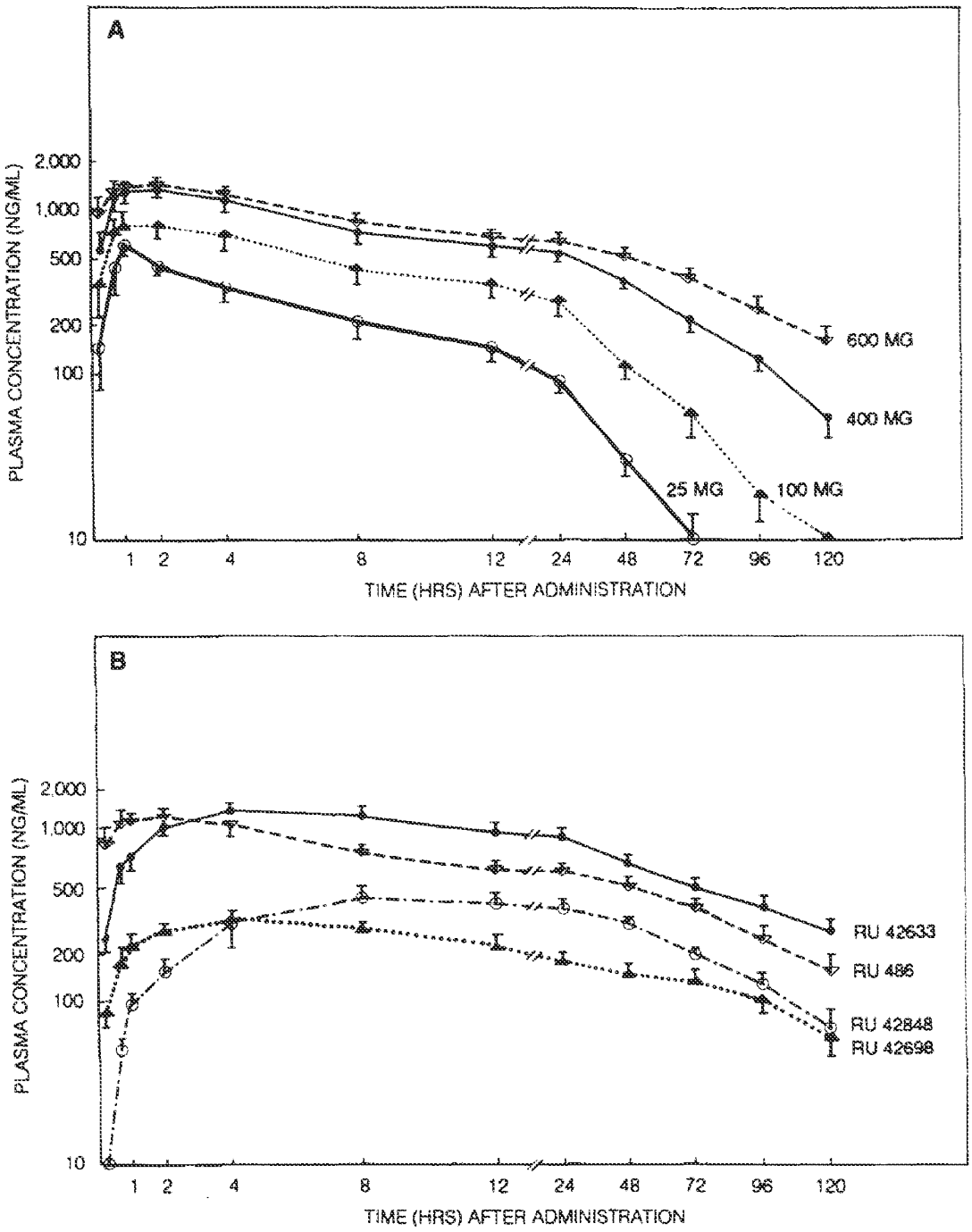

FIGURE 4. A. Plasma concentrations of RU 486 after single oral doses of RU 486 to pregnant women. B. Plasma concentrations of RU 486 and its metabolites after oral administration of 600 mg RU 486 to pregnant women.

TABLE 3. Calculated pharmacokinetic parameters for various doses of RU 486 in pregnant and non-pregnant women. Values are means with SD in parentheses

	Non-pregnant					Pregnant			
Dose (mg)	25	100	200	400	600	25	100	400	600
Cmax	820	1660	1670	2090	2290	750	1320	1730	1910
(ng/ml)	(350)	(604)	(405)	(570)	(600)	(184)	(400)	(360)	(376)
Tmax(h)	1.7	1.7	1.6	1.4	1.6	1.8	2.1	1.6	1.5
	(0.7)	(1.1)	(0.7)	(0.5)	(1.2)	(1.2)	(1.3)	(1.2)	(1.4)
Tel(h)	18.9	26.0	37.6	39.6	50.2	12.6	26.0	31.4	50.9
	(11.7)	(7.3)	(18.5)	(13.9)	(31.0)	(7.5)	(16.9)	(12.8)	(26.4)
Cl(l/h)	3.1	4.3	6.4	6.8	6.9	4.6	7.0	9.5	9.7
	(1.1)	(1.2)	(3.5)	(2.9)	(1.8)	(2.9)	(4.1)	(3.6)	(3.7)
Vd(l)	76	160	297	342	448	63	201	390	620
	(50)	(67)	(129)	(73)	(134)	(22)	(92)	(108)	(220)
AUC	9.1	35.3	39.9	67.9	95.6	7.3	18.4	47.2	74.0
(μg/l/h)	(3.5)	(6.8)	(17.2)	(22.2)	(38.4)	(3.3)	(8.3)	(14.3)	(35.1)

almost as high as some of those who received 600 mg. Although Tmax showed wide intersubject variation within each dose group, the mean values for the groups were not statistically significantly different. Values for some parameters, e.g. Cmax and AUC, were consistently higher in the non-pregnant than in the pregnant women for similar doses, whereas the reverse was the case for the clearance (Cl) values. The differences, however, were not statistically significant. Values for Tel and Vd were not different between the pregnant and non-pregnant groups. Whilst it would be expected that values for Cmax and AUC would increase with increase in dose, values for Tel, Cl and Vd also did, and the differences between the highest and lowest doses were statistically significant ($P < 0.05$).

Differences in the mean Cmax values between the lowest and highest doses of RU 486 were two- to three-fold, but for AUC the difference was about ten-fold. This discrepancy arose because Tel increased three- to four-fold with dose, a change resulting from changes in Vd and Cl which determine Tel. Both Vd and Cl increased with dose, the increase in Vd (six- to nine-fold) being proportionately greater than that of Cl (approximately two-fold). The increase in Vd with dose suggests that RU 486 binds only weakly to plasma protein and that this binding is of limited capacity. Clearance also appeared to reach a limiting value at doses above 200 mg and this was probably the major factor in determining the elevated plasma levels of RU 486 over a long duration. With doses of RU 486 greater than 100 mg, plasma levels remained high for up to 48 h and did not become undetectable for 96 to 120 h.

Calculated parameters for the mono-demethylated (RU 45233), di-demethylated (RU 42848) and hydroxylated (RU 42698) metabolites are shown in Tables 4, 5 and 6, respectively.

Values of Cmax for RU 42633 were similar to those of RU 486 (Table 4), although the peak occurred later (mean Tmax about 1.6 h for RU 486 and 4.5 to 5 h for RU 42633) and, consequently, the serum levels remained higher for a longer duration. The findings are consistent with RU 42633 being a rapidly formed metabolite of RU 486. RU 486 was also rapidly transformed to RU 42698 (mean Tmax about 4 h) (Table 6) but its plateau concentrations were only about 20% of those of RU 486 suggesting that RU 42698 is only a minor metabolite of RU 486. Its lower serum concentration was not due to it being more rapidly metabolised since its Tel was not significantly different from that of RU 486. RU 42848 (Table 5) showed a different pattern from the other metabolites and reached Cmax, which was only about 5% - 20% that of RU 486 and RU 42633, much more slowly (mean Tmax about 14 h). This suggests that the removal of the second methyl group is a much slower process than removal of the first. This slow removal of the second methyl group accounts for the much lower plasma concentrations of RU 42848, since the Tel for this metabolite was not significantly different from that of RU 42633.

TABLE 4. Calculated pharmacokinetic parameters for the mono-demethyl metabolite RU 42633 after administration of various doses of RU 486 to pregnant and non-pregnant women. Values are means with SD in parentheses

	Non-pregnant					Pregnant			
Dose (mg)	25	100	200	400	600	25	100	400	600
Cmax	487	1433	1396	2136	2031	478	1007	1749	1692
(ng/ml)	(252)	(638)	(469)	(829)	(781)	(139)	(323)	(773)	(507)
Tmax(h)	3.6	4.1	4.4	6.2	5.2	6.9	5.2	4.9	4.8
	(1.5)	(1.8)	(1.1)	(4.1)	(0.7)	(7.1)	(2.0)	(1.4)	(2.0)
Tel(h)	35.4	25.4	49.0	58.0	51.1	19.8	33.1	40.9	124
	(22.1)	(8.2)	(22.0)	(40.0)	(19.9)	(7.1)	(12.7)	(16.7)	(145)
Cl(l/h)	17	23	28	38	45	20	36	57	57
	(6)	(9)	(9)	(17)	(20)	(10)	(18)	(29)	(33)
Vd (lx10^2)	7.9	8.6	18	26	30	4.9	18	30	59
	(4.3)	(3.4)	(5)	(14)	(12)	(1.1)	(12)	(12)	(30)
AUC	17.4	42.5	79.2	132.1	160.4	14.8	34.1	86.8	172.8
(µg/l/h)	(7.9)	(16.0)	(26.2)	(65.8)	(64.6)	(5.3)	(14.8)	(35.3)	(160.6)

TABLE 5. Calculated pharmacokinetic parameters for the di-demethyl metabolite RU 42848 after administration of various doses of RU 486 to pregnant and non-pregnant women. Values are means with SD in parentheses

	Non-pregnant					Pregnant			
Dose (mg)	25	100	200	400	600	25	100	400	600
Cmax	45	185	206	418	544	76	125	548	504
(ng/ml)	(10)	(118)	(126)	(184)	(254)	(35)	(55)	(301)	(238)
Tmax(h)	29.0	19.6	14.4	10.8	12.9	14.6	14.3	12.5	18.8
	(12.2)	(11.2)	(6.0)	(3.4)	(5.3)	(8.0)	(12.2)	(5.3)	(12.6)
Tel(h)	29.8	24.2	76.2	58.8	66.2	19.0	90.0	39.7	42.3
	(66.2)	(106)	(82.0)	(58.7)	(33.6)	(14.5)	(80.0)	(24.4)	(20.7)
Cl(l/h)	59	81	179	208	208	101	123	158	193
	(38)	(56)	(97)	(72)	(116)	(44)	(72)	(82)	(69)
Vd ($lx10^2$)	51	80	130	147	161	21	114	92	100
	(10)	(41)	(66)	(125)	(64)	(9)	(55)	(75)	(25)
AUC	2.6	7.9	17.8	22.7	46.2	3.15	11.5	33.3	36.7
(μg/l/h)	(3.6)	(13.8)	(14.0)	(11.7)	(42.8)	(1.7)	(9.4)	(17.3)	(16.7)

TABLE 6. Calculated pharmacokinetic parameters for the hydroxylated metabolite (RU 42698) after administration of various doses of RU 486 to pregnant and non-pregnant women. Values are means with SD in parentheses

	Non-pregnant					Pregnant			
Dose (mg)	25	100	200	400	600	25	100	400	600
Cmax	154	292	330	378	417	167	250	365	346
(ng/ml)	(53)	(101)	(77)	(87)	(62)	(76)	(60)	(96)	(54)
Tmax(h)	3.7	4.1	3.7	4.6	9.6	3.9	3.6	7.1	4.3
	(1.3)	(1.7)	(1.3)	(2.0)	(12.4)	(1.8)	(1.8)	(6.6)	(1.6)
Tel(h)	16.7	24.5	40.5	54.7	29.1	8.9	30.1	46.8	56.2
	(9.2)	(9.2)	(9.2)	(35.3)	(97.9)	(1.1)	(18.3)	(34.8)	(138.8)
Cl(l/h)	82	142	173	212	160	105	208	205	240
	(31)	(46)	(74)	(63)	(179)	(49)	(150)	(50)	(191)
Vd ($lx10^2$)	17	46	96	167	249	14	65	131	289
	(8)	(16)	(31)	(124)	(252)	(9)	(28)	(75)	(119)
AUC	3.5	8.0	13.2	20.8	27.4	2.9	7.2	20.5	24.0
(μg/l/h)	(1.3)	(2.9)	(4.4)	(6.9)	(22.6)	(1.1)	(3.8)	(4.3)	(20.0)

Discussion

The pharmacokinetics of various single doses have been previously (8) studied in groups of different non-pregnant women whereas in our study the doses were administered consecutively to the same women. As found in most previous investigations (cf 6), absorption of RU 486 was rapid, with peak concentrations in most women occurring between 1 and 2 h, irrespective of dose. The serum concentrations we found also agree with those reported previously.

In a study (8) of four different doses of RU 486 (100, 400, 600 and 800 mg), there were no significant differences in plasma concentrations within the first 48 h. In our study, although there was an overlap in the concentrations with doses of 100 mg and above, the curves for the mean values for each dose were differentiated. This also applied to the plasma concentrations of the metabolites with the exception of the di-demethylated compound. Lähteenmäki et al. (8) found that with doses above 100 mg, plasma concentrations of RU 486 and the three metabolites showed little decrease during the first 48 h after dosing. Our findings were similar with the exception of the 25 mg dose where a definite decrease had occurred by 48 h and levels became undetectable by 96 h. By 120 h, levels after the three higher doses (200, 400 and 600 mg) were still readily measurable. Similar findings applied to the plasma concentrations of the metabolites.

Tel in our investigation increased with increase in dose but this may be an artifact due to the difficulties of measuring this parameter accurately at the higher dose levels. Our value for Tel (about 20 h) in non-pregnant women after the 25-mg dose agrees with the mean value of about 25 h reported in previous studies (cf 6) using low doses of RU 486. If this is the approximate true rate of elimination of RU 486, plasma concentrations after administration of higher doses should decline more rapidly than they do. In blood, RU 486 binds to an α_1-acid glycoprotein (7); this binding is weak - values of Vd are not so low as to suggest tight binding - and it is of limited capacity. Consequently, this weak binding is unlikely to account for the long duration of the elevated plasma levels of RU 486. The binding also appears to be saturated at relatively low concentrations of RU 486.

As postulated previously (6) on the basis of the Vd, the low clearance and the much higher transfer constant from the inner to the peripheral compartment than from the peripheral to inner compartment, the pharmacokinetic parameters suggest retention of RU 486 in some tissues from which the drug is only slowly released. This is also supported by our data on the three major metabolites of RU 486; like the parent compound, these metabolites also maintain high serum concentrations over extended periods but they show much lower binding to the glycoprotein. This suggests that the binding of RU 486 to this protein does not play an

important role in the low clearance of the antiprogestin. RU 486, and to an even greater extent the demethylated metabolites, are taken up *in vivo* by abdominal adipose tissue [13], the concentration of RU 486 in adipose tissue being higher than that in serum, although for the metabolites the reverse is the case. Considering that in the average subject depot adipose tissue may account for about 18% of total body weight, the amount of RU 486 localising in this tissue may be considerable. After a dose of 200 mg RU 486, the mean value for its concentration in abdominal adipose tissue was 447 ng/g [13]; in a 65-kg woman, this would equate to about 5.2 mg. However, this may be a minimal value since RU 486 may not localise to the same extent in the various fat depots in the body. For example, in animal experiments with ethynyl estradiol, the proportion of the dose detected in various fat depots varied widely, with that in mesenteric fat being about five times that in abdominal fat [14].

There were no significant differences in the plasma concentrations or pharmacokinetic parameters of RU 486 and its metabolites between the non-pregnant and pregnant women.

The finding that increasing the dose of RU 486 from 200 to 600 mg produces little increase in its plasma concentrations for up to 72 h might suggest that, clinically, the lower dose should be as effective as the higher one. Also, little if anything, would probably be gained by giving multiple doses of RU 486 instead of a single dose. Recently reported data on the efficacy of different multiple and single doses of RU 486, used in combination with the prostaglandin analogue gemeprost for termination of early pregnancy, support these conclusions [15,16].

Acknowledgments

This investigation received financial support from the Special Programme for Research, Development and Research Training in Human Reproduction of the World Health Organization. Mr Jiang Nai-xiong of the Shanghai Institute of Computer Technology assisted with the data analysis and Mrs Bai Xiu-mei of the Shanghai Institute for Planned Parenthood Research with the steroid assays. Skillful assistance in preparing the manuscript for publication was provided by Mrs B. Fontaine. Tablets of RU 486 and reference samples of the compound and its metabolites were kindly provided by Roussel-Uclaf, Paris, France.

References

1. Philibert D, Moguilewsky M, Mary I *et al.* Pharmacological profile of RU 486 in animals. In: Baulieu EE, Segal SJ, eds. *The Antiprogestin Steroid RU 486 and Human Fertility Control*. New York: Plenum Press, 1985: 49-68.
2. Bygdeman M, Swahn ML. Progesterone receptor blockage. Effect on uterine contractility and early pregnancy. *Contraception* 1985; 32: 45-51.

3. Cameron IT, Michie AF, Baird DT. Therapeutic abortion in early pregnancy with antiprogestogen RU 486 alone or in combination with prostaglandin analogue (Gemeprost). *Contraception* 1986; 34: 459-68.
4. Dubois C, Ulmann A, Aubeny E *et al.* Contragestion par le RU 486: intérêt de l'association à un dérivé prostaglandine. *C R Acad Sci (Paris)* 1988; 306: 57-61.
5. Puri CP, Van Look PFA. Newly developed competitive progesterone antagonists for ferility control. *Front Horm Res* 1991; 19: 127-67.
6. He Chang-hai, Shi Yong-en, Ye Zhi-hou *et al.* Pharmacokinetic study of orally administered RU 486 in non-pregnant women. *Contraception* 1989; 40: 449-60.
7. Heikinheimo O, Lähteenmäki PLA, Koivunen E *et al.* Metabolism and serum binding of RU 486 in women after various single doses. *Hum Reprod* 1987; 2: 379-85.
8. Lähteenmäki P, Heikinheimo O, Croxatto H *et al.* Pharmacokinetics and metabolism of RU 486. *J Steroid Biochem* 1987; 27: 859-63.
9. Cekan S, Aedo AR, Segerstéen E, Van Look PFA, Messinis I, Templeton A. Levels of the antiprogestin RU 486 and its metabolites in human blood and follicular fluid following oral administration of a single dose. *Hum Reprod* 1989; 4: 131-5.
10. Van Look PFA, Bygdeman M. Antiprogestational steroids: a new dimension in human fertility regulation. In: Milligan S, ed. *Oxford Reviews of Reproductive Biology. Volume 11.* Oxford: Oxford University Press, 1989: 1-60.
11. Gibaldi M, Perrier D. Pharmacokinetics. New York: Dekker, 1982
12. Yamaoka K, Nakagawa T, Uno T. Statistical moments in pharmacokinetics. *J Pharmacokinet Biopharm* 1978; 6: 547-56.
13. Heikinheimo O, Haukkamaa M, Lähteenmäki P. Distribution of RU 486 and its demethylated metabolites in humans. *J Clin Endocrinol Metab* 1989; 68: 270-5.
14. Reed MJ, Fotherby K. Metabolism of ethynyloestradiol in the guinea-pig. *J Steroid Biochem* 1975; 6: 121-5.
15. World Health Organization. Pregnancy termination with mifepristone and gemeprost: a multicenter comparison between repeated doses and a single dose of mifepristone. *Fertil Steril* 1991; 56: 32-40.
16. Van Look PFA, von Hertzen H. Antiprogestins in fertility regulation. *Magyar Nórvosok Lápja* 1992; 55: 215-22.

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PHARMACOKINETICS OF THE ANTIPROGESTERONE RU 486 IN WOMEN DURING MULTIPLE DOSE ADMINISTRATION

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Summary—Serum levels of RU 486 were measured by high performance liquid chromatography (HPLC) following oral intake of 12.5, 25, 50 and 100 mg twice daily (b.i.d.) for 4 days, 50 mg b.i.d. for 7 days, as well as a single dose of 200 mg of RU 486. The pharmacokinetics of RU 486 were not linear: when the daily dose of RU 486 was 100 mg or more, the serum levels were similar. The pharmacokinetic behaviour of RU 486 during the treatment period was similar between the study subjects, whereas the elimination phase pharmacokinetics showed wide individual variation. Also the mean elimination phase half-lifes ($t_{1/2}$) of RU 486 varied from 25.5 to 47.8 h in the groups of different regimen, yet the variation between different groups was not statistically significant. The areas under the concentration curves (AUC) were calculated. In the multiple dose study (mds) the $AUC_{0\to12h}$:s decreased when the administered dose of RU 486 was increased. The $AUC_{0\to12h}$ seen after administration of 100 mg b.i.d. × 4d. (mean ± SEM = 0.43 ± 0.04 μmol/l × h/mg) was significantly ($P < 0.05$) lower than the $AUC_{0\to12h}$:s obtained with administration of 12.5 mg b.i.d. × 4d. (1.49 ± 0.37 μmol/l × h/mg), 25 mg b.i.d. × 4d. (1.09 ± 0.15 μmol/l × h/mg), and 50 mg b.i.d. × 7d. (0.72 ± 0.11 μmol/l × h/mg). The $AUC_{0\to\infty}$ obtained by administration of a single dose of 200 mg of RU 486 (sds) was 0.67 ± 0.21 μmol/l × h/mg. It is concluded that if multiple dose administration of RU 486 is preferred, daily administration of relatively small doses of RU 486 over several days seem to be advantageous.

INTRODUCTION

In attempts to terminate early human pregnancy, various regimens of the antiprogesterone RU 486 have been used. In the studies published so far, the overall success rate with treatment periods of 2–7 days, and daily doses of RU 486 ranging from 50 to 400 mg, has varied from 60 to 85% [1–6]. However, no clear dose–response correlation with clinical performance has been found [1–4]. Preliminary reports suggest that in very early pregnancy a large single dose of RU 486 (i.e. 600 mg) is clinically as effective as multiple dose administration of the compound [7].

Our earlier work on the initial pharmacokinetics of RU 486 following single oral doses ranging from 100 to 800 mg revealed that serum levels of RU 486 were generally not significantly different; partly because of saturation of the serum binding capacity for RU 486, and effective metabolism of the compound [8]. Serum levels of demethylated and hydroxylated metabolites of RU 486 increased along with the increased dose following single oral administration of RU 486 to female volunteers [8]. Hence, to study the pharmacokinetics of RU 486 in women during multiple dose administration of the compound, serum levels of RU 486 following various regimens were examined.

EXPERIMENTAL

RU 486 (17β-hydroxy-11β-(4-dimethylaminophenyl)-17α-(propynyl)-estra-4,9-dien-3-one) tablets (5, 10 and 50 mg), [6,7-^{3}H]RU 486 and the corresponding antibody were kindly donated by Roussel-Uclaf Research Center (Romainville, France). Healthy normally menstruating female volunteers, aged 22–40 yr and weighing 46–70 kg, participated in the study.

Multiple dose study (mds)

Groups ingesting 12.5, 25, 50 and 100 mg of RU 486 twice daily (b.i.d.) for 4 days, and 50 mg b.i.d. for 7 days, each consisted of six volunteers. Thus the total doses of RU 486 were 100, 200, 400, 800 and 700 mg, respectively. Volunteers were advised to ingest RU 486 at 9.00–10.00 and at 21.00–22.00 h, beginning on day 12 of the luteal phase (day 0) of the cycle during an hCG-induced pseudopregnancy [for details, see ref. 9]. Blood samples were collected daily at 9.00 h prior to ingestion of RU 486. In the groups ingesting RU 486 for 4 days or 7 days, serum samples were collected daily up to day 5 or day 7, respectively. Figure 1 depicts the protocol of RU 486 administration and sample collection. Some samples were also collected at 9.00 h during the 12 days following the end of RU 486 administration.

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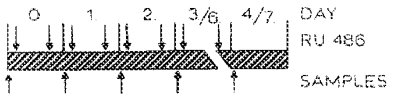

Fig. 1. The protocol of RU 486 administration and collection of serum samples in the multiple dose study.

Single dose study (sds)

The group ingesting a single dose of 200 mg of RU 486 in the mid-luteal phase of the cycle (6–8 days after the LH-surge) consisted of 4 female volunteers. Blood samples were collected at −1/2, 0, 1, 2, 4, 6 and 10 h; thereafter daily up to 7 days and on days 10 and 14.

Serum levels of RU 486 were measured using Chromosorb®-column chromatography prior to quantitation by high performance liquid chromatography (HPLC) [10]. In these HPLC-studies the intra- and interassay coefficients of variation were 6.9 and 11.5%, respectively.

In mds the concentrations of RU 486 measured on days 1–4 and 1–7 following 4 and 7-day treatments, respectively, are referred to as C_{min}. The normalized areas under the serum concentration curves ($AUC_{0\rightarrow 12\,h}$) were calculated over one dosage interval by trapezoidal rule using the C_{min}:s measured on days 3 and 4, and thereafter divided by the corresponding dose. In sds the $AUC_{0\rightarrow\infty}$ was calculated by the trapezoidal rule, and thereafter divided by the dose.

In mds the half-lifes ($t_{1/2}$) were calculated from the concentrations of RU 486 measured following termination of RU 486 administration, and in sds from the concentrations of RU 486 measured after 24 h.

One-way analysis of variance (ANOVA) was used to assess the difference in AUC and $t_{1/2}$ between the groups of different regimen. The AUC:s obtained by various regimens were thereafter compared using the Welch two-tailed t-test. In mds the effect of time and regimen of RU 486 on C_{min}:s measured on days 1–4 were evaluated using two-way ANOVA. The ANOVA:s were performed with the StatWorks—statistical software (Cricket Software, Inc., Philadelphia, PA, U.S.A.).

RESULTS

Figure 2 shows the serum concentrations of RU 486 (mean + SEM) following oral administration of 12.5, 25, 50 and 100 mg of RU 486 b.i.d. for 4 days.

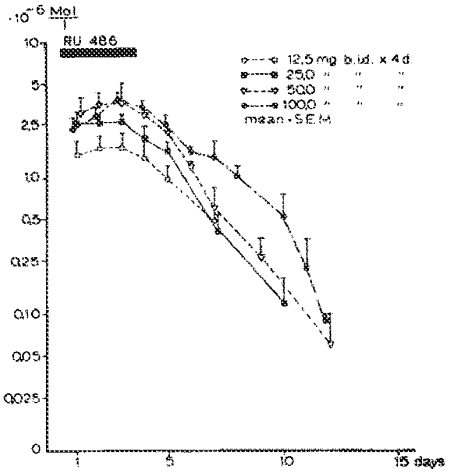

Fig. 2. Serum levels of RU 486 (mean + SEM) following ingestion of 12.5, 25, 50 and 100 mg of RU 486 b.i.d. for 4 days.

In all groups the highest mean C_{min}:s were measured on day 3, and they were 1.7, 2.6, 3.6 and 3.8 μmol/l in the groups receiving 12.5, 25, 50 and 100 mg of RU 486 b.i.d., respectively. For the first 2 days of the RU 486 treatment, the C_{min}:s were at the same level in the groups ingesting 25, 50 or 100 mg of RU 486 b.i.d. Throughout the study, the C_{min} of RU 486 seen after the dose of 12.5 mg b.i.d. were approximately half of those seen after the higher doses of 50 and 100 mg b.i.d. (Table 1).

The individual (open symbols) and the mean + SEM (solid circles) serum concentrations of RU 486 following 7-day administration of 50 mg of RU 486 b.i.d. are depicted in Fig. 3. Serum levels were similar to those seen after the 4-day treatment. The highest mean C_{min} of RU 486 (3.3 μmol/l) was measured on day 3. The mean concentrations were measured to remain above 2.2 μmol/l throughout the 7-day treatment period, and thereafter they began to decline. During the treatment period the individual C_{min}:s of RU 486 were similar in all six volunteers. However, the elimination phase pharmacokinetics showed a wide range of variation. The $t_{1/2}$ of RU 486 in these patients was 40.9 ± 6.2 h (mean ± SEM) (Table 2). In volunteer No. 1, RU 486 was detectable in serum up to 12 days following termination of the RU 486 administration.

In the samples collected following administration

Table 1. Serum concentrations (μmol/l) of RU 486 [mean ± SEM, (n)] following ingestion of 12.5 mg (A), 25 mg (B), 50 mg (C) and 100 mg (D) b.i.d. for 4 days and 50 mg b.i.d. for 7 days (E)

Day	A	B	C	D	E
1.	1.5 ± 0.4 (5)	2.6 ± 0.6 (5)	3.1 ± 0.9 (6)	2.3 ± 0.5 (6)	1.8 ± 0.3 (6)
2.	1.7 ± 0.4 (6)	2.5 ± 0.4 (5)	3.5 ± 0.8 (6)	2.8 ± 0.5 (6)	2.5 ± 0.3 (6)
3.	1.7 ± 0.5 (6)	2.6 ± 0.3 (6)	3.6 ± 1.4 (5)	3.9 ± 0.4 (6)	3.3 ± 0.6 (5)
4.	1.4 ± 0.5 (6)	2.0 ± 0.4 (6)	2.9 ± 0.4 (5)	3.3 ± 0.4 (6)	3.0 ± 0.4 (6)
5.	1.0 ± 0.2 (4)	1.6 ± 0.3 (4)	2.2 ± 0.2 (5)	2.5 ± 0.4 (3)	3.0 ± 0.3 (5)
6.	0.4 ± 0.3 (3)		1.2 ± 0.1 (3)		2.6 ± 0.4 (5)
7.	0.5 ± 0.1 (3)	0.4 ± 0.1 (5)	0.6 ± 0.2 (3)	1.4 ± 0.5 (3)	2.3 ± 0.3 (3)

Table 2. $AUC_{0\to12h}$:s and $t_{1/2}$:s [mean ± SEM, (n)] following ingestion of 12.5, 25, 50 and 100 mg b.i.d. for 4 days and 50 mg b.i.d. for 7 days. Also $AUC_{0\to\infty}$ and $t_{1/2}$ following ingestion of a single dose of 200 mg is included.

Regimen	AUC (μmol/l × h/mg)	$t_{1/2}$ (hours)
12.5 mg b.i.d. × 4d	1.49 ± 0.37 (6)	29.5 ± 3.6 (5)
25.0 mg b.i.d. × 4d	1.09 ± 0.15 (6)	25.5 ± 1.4 (6)
50.0 mg b.i.d. × 4d	0.78 ± 0.21 (5)	31.8 ± 4.0 (6)
100.0 mg b.i.d. × 4d	0.43 ± 0.04 (6)	47.8 ± 7.8 (6)
50.0 mg b.i.d. × 7d	0.72 ± 0.11 (5)	40.9 ± 6.2 (5)
200 mg single dose	0.67 ± 0.21 (4)	29.1 ± 8.3 (4)
ANOVA f	3.167	1.922
df	5,26	6,24
P	$P < 0.025$	n.s.

of 50 mg of RU 486 b.i.d. for 7 days, the concentrations of RU 486 were also measured by RIA following the Chromosorb®-column chromatography as described earlier [10]. There was a good correlation between the serum levels of RU 486 measured by HPLC and RIA (Fig. 4). The correlation coefficient was 0.92 ($n = 80$), but at the serum concentrations exceeding 0.64 μmol/l RIA gave higher values than HPLC. The equation for the linear regression line was HPLC = 0.55 RIA + 0.29 μmol/l.

Figure 5 depicts the mean concentrations (+SEM) of RU 486 in four women after single oral intake of 200 mg of RU 486. The peak levels of RU 486 (mean ± SEM = 4.9 ± 1.2 μmol/l) were measured at 1 h after ingestion. After the initial redistribution period within 6 h, a plateau was reached until 24 h. The mean (±SEM) concentration of RU 486 at 1, 2 and 3 days were 1.8 ± 0.4, 1.1 ± 0.3 and 0.6 ± 0.3 μmol/l, respectively. The $t_{1/2}$ of RU 486 in these subjects was 29.1 ± 8.3 h (mean ± SEM, Table 2).

The serum concentrations of RU 486 measured for the first 7 days in the mds are displayed in Table 1. In all groups of different regimen the highest mean C_{min}:s were measured 3 days after beginning of the RU 486 treatment. Two-way ANOVA did not indicate statistically significant effect of time on C_{min}:s measured on days 1–4 in the groups of different regimen (ANOVA $f = 1.660$, df = 3,113, $P = 0.182$).

Table 2 shows the AUC:s and $t_{1/2}$:s of RU 486 in all the groups of different regimen studied. One-way ANOVA revealed statistically significant variation in the AUC:s ($P < 0.025$) calculated for the different groups. In the mds the $AUC_{0\to12h}$:s decreased when the administered dose of RU 486 was increased, the smallest $AUC_{0\to12h}$ was obtained with the regimen of 100 mg b.i.d. for 4 days. The $AUC_{0\to12h}$:s following ingestion of 12.5 mg ($P < 0.05$), 25.0 mg ($P < 0.005$) b.i.d. × 4d, and 50 mg b.i.d. × 7d ($P < 0.05$) were statistically significantly different when compared by the Welch two-tailed t-test to the $AUC_{0\to12h}$ following ingestion of 100 mg of RU 486 b.i.d. × 4d.

The mean $t_{1/2}$:s showed a wide range of variation between the groups of different RU 486 regimen, however one-way ANOVA did not indicate statistically significant variation between the $t_{1/2}$:s measured in the different groups.

DISCUSSION

Various oral doses of RU 486 have been used in clinical work. Large doses of ≥400 mg of RU 486 are required for clinical antiglucocorticoid effects [11, 12], whereas the optimal regimen of RU 486 for antiprogesterone action remains obscure [1–4]. Daily doses of 50 mg or more of RU 486 have been used in previous clinical studies in order to terminate early human pregnancy [1–6]. With two different regimens of RU 486, i.e. 25 mg and 50 mg b.i.d. for 7 days, Odlind and Birgerson reported equal success rates of 61% [4]. Using more strict patient selection and three different regimens of RU 486, namely 50 mg b.i.d. for 4 days, 50 mg 3 times daily for 4 days, and 400 mg daily for 2 days, Couzinet *et al.* were able to terminate early pregnancy equally in 82, 88 and 85% of their patients, respectively [3]. Success rates of 60 and 72% reported by Cameron *et al.* and by Shoupe *et al.* following ingestion of 150 mg daily for 4 days and 100 mg daily for 7 days, respectively, are in the same range as the other clinical data published so far [5, 6]. Recent reports suggest that administration of RU 486 at daily doses of 25 and 50 mg might be on the threshold of being effective for induction of uterine bleeding or for termination of early pregnancy, respectively [H. Croxatto, pers. commun., 13].

In previously published clinical articles, the serum levels of RU 486 have been measured by direct RIA [3, 14, 15], which also measures some of the metabolites of RU 486 [14]. The lower precision and accuracy of RIA at high concentrations of RU 486 [10] could explain the higher values obtained by this method (Fig. 4). Due to its higher accuracy at high serum levels of RU 486, the specific HPLC method was chosen for the present study.

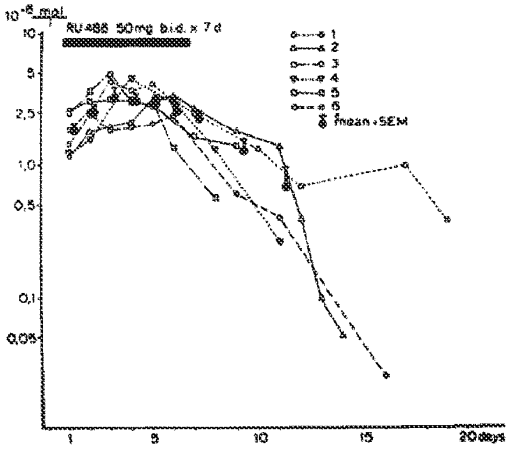

Fig. 3. The individual (open symbols) and mean + SEM (closed circles) serum concentrations of RU 486 following intake of 50 mg b.i.d. for 7 days. the $t_{1/2}$ of RU 486 (mean ± SEM) in these volunteers was 40.9 ± 6.2 h.

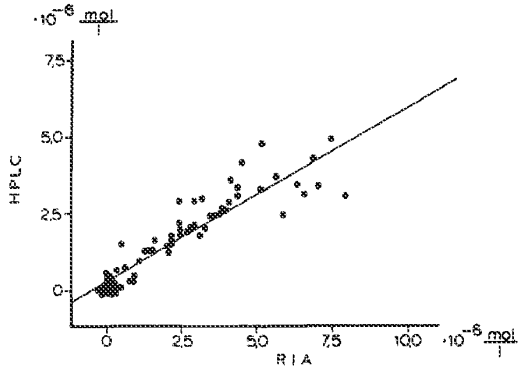

Fig. 4. Comparison of HPLC and RIA after Chromosorb®-column chromatography in the assay of RU 486 in serum. Serum samples were collected following oral intake of 50.0 mg b.i.d. for 7 days. The equation for the linear regression line was HPLC = 0.55 RIA + 0.29 μmol/l, and the correlation coefficient was 0.92 ($n = 80$).

Previous work on the pharmacokinetics of RU 486 has shown that by increasing a single oral dose from 100 to 800 mg, the serum levels of RU 486 cannot be greatly elevated [8]. A similar phenomenon has also been reported to occur during multiple dose administration of the compound [16]. The equal C_{min}:s of RU 486 during the treatment period following intake of daily doses exceeding 50 mg (Table 1) is at least partly explained by saturation of alpha 1-acid glycoprotein, the specific transport protein of RU 486 [8, 17].

The serum concentrations of the monodemethylated, didemethylated and hydroxylated metabolites of RU 486 increased significantly when the single oral dose of RU 486 was increased from 100 to 800 mg; thus equalling or exceeding the serum levels of the parent RU 486 [8]. These metabolites bear lower affinities of 9–21% (RU 486 = 100%) to the human progesterone receptor [18]. Even though the monodemethylated and hydroxylated metabolites behave as weak antiprogesterones in rat [19], the antiprogestagenic nature of the metabolites of RU 486 in humans has not been confirmed. Thus, from

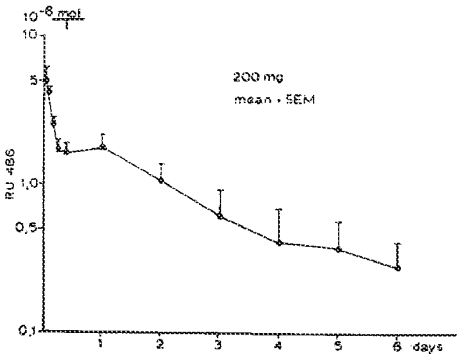

Fig. 5. Serum concentrations of RU 486 in four female volunteers (mean + SEM) following oral intake of a single dose of 200 mg of RU 486.

the pharmacokinetic point of view, the optimal dosage could be the one leading to the highest serum and target tissue levels of RU 486: the strongest competitor for the progesterone receptor and the best characterized antiprogesterone of these steroids.

In agreement with previous pharmacokinetic data [10, 16], 4 and 7-day treatment with daily doses of 100 and 200 mg of RU 486 resulted in nearly identical C_{min}:s of RU 486 during the treatment period (Figs 2 and 3, Table 1). In the mds the $AUC_{0\rightarrow 12\,h}$:s decreased when the administered dose of RU 486 was increased (Table 2). The $AUC_{0\rightarrow 12\,h}$ seen after administration of 100 mg b.i.d. for 4 days was significantly lower than the $AUC_{0\rightarrow 12\,h}$:s obtained with administration of 12.5 mg b.i.d. ($P < 0.05$), 25 mg b.i.d. ($P < 0.005$) for 4 days, and 50 mg b.i.d. ($P < 0.05$) for 7 days. This may further suggest that if multiple dose administration of RU 486 is preferred, daily administration of relatively small (i.e. around 50–100 mg/day) single doses of RU 486 might be advantageous. This might also decrease possible side-effects of RU 486 associated with high oral doses [6, 15].

The elimination phase pharmacokinetics of RU 486 showed a wide range of individual variation (Fig. 3), suggesting large individual variation in the capacity to metabolize and excrete RU 486. The mean $t_{1/2}$:s of RU 486 varied from 25.5 to 47.8 h in the groups of different regimens (Table 2), however the variation was not statistically significant.

A large single dose of RU 486 (i.e. 600 mg) has been reported to be clinically equally effective as multiple dose administration in very early pregnancy [7]. The $AUC_{0\rightarrow\infty}$ following intake of a single dose of 200 mg of RU 486 was in the same range with the $AUC_{0\rightarrow 12\,h}$:s seen in mds (Table 2) indicating that single dose administration of RU 486 may be as efficient as multiple dose administration. Also, due to the long $t_{1/2}$ of RU 486 [Table 2, refs 10, 19], single dose administration might lead to sufficiently high and prolonged serum levels of RU 486 to ensure saturation of the progesterone receptors. In addition, in order to avoid possible misuse of RU 486 [3], single dose administration of the compound would be preferable. On the other hand, the clinical potency of the single dose administration of RU 486 declined from 89% in pregnancies of less than 5 weeks amenorrhoea to 58% when the duration of pregnancy exceeded 6 weeks [7]. Therefore multiple dose administrations of RU 486 might be needed in more advanced pregnancies.

Previously, with daily doses of 50 mg or above, the abortifacient properties of RU 486 have been reported to lack dose-dependency [1–6]. Following multiple daily administration of 100 mg or more of RU 486, the C_{min}:s were similar during the treatment period (Table 1). This phenomenon is partly due to saturation of the specific serum transport capacity for RU 486, and effective metabolism of the compound [8]. Therefore, due to saturation of the serum binding

capacity for RU 486 [Fig. 2, ref. 8], the quantitation of RU 486 in serum following intake of doses exceeding 50 mg may not be very informative. It is concluded that from the pharmacokinetic point of view, administration of RU 486 as relatively small daily dose administered over several days seem to be advantageous.

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REFERENCES

1. Kovacs L., Sas M., Resch B. A., Ugocsai G., Swahn M. L., Bygdeman M. and Rowe P. J.: Termination of very early pregnancy of RU 486—an antiprogestational compound. *Contraception* **29** (1984) 399–410.
2. Vervest H. A. M. and Haspels A. A.: Preliminary results with the antiprogestational compound RU-486 (mifepristone) for interruption of early pregnancy. *Fert. Steril.* **44** (1985) 627–632.
3. Couzinet B., Le Strat N., Ulmann A., Baulieu E. E. and Schaison G.: Termination of early pregnancy by the progesterone antagonist RU 486 (mifepristone). *N. Engl. J. Med.* **315** (1986) 1565–1569.
4. Birgerson L. and Odlind V.: Early pregnancy termination with antiprogestins: a comparative clinical study of RU 486 given in two dose regimens and Epostane. *Fert. Steril.* **48** (1987) 565–570.
5. Cameron I. T., Michie A. F. and Baird D. T.: Therapeutic abortion in early pregnancy with antiprogestogen RU 486 alone or in combination with prostaglandin analogue (Gemeprost). *Contraception* **34** (1986) 459–468.
6. Shoupe D., Mishell D. R. Jr, Brenner P. F. and Spitz I. M.: Pregnancy termination with a high and medium dosage regimen of RU 486. *Contraception* **33** (1986) 455–461.
7. Elia D.: Uses of RU 486: a clinical update. *IPPF Med. Bull.* **20** (1986) 1–2.
8. Heikinheimo O., Lähteenmäki P. L. A., Koivunen E., Shoupe D., Croxatto H., Luukkainen T. and Lähteenmäki P.: Metabolism and serum binding of RU 486 in women after various single doses. *Human Reprod.* **2** (1987) 379–385.
9. Croxatto H. B., Spitz I. M., Salvatierra A. M. and Bardin W. C.: The demonstration of the antiprogestin effects of RU 486 when administered to the human during hCG-induced pseudopregnancy. In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Edited by E. E. Baulieu and S. J. Segal). Plenum Press, New York (1985) pp. 263–269.
10. Heikinheimo O., Tevilin M., Shoupe D., Croxatto H. and Lähteenmäki P.: Quantitation of RU 486 in human plasma by HPLC and RIA after column chromatography. *Contraception* **34** (1986) 613–624.
11. Bertagna X., Bertagna C., Luton J.-P., Husson J.-M. and Girard F.: The new steroid analog RU 486 inhibits glucocorticoid action in man. *J. clin. Endocr. Metab.* **59** (1984) 25–28.
12. Nieman L. K., Chrousos G. P., Kellner C., Spitz I. M., Nisula B. C., Cutler G. B., Merriam G. R., Bardin C. W. and Loriaux D. L.: Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *J. clin. Endocr. Metab.* **61** (1985) 536–540.
13. Mishell D. R. Jr, Shoupe D., Brenner B. F., Lacarra M., Horenstein J., Lähteenmäki P. and Spitz I.: Termination of early gestation with the anti-progestin steroid RU 486: medium versus low dose. *Contraception* **35** (1987) 307–321.
14. Salmon J. and Mouren M.: Radioimmunoassay of RU 486. In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Edited by E. E. Baulieu and S. J. Segal). Plenum Press, New York (1985) pp. 99–101.
15. Bertagna X., Bertagna C., Laudat M.-H., Husson J.-M., Girard F. and Luton J.-P.: Pituitary–adrenal response to the antiglucocorticoid action of RU 486 in Cushing's syndrome. *J. clin. Endocr. Metab.* **63** (1986) 639–642.
16. Swahn M. L., Wang G., Aedo A. R., Cekan S. Z. and Bygdeman M.: Plasma levels of antiprogestin RU 486 following oral administration of non-pregnant and early pregnant women. *Contraception* **34** (1986) 469–481.
17. Philibert D., Moguilewsky M., Bonnat C., Busigny M. and Pottier J.: Influence of human alpha 1-acid glycoprotein (AAG) on pharmacokinetics and biological activity of RU 486. *Sixty-Eighth Meeting of the Endocrine Society*, Anaheim, CA, 1986, Abstract 1006.
18. Heikinheimo O., Kontula K., Croxatto H., Spitz I., Luukkainen T. and Lähteenmäki P.: Plasma concentrations and receptor binding of RU 486 and its metabolites in humans. *J. steroid Biochem.* **26** (1987) 279–284.
19. Deraedt R., Bonnat C., Busigny M., Chatelet P., Cousty C., Mouren M., Philibert D., Pottier J. and Salmon J.: Pharmacokinetics of RU 486. In *The Antiprogestin Steroid RU 486 and Human Fertility Control* (Edited by E. E. Baulier and S. J. Segal). Plenum Press, New York (1985) pp. 103–122.

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Original research article

The pharmacokinetics of mifepristone in humans reveal insights into differential mechanisms of antiprogestin action

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Abstract

The pharmacokinetics of mifepristone is characterized by rapid absorption, a long half-life of 25–30 h, and high micromolar serum concentrations following ingestion of doses of ≥100 mg of the drug. The serum transport protein—α 1-acid glycoprotein (AAG)—regulates the serum kinetics of mifepristone in man. Binding to AAG limits the tissue availability of mifepristone, explaining its low volume of distribution and low metabolic clearance rate of 0.55 L/kg per day. In addition, the similar serum levels of mifepristone following ingestion of single doses exceeding 100 mg can be explained by saturation of the binding capacity of serum AAG. Mifepristone is extensively metabolized by demethylation and hydroxylation, the initial metabolic steps being catalyzed by the cytochrome P-450 enzyme CYP3A4. The three most proximal metabolites, namely, monodemethylated, didemethylated and hydroxylated metabolites of mifepristone, all retain considerable affinity toward human progesterone and glucocorticoid receptors. Also, the serum levels of these three metabolites are in ranges similar to those of the parent mifepristone. Thus, the combined pool of mifepristone—plus its metabolites—seems to be responsible for the biological actions of mifepristone. Recent clinical studies on pregnancy termination and emergency contraception have focused on optimization of the dose of mifepristone. In these studies it has become apparent that the doses efficient for pregnancy termination differ from those needed in emergency contraception—mifepristone is effective in emergency contraception at a dose of 10 mg, which results in linear pharmacokinetics. However, the ≥200 mg doses of mifepristone needed for optimal abortifacient effects of mifepristone result in saturation of serum AAG and thus nonlinear pharmacokinetics. In view of the pharmacokinetic data, it may be speculated that dosing of mifepristone for pregnancy termination and for emergency contraception could be reduced to approximately 100 mg and 2–5 mg, respectively. It remains to be seen whether the newly synthesized, more selective antiprogestins will prove more efficacious in the clinical arena.

Keywords: Metabolism; High performance-liquid chromatography; Radioimmunoassay; Emergency contraception; Medical abortion; Dose-response relationships

1. Introduction

Recent clinical studies on the use of mifepristone in medical termination of pregnancy and in emergency contraception have focused on optimization of mifepristone regimens. In termination of first-trimester pregnancy, a 200-mg dose of mifepristone, in combination with vaginally administered prostaglandin, is equally effective as a higher dose (600 mg) of mifepristone [1–3]. In these studies, the percentages of complete abortions have ranged 88–96% [1–3]. The results of preliminary studies have suggested that even a 100-mg dose of mifepristone might be equally effective [4]. However, in a randomized multicenter study arranged by the World Health Organization (WHO), 50 mg of mifepristone combined with vaginally administered prostaglandin was 1.6 times more likely to fail in termination of first trimester pregnancy when compared with a regimen containing 200 mg of mifepristone [5].

In emergency contraception, considerably lower doses of mifepristone are needed. In a randomized study arranged by the WHO, a 10-mg dose of mifepristone was equally effective as 50 mg or 600 mg doses, each preventing 84–86% of pregnancies [6]. In fact, the lowest effective dose of mifepristone in emergency contraception has not been characterized. The more than 10-fold difference in the doses of

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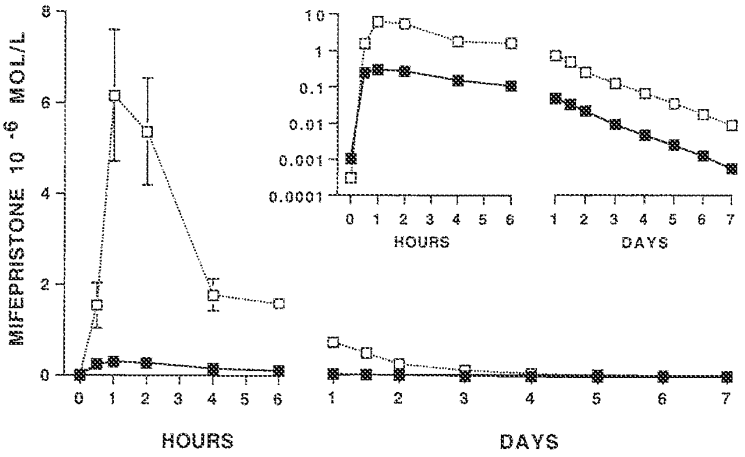

Fig. 1. Serum levels (mean ± SE) of mifepristone following administration of 2 mg (■) and 25 mg (□) to five female volunteers. The data are depicted on both linear (lower) and semilogarithmic (upper) scales. Redrawn from Kekkonen et al. [17].

mifepristone required for optimal clinical effects in emergency contraception and in pregnancy termination suggests that different biological mechanisms mediate these clinical effects of mifepristone.

The antiglucocorticoid effects of mifepristone are in sharp contrast with its antiprogestagenic effects in pregnancy termination or in emergency contraception. Early studies by Bertagna et al. [7] and Gaillard et al. [8] showed that activation of the hypothalamic-pituitary-adrenal (HPA) axis in response to mifepristone is clearly a dose-dependent phenomenon, and significant increases in the circulating concentrations of adrenocorticotropic hormone and cortisol are seen following administration of ≥200 mg of the drug. Moreover, more pronounced activation of the HPA axis is seen as the dose of mifepristone is increased [7,8].

The differences in the clinical effects of mifepristone are also related to its pharmacokinetics—the high efficacy of mifepristone in emergency contraception is seen in the dose range that results in linear kinetics of the drug in serum. However, the doses required for termination of pregnancy or activation of the HPA axis result in saturation level, non linear kinetics of mifepristone. In this article we review the pharmacokinetics of mifepristone in humans, with special emphasis on the relationships between its pharmacokinetics and clinical efficacy.

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2.1. Assay systems for mifepristone

arious assay methods such as radioimmunoassay (RIA) [9], radioreceptorassay (RRA) [10,11] and assays based on high-performance liquid chromatography (HPLC) have been used to measure serum mifepristone levels [12–14]. It soon became apparent that mifepristone is extensively metabolized, and due to the cross-reacting metabolites, direct RIA and RRA failed to distinguish the parent mifepristone from its metabolites [15]. However, the micromolar serum levels of mifepristone—seen following ingestion of doses currently used in clinical practice—allowed us to develop methods based on HPLC for detailed analysis of the pharmacokinetics and metabolism of mifepristone [16]. Column chromatography can be used to separate the metabolites from the parent mifepristone, which can then be measured specifically either by RIA or HPLC [13].

2.2. Absorption and distribution of mifepristone

Following oral ingestion, mifepristone is rapidly absorbed and the time to peak serum levels (t_{max}) is approximately 1–2 h [11–13]. Also, when analyzed by specific RIA or HPLC, the t_{max} values have been similar within the dose range of 200–600 mg of mifepristone [16,17]. Peak concentrations (C_{max}) rise according to the dose of mifepristone within the dose range of 2–25 mg [17]. However, at higher doses of 100–800 mg, C_{max} values do not differ significantly, most likely as a result of saturation of the serum binding capacity for mifepristone [16]. The bioavailability has been estimated to be 40% following oral intake of 100 mg of mifepristone [18]. nfortunately, attempts to bypass the first-pass metabolism by means of vaginal administration resulted in low serum levels of mifepristone [19].

2. .Serum levels of mifepristone

The pharmacokinetics of mifepristone have been studied following single oral doses ranging 2–800 mg. Following ingestion of 2 and 25 mg doses, the levels of mifepristone, as well as the areas under the concentration curves (A Cs), rise according to the dose (Fig. 1) [17]. However, following

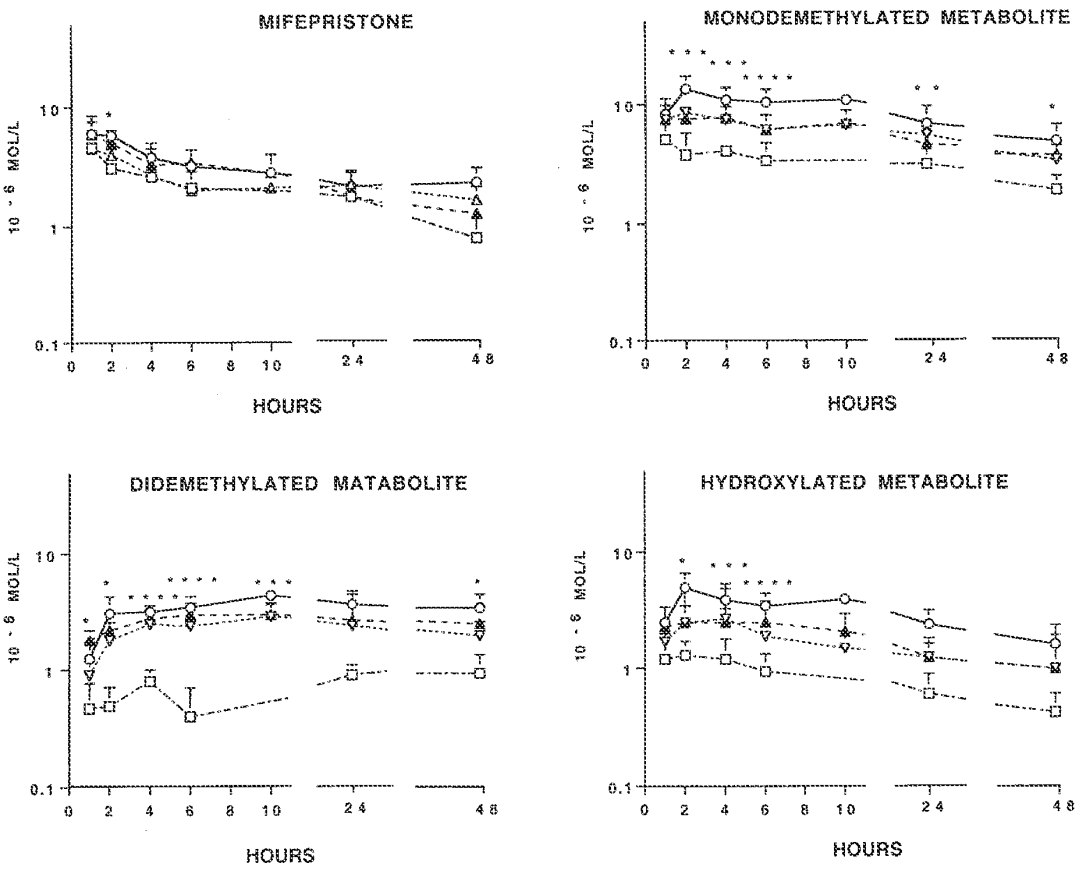

Fig. 2. Serum levels (mean ± SE) of mifepristone and its monodemethylated, hydroxylated and didemethylated metabolites following administration of single doses of 100, 400, 600 and 800 mg to female volunteers. Statistically significant differences in the serum levels between the groups ingesting 100 and 800 mg are indicated by asterisks (*p < 0.05; **p < 0.01; ***p < 0.005; ****p < 0.001). Redrawn from Heikinheimo et al. [16].

intake of single doses of 100, 400, 600 and 800 mg, the concentrations of mifepristone have all been observed to be at ~2.5 μmol/L at 24 h (Fig. 2) [16] despite the nearly 10-fold difference in the dose ingested.

When administered repeatedly, a similar phenomenon in the plateau levels is seen when the daily dose of mifepristone exceeds 100 mg [20]. Figure 3 shows the individual and mean levels of mifepristone in a group of six women given 50 mg twice a day for 7 days. The individual levels of mifepristone were similar among the sub ects, and the individual half-lives of mifepristone varied from 26–48 h. The micromolar serum concentrations of mifepristone also persist during prolonged daily treatment with 200 mg for up to 20 months [21].

2.4. Serum binding characteristics of mifepristone

In human serum, 94–99% of mifepristone is protein bound [10,16]. Early studies by Moguilewsky and Philibert [22] indicated that human serum, unlike rat serum, contains a high-affinity binding protein for mifepristone, which was soon identified as α 1-acid glycoprotein (AAG). The highly significant correlations between serum levels of mifepristone and AAG suggested that AAG has a great impact on the pharmacokinetics of mifepristone in man [16,23]. Studies involving centrifugal ultrafiltration dialysis showed that a serum concentration of mifepristone of 2.5 μmol/L represents saturation of AAG binding capacity (Fig. 4) [16]. In addition, albumin appears to have a high-capacity role in the serum transport of mifepristone [16].

Thus, in humans, serum AAG appears to limit the tissue availability of mifepristone. However, mifepristone exceeding the binding capacity of AAG may be more susceptible to excretion or possibly diffusion into peripheral tissues [24]. In accordance with the low volume of distribution, tissue mifepristone levels have been observed to be in the same range or lower than serum levels following intake of 200 mg of mifepristone prior to hysterectomy [24].

2. . etabolism of mifepristone in humans

The elimination phase half-life of mifepristone ($t_{1/2}$) has been reported to vary between 24 and 48 h when analyzed

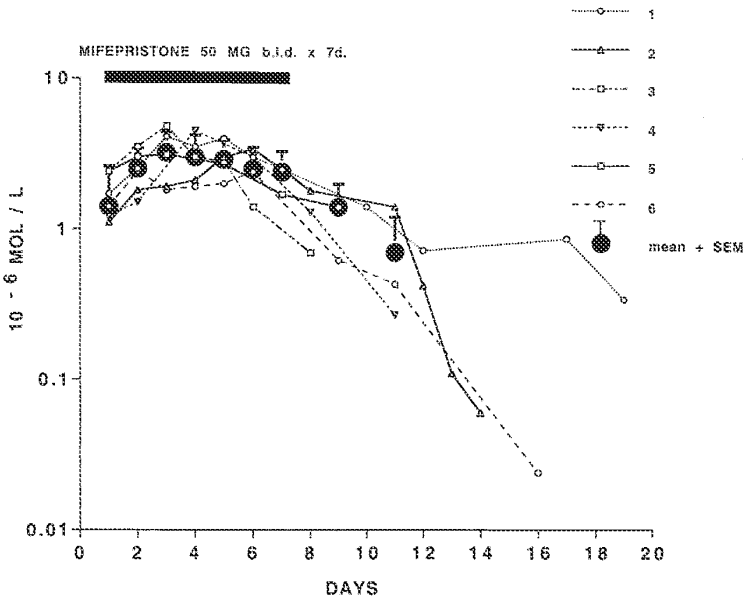

Fig. 3. Individual and mean (±SE) levels of mifepristone during intake of 50 mg twice a day for 7 days in six female volunteers. Redrawn from Heikinheimo [20].

by HPLC [14,20]. However, investigators employing either RIA or RRA have reported $t_{1/2}$ values between 54 and 90 h [11,25], this most likely a result of the presence of cross-reacting metabolites of mifepristone.

The metabolism of mifepristone is initiated by rapid demethylation and hydroxylation in humans, rats and monkeys [18]. The enzyme CYP3A4 has been shown to be the primary cytochrome P-450 enzyme responsible for the oxidative metabolism of mifepristone in human liver microsomes [26]. Following oral intake of 100 mg or more, constant serum levels of mifepristone, but increasing concentrations of the monodemethylated, didemethylated and hydroxylated metabolites of mifepristone are found, with serum levels of the monodemethylated metabolite exceeding those of the parent compound [16,27]. Following administration of mifepristone at doses over 400 mg, the concentrations of the didemethylated and hydroxylated metabolites also exceed those of the parent compound (Fig. 2) [16]. Peak levels of the monodemethylated and hydroxylated metabolites are reached by 2–4 h. The time course of the didemethylated metabolite is somewhat different, with peak levels being measured only after 10 h following ingestion of mifepristone.

The demethylated and hydroxylated metabolites are further metabolized and excreted into bile. In humans, only a very small fraction of mifepristone can be detected in urine [18].

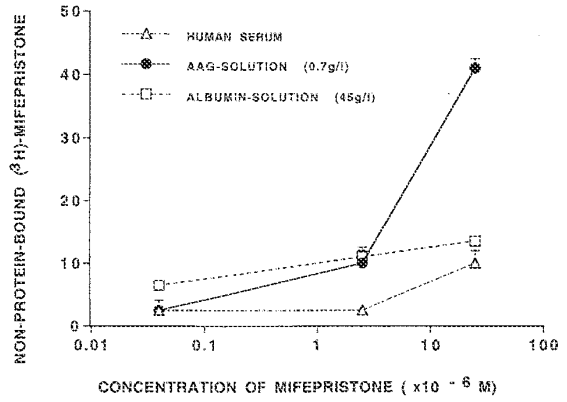

Fig. 4. Percentage of serum non-protein–bound mifepristone (mean ± SE) in human serum, in phosphate-buffered saline (PBS) containing human alpha 1-acid glycoprotein (AAG), and in PBS containing human albumin. Redrawn from Heikinheimo et al. [16].

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Tables 1 and 2 summarize the relative binding affinities (RBAs) of mifepristone, the monodemethylated, hydroxylated and didemethylated metabolites, as well as those of reference steroids, to the human progesterone receptor (hPR) and glucocorticoid receptor (hGR) [15]. The relatively high receptor-binding affinities of mifepristone s metabolites in combination with the high serum levels of the metabolites suggest that some of the biological effects of mifepristone may be mediated via both the parent compound as well as the pool of metabolites.

The efficacy of mifepristone in pregnancy termination

Table 1
Relative binding affinities (RBAs) of mifepristone and its three metabolites to the human uterine progesterone receptor

Compound	RBA %
ORG-2058	374
Mifepristone	100
Progesterone	43
Monodemethylated metabolite	21
Hydroxylated metabolite	15
Didemethylated metabolite	9

cannot be improved by increasing the dose beyond 200 mg [1–3]. Thus, based on the similar serum concentrations of mifepristone, but increasing levels of the metabolites following intake of ≥100 mg of mifepristone (Fig. 2), it may be speculated that the lower affinities of the metabolites towards hPR (Table 1) imply minor importance of these metabolites in the abortifacient action of mifepristone.

In comparison with hPR, the RBAs of the monodemethylated, hydroxylated and didemethylated metabolites toward hGR (Table 2) are more pronounced. The antiglucocorticoid effects of mifepristone increase in a dose-dependent manner following ingestion of doses of ≥200 mg [7,8]. Thus, based on the similar serum levels of parent mifepristone but increasing levels of the metabolites, it may be speculated that the metabolites are important in the antiglucocorticoid actions of mifepristone.

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nderstanding the pharmacokinetics of mifepristone has aided the design of studies aimed at optimizing mifepristone regimens. In several randomized multicenter studies, it has become clear that a 200-mg dose, but not a 50-mg dose, of mifepristone in combination with prostaglandin is effective in pregnancy termination [1–3,5]. In fact, even a 100-mg dose of mifepristone might be acceptably effective [4]. In view of the saturation stage pharmacokinetics of mifepristone following intake of doses of 100 mg and more, the efficacy of the 100 mg dose is not surprising. Thus, for termination of pregnancy, the saturation stage serum kinetics of mifepristone appear important. It may be speculated that the abortifacient properties—decidual bleeding, increased uterine contractility and sensitivity to prostaglandins—require complete saturation of the uterine progesterone receptors.

Table 2
Relative binding affinities (RBAs) of mifepristone and its three metabolites to the human placental glucocorticoid receptor

Compound	RBA %
Mifepristone	100
Monodemethylated metabolite	61
Hydroxylated metabolite	48
Didemethylated metabolite	45
Dexamathasone	23
Cortisol	9

When women with complete and incomplete termination of pregnancy following administration of a single dose of 600 mg of mifepristone were compared, the serum levels of mifepristone and those of the three metabolites were indistinguishable [28]. It therefore appears that individual uterine sensitivity to progesterone withdrawal, and not differences in the pharmacokinetics of mifepristone, dictate the eventual clinical outcome of each sub ect.

In emergency contraception, mifepristone doses in the range of 10–600 mg behave similarly, inhibiting 84–85% of pregnancies [6]. Therefore, the mechanism by which mifepristone acts as an emergency contraceptive is clearly different from its ability to start a cascade resulting in termination of pregnancy. Continuous daily administration of 2 mg of mifepristone or more inhibits ovulation in women [29,30]; this inhibition occurs most likely via central mechanisms [29,30]. As inhibition or delay of ovulation also appears to be a ma or mechanism of action in emergency contraception [31], 10 mg of mifepristone, and thus linear range serum levels of the drug, are sufficient for the presumed ovulation inhibition. It may be speculated that an even lower dose than 10 mg of mifepristone might be effective in emergency contraception. As the endometrium appears to be very sensitive to the effects of mifepristone [32,33], possible actions on the endometrium might complement the efficacy of mifepristone in emergency contraception.

Mifepristone has several pharmacokinetic features that make it very useful in both termination of pregnancy and in emergency contraception. It is rapidly absorbed and the bioavailability of mifepristone is sufficient for clinical use. The long $t_{1/2}$ of mifepristone allows effective single-dose treatment, and thus controlled distribution for both clinical indications. It may be argued that identification of the minimal effective dose, which may be approximately 100 mg for pregnancy termination and 2–5 mg for emergency contraception, is important. It remains to be seen whether some of the newly synthesized antiprogestins with higher selectivity will be clinically superior to mifepristone.

Ac no d nts

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[1] World Health Organization. Task force on post-ovulatory methods of fertility regulation. Termination of pregnancy with reduced doses of mifepristone. BM 1993;307:532–7.

[2] World Health Organization. Task force on post-ovulatory methods of fertility regulation. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomised trial. Br Obstet Gynecol 2000;107:524–30.
[3] World Health Organization. Task force on post-ovulatory methods of fertility regulation. Medical abortion at 57 to 63 days gestation with a lower dose of mifepristone and gemeprost. A randomized controlled trial. Acta Obstet Gynecol Scand 2001;80:447–51.
[4] Creinin M, Pymar H, Schwartz . Mifepristone 100 mg abortion regimens. Obstet Gynecol 2001;98:434–9.
[5] World Health Organization. Task force on post-ovulatory methods of fertility regulation. Lowering the doses of mifepristone and gemeprost for early abortion: a randomised controlled trial. Br Obstet Gynecol 2001;108:738–42.
[6] World Health Organization. Task force on post-ovulatory methods of fertility regulation. Comparison of three single doses of mifepristone as emergency contraception: a randomized trial. Lancet 1999;353: 697–702.
[7] Bertagna , Bertagna C, Luton -P, Husson -M, Girard F. The new steroid analog R 486 inhibits glucocorticoid action in man. Clin Endocrinol Metab 1984;59:25–8.
[8] Gaillard R, Riondel A, Müller AF, Herrmann W, Baulieu E-E. R 486: a steroid with antiglucocorticosteroid activity that only disinhibits the human pituitary-adrenal system at a specific time of day. Proc atl Acad Sci SA 1984;81:3879–82.
[9] Salmon , Mouren M. Radioimmunoassay of R 486. In: Baulieu E-E, Segal S, editors. The antiprogestin steroid R 486 and human fertility control. ew York: Plenum Press, 1985. p. 99–101.
[10] Kawai S, ieman L, Brandon D, delsman R, Loriaux L, Chrousos G. Pharmacokinetic properties of the antiglucocorticoid and antiprogesterone steroid R 486 in man. Pharmacol Exp Ther 1987;241: 401–6.
[11] Földesi I, Falkay G, Kovacs L. Determination of R 486 (mifepristone) in blood by radioreceptorassay; a pharmacokinetic study. Contraception 1996;54:27–32.
[12] Swahn ML, Wang G, Aedo AR, Cekan S, Bygdeman M. Plasma levels of antiprogestin R 486 following oral administration to nonpregnant and early pregnant women. Contraception 1986;34:469–81.
[13] Heikinheimo O, Tevilin M, Shoupe D, Croxatto H, Lähteenmäki P. uantitation of R 486 in human plasma by HPLC and RIA after column chromatography. Contraception 1986;34:613–23.
[14] He CH, Shi YE, Ye H, hang GG, iang , an Look PF, et al. Pharmacokinetic study of orally administered R 486 in non-pregnant women. Contraception 1989;40:449–60.
[15] Heikinheimo O, Kontula K, Croxatto H, Spitz I, Luukkainen T, Lähteenmäki P. Plasma concentrations and receptor binding of R 486 and its metabolites in humans. Steroid Biochem 1987;26:279–84.
[16] Heikinheimo O, Lähteenmäki PL, Koivunen E, Shoupe D, Croxatto H, Luukkainen T, et al. Metabolism and serum binding of R 486 in women after various single doses. Hum Reprod 1987;2:379–85.
[17] Kekkonen R, Heikinheimo O, Mandelin E, Lähteenmäki P. Pharmacokinetics of mifepristone after low oral doses. Contraception 1996; 54:229–34.
[18] Deraedt R, Bonnat C, Busigny M, et al. Pharmacokinetics of R 486. In: Baulieu E-E, Segal S, editors. The antiprogestin steroid R 486 and human fertility control. ew York: Plenum Press, 1985. p. 103–22.
[19] Heikinheimo O, Croxatto H, Salvatierra A, Chang C, Luukkainen T, Lähteenmäki P. Intravaginal administration of R 486 in humans and rats: inadequate absorption in humans. Hum Reprod 1987;2:645–8.
[20] Heikinheimo O. Pharmacokinetics of the antiprogesterone R 486 in women during multiple dose administration. Steroid Biochem 1989; 32:21–5.
[21] Heikinheimo O, Ranta S, Grunberg S, Spitz I. Alterations in the pituitary- thyroid and pituitary-adrenal axes—consequences of long-term mifepristone treatment. Metabolism 1997;46:292–6.
[22] Moguilewsky M, Philibert D. Biochemical profile of R 486. In: Baulieu E-E, Segal S, editors. The antiprogestin steroid R 486 and human fertility control. ew York: Plenum Press, 1985. p. 87–97.
[23] Grimaldi B, Barre , Tillement -P. Les roles respectifs des liasons aux proteines sanguines et tissulaires de la mifepristone (R 486) dans sa distribution quantitative dans l organisme. C R Acad Sci Paris, t.315, Serie III, 1992:93–9.
[24] Heikinheimo O, Haukkamaa M, Lähteenmäki P. Distribution of R 486 and its demethylated metabolites in humans. Clin Endocrinol Metab 1989;68:270–5.
[25] Liu H, Garzo G, Yen SSC. Pharmacodynamics of the antiprogesterone R 486 in women after oral administration. Fertil Steril 1988; 50:245–9.
[26] ang GR, Wrighton SA, Benet L . Identification of CYP3A4 as the principal enzyme catalyzing mifepristone (R 486) oxidation in human liver microsomes. Biochem Pharmacol 1996;52:753–61.
[27] Shi YE, Ye H, He CH, hang G , u , an Look PF, et al. Pharmacokinetic study of R 486 and its metabolites after oral administration of single doses to pregnant and non-pregnant women. Contraception 1993;48:133–49.
[28] Heikinheimo O, Ylikorkala O, Turpeinen , Lähteenmäki P. Pharmacokinetics of the antiprogesterone R 486: no correlation to clinical performance of R 486. Acta Endocrinol 1990;123:298–304.
[29] Ledger W, Sweeting , Hillier H, Baird D. Inhibition of ovulation by low-dose mifepristone (R 486). Hum Reprod 1992;7:945–50.
[30] Croxatto H, Salvatierra AM, Croxatto H, Fuentealba B. Effects of continuous treatment with low dose mifepristone throughout one menstrual cycle. Hum Reprod 1993;8:201–7.
[31] Croxatto HB, Devoto L, Durand M, Ezcurra E, Larrea F, agle C, et al. Mechanism of action of hormonal preparations used for emergency contraception: a review of literature. Contraception 2001;63: 111–21.
[32] Batista M, Cartledge T, ellmer A, ieman L, Merriam G, Loriaux L. Delayed endometrial maturation induced by daily administration of the antiprogestin R 486: a potential new contraceptive strategy. Am Obstet Gynecol 1992;167:60–5.
[33] Gemzell-Danielsson K, Westlund P, ohannisson E, Swahn M-L, Bygdeman M, Seppälä M. Effect of low weekly doses of mifepristone on ovarian function and endometrial development. Hum Reprod 1996;11:256–64.

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REVIEW

Mifepristone (RU 486) in Cushing's syndrome

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Abstract

Context: Mifepristone (RU 486) blocks the action of cortisol by binding to the glucocorticoid receptor and, therefore, is of potential therapeutic value in Cushing's syndrome. However, research in endogenous hypercortisolism has been hampered by the controversy related to the use of mifepristone for inducing abortion. Currently, new studies are planned to better define the role of RU 486 in Cushing's syndrome. This paper reviews the available evidence concerning the therapeutic effects and adverse events of RU 486 in Cushing's syndrome.

Evidence acquisition: Original articles and reviews were identified using a PubMed search strategy covering the time period until February 2007.

Evidence synthesis: Treatment of Cushing's syndrome with mifepristone has been reported in a total of 18 patients, with daily doses ranging from 5 to 30 mg/kg. Case reports indicate that the mifepristone-induced receptor blockade may lead to significant clinical improvement in patients with Cushing's syndrome in whom surgery and inhibitors of adrenal steroidogenesis fail to control hypercortisolism. Due to its rapid onset of action, mifepristone may be particularly useful in acute crises, e.g. in cortisol-induced psychosis. Side effects include adrenal insufficiency and, as a result of its antiprogestin action, endometrial hyperplasia in long-term treatment. Adrenal insufficiency can be assessed only by careful clinical evaluation, as the hormonal parameters are not reliable during receptor blockade, and is rapidly reversed by exogenous dexamethasone. Well-designed larger clinical trials are needed to better assess the value of this interesting drug in the treatment of Cushing's syndrome.

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Introduction

Mifepristone (RU 486) is the first glucocorticoid receptor (GR) antagonist developed for clinical testing, and it is still the only drug with this property used in humans.

Mifepristone was discovered in the early 1980s at the French pharmaceutical company RU (Roussel-Uclaf) as part of a special research project to develop antiglucocorticoid compounds (1, 2). It soon became evident that the compound with the code name Roussell-Uclaf 38 486, later shortened to RU 486, also possessed strong antiprogestin activity. This led investigators to explore the effects of this new drug mainly in progesterone-dependent conditions, e.g. in pregnancy. It was found that the combination of mifepristone with a prostaglandin resulted in complete abortion in almost 100% of cases. These findings were so impressive that RU 486 became primarily known as the 'abortion pill', although a multitude of potential clinical applications had been predicted at its discovery. Many other usages have been tested, but so far only in preliminary studies, as research projects were strongly hampered by the political controversy surrounding the 'abortion pill' (3).

To date, mifepristone is approved in several countries for medical termination of pregnancy and for cervical dilatation prior to surgical termination of pregnancy. In no country, however, it has been approved for the use in clinical conditions with hypercortisolism. In Cushing's syndrome caused by ectopic adrenocorticotrophin (ACTH)-producing tumours or adrenocortical carcinoma, surgical resection of the tumour can often only partially or temporarily control glucocorticoid hypersecretion. All drugs currently used for control of hypercortisolism in this setting, including ketoconazole, aminoglutethimide, metyrapone and mitotane, decrease adrenal steroid secretion and are frequently associated with significant side effects. A GR antagonist would therefore be an attractive alternative treatment option, and the studies are underway to better define the use of RU 486 in Cushing's syndrome. We here, therefore, review the antiglucocorticoid actions of RU 486 and the hitherto existing clinical experience concerning its use in Cushing's syndrome. Original articles and reviews were identified using a PubMed search strategy covering the time period until February 2007. The following search terms were used in varying combinations: mifepristone, RU 486, Cushing's

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syndrome, hypercortisolism, glucocorticoid, side effects and long-term treatment. In addition, several book chapters related to mifepristone and a conference presentation were used.

Pharmacokinetics

Mifepristone (11-[4-(dimethylamino)phenyl]-17-hydroxy-17-[1-propynyl]-[11β,17β]-oestra-4,9-diene-3-one; Fig. 1) is a derivative of the synthetic progestin norethindrone. After oral ingestion, the drug is quickly absorbed, and peak serum concentrations in the micromolar range are reached within 1–2 h (4–7). After doses ranging from 50 to 100 mg, the serum concentration increases progressively, but little or no further increase is seen after doses of 100–800 mg. The concentrations of several metabolites, in contrast, increase in a dose-dependent manner and exceed that of the parent compound when large doses of RU 486 are administered (7, 8). Mifepristone is highly protein bound in human serum, unlike in rats, due to the presence of α1-acid glycoprotein (orosomucoid). Progressive saturation of this high-affinity binding protein may contribute to the non-linear pharmacokinetics of RU 486, since the unbound mifepristone is rapidly metabolized in the liver by demethylation and hydroxylation or is extravasated into tissues. The initial steps in the metabolic process are catalysed by the cytochrome P450 enzyme CYP3A4, and the metabolites are excreted with the faeces (9).

The plasma half-life of mifepristone has been reported to vary between 24 and 48 h when analysed by high performance liquid chromatography (HPLC), and between 55 and 90 h when RIA or radioreceptor assays are used. Even if these values were most likely altered by the presence of cross-reacting metabolites, RU 486 exhibits an unusual long plasma half-life when compared with other steroids, which range from minutes (progesterone) to 3–5 h (dexamethasone) (9, 10). This characteristic can also be explained by the extensive binding of the drug. The metabolites also have a long half-life and, to a lesser extent, they also exhibit biological activity (10).

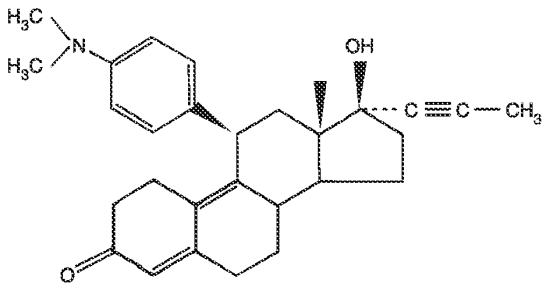

Figure 1 Chemical structure of Mifepristone.

Mechanisms of action

Mifepristone binds to the human GR with an affinity three to four times higher than that of dexamethasone and about 18 times higher than that of cortisol (11). Binding of mifepristone to the receptor hinders the receptor from releasing from the associated heat shock proteins, thus preventing translocation of the RU 486/receptor complex to the nucleus. Some of the complexes, however, manage to reach the target DNA, but then transcriptional activity is significantly diminished (12).

The antiglucocorticoid effects of mifepristone are dose dependent. They occur at single doses of 4 mg/kg and higher, whereas antiprogestin activity is already apparent at much lower doses (13, 14). Since mifepristone blocks the GR in a competitive manner, the effect can be reversed by glucocorticoid administration. Precisely, 1 mg dexamethasone abolishes the effects of 400 mg RU 486. However, the antiglucocorticoid effect of RU 486 reappears 1 day later due to its long plasma half-life (15).

Besides its antiglucocorticoid and antiprogestin activity, mifepristone is also a weak antiandrogen. The relative binding affinities of mifepristone for the progesterone receptor and the androgen receptor are five times higher than for progesterone and four times lower than for testosterone respectively. In contrast, mifepristone does not bind to mineralocorticoid and oestradiol receptors (13).

In the absence of endogenous or exogenous glucocorticoids, mifepristone also exhibits some glucocorticoid agonist activity, as shown by Laue (16). After a short period of glucocorticoid deprivation, patients with primary adrenal insufficiency received an oral dose of either placebo, hydrocortisone or mifepristone, followed by a corticotrophin-releasing hormone (CRH) stimulation test. CRH induced significant elevation of plasma ACTH in all placebo-treated patients, whereas hydrocortisone led to significant suppression of the ACTH response. RU 486 caused some suppression of the ACTH response. Its agonist activity was calculated to be about 1/250th of that of cortisol. However, mifepristone was unable to prevent fatal adrenal insufficiency in adrenalectomized monkeys (17). Thus, glucocorticoid antagonism is the predominant action *in vivo*.

Mifepristone affects both the central actions of cortisol (its negative feedback on CRH/ACTH secretion) and its peripheral actions. In animals and humans with an intact hypothalamic–pituitary–adrenal (HPA) axis, RU 486 antagonizes the negative feedback of cortisol by blocking central GRs (2, 18). The increase in plasma ACTH and cortisol levels induced by RU 486 is particularly evident in the early morning hours, when ACTH and cortisol concentrations are physiologically peaking (19). Mifepristone also antagonizes the dexamethasone-induced cortisol suppression (2). Although long-term administration of RU 486 produces persistent elevation of ACTH and cortisol levels, the response to

CRH and the circadian rhythm of ACTH and cortisol secretion are not affected. Thus, the central regulatory mechanisms remain intact (20).

Concerning the peripheral actions of cortisol, it was shown in healthy volunteers that mifepristone antagonizes acute effects of cortisol on protein and glucose metabolism (21). In addition, RU 486 inhibits the cortisol-induced peripheral vasoconstriction that was demonstrated by attenuated skin blanching after administration of topical steroids (22). A slight increase in circulating eosinophils during treatment with RU 486 was also reported in some, but not in all, studies.

In a study by Bertagna *et al.* ten healthy male volunteers were given RU 486 at a daily dose of 200 mg (~3 mg/kg) for 8 days (23). The treatment resulted in a clear activation of the HPA axis, demonstrated by elevated ACTH and cortisol levels. This biochemically detectable antiglucocorticoid effect was not accompanied by relevant clinical symptoms of adrenal insufficiency. Bertagna and colleagues concluded that in subjects with an intact HPA axis, the central effect of the drug (upregulation of the HPA axis) prevents peripheral glucocorticoid deficiency by maintaining an adequate equilibrium between endogenous cortisol levels and circulating RU 486. Bertagna and his team also investigated the response of the HPA axis to RU 486 in patients with Cushing's syndrome (24). Five patients with Cushing's disease and two patients with non-pituitary Cushing's syndrome received 400 mg mifepristone daily on 3 consecutive days. In all patients with Cushing's disease, RU 486 administration was associated with further stimulation of the already activated HPA axis, particularly demonstrated by a marked increase in urinary cortisol excretion. In the two patients with non-pituitary Cushing's syndrome, in contrast, no significant changes in hormone secretion were observed after administration of RU 486. Thus, the hormonal response to mifepristone in Cushing's syndrome depends on the underlying cause of hypercortisolism. Unlike persons with an intact HPA axis, there were two patients with Cushing's disease who developed potential signs of glucocorticoid insufficiency (nausea and headache in one case and lethargy in the other case) and who had to be treated with dexamethasone.

RU 486 in Cushing's syndrome

Up to now, 18 patients have been reported to have received RU 486 for treatment of hypercortisolism (for an overview, see Table 1).

The first patient, a 25-year-old male with ectopic ACTH syndrome due to an intrathoracic carcinoid tumour, was reported by Nieman in 1985 (25). The initial dose of 5 mg/kg mifepristone per day was increased every 1–2 weeks to a maximum of 20 mg/kg. The clinical signs of hypercortisolism – namely central obesity, high blood pressure, hypokalaemic alkalosis, elevated plasma glucose levels and depression – clearly improved during treatment with RU 486. No side effects were observed. After 9 weeks, RU 486 was no longer available, and the treatment had to be stopped. To control hypercortisolism, bilateral adrenalectomy was performed.

In the following years, Nieman and co-workers studied the effects of RU 486 in ten more patients with Cushing's syndrome (26, 27). In six of them, the clinical response was excellent, and the treatment was generally well tolerated. However, in the remaining four patients, treatment with RU 486 had to be stopped after 3–14 days because of adverse events. These included severe nausea, prostration and hypotension. One patient developed *Pneumocystis carinii* pneumonia.

Treatment duration in the above six other cases – four cases with ectopic ACTH syndrome, one adrenal adenoma and one adrenocortical carcinoma – ranged from 6 weeks to 12 months. Mifepristone was applied in doses ranging from 5 to 22 mg/kg per day. Reported side effects included moderate nausea, development of gynecomastia, impotence and Hashimoto's thyroiditis. There was one episode of adrenal insufficiency in a 63-year-old woman with ectopic ACTH syndrome. In most patients, plasma ACTH and cortisol remained significantly elevated, but unlike the reports in subjects with an intact HPA axis, these patients had no further increase in ACTH and cortisol levels. Intriguingly, in two patients, plasma and urinary cortisol levels even decreased while plasma ACTH levels remained unchanged, so that inhibition of adrenal cortisol synthesis by mifepristone was suggested (26, 27).

Van der Lely reported two patients with adrenal carcinoma in whom RU 486 reversed acute cortisol-induced psychosis within 24 h (28). Both patients died some weeks later due to tumour progression. There were two other cases of adrenocortical carcinoma treated with RU 486, but only limited information on these patients has been provided (29, 30).

In Cushing's disease, the HPA axis is characterized by an upregulated set point, and patients with Cushing's disease also react to RU 486 with further activation of the HPA axis. This may limit the therapeutic value of RU 486 in such patients, because a mifepristone-induced increase in ACTH and cortisol levels may overcome the receptor blockade. However, in one patient with an ACTH-secreting pituitary macroadenoma, treatment with RU 486 resulted in clear clinical improvement (31). The patient was a 51-year-old, severely ill male suffering from cortisol-induced psychosis, multiple metabolic disturbances and cardiomyopathy. Transsphenoidal resection of the tumour was incomplete, ketoconazole was not tolerated and mitotane failed to control hypercortisolism. The patient underwent pituitary irradiation, and treatment with RU 486 was initiated to bridge the time until radiotherapy would show benefit. Cardiomyopathy, psychosis and the metabolic disturbances improved impressively. In the

Table 1 Patients with Rousell-Uclaf 38 486 (RU 486) therapy for Cushing's syndrome.

Patient	Disease	RU 486 dosage	Duration of treatment	Response	Side effects	Reference
25 years, male	EAS	5–20 mg/kg daily	9 weeks	Clinical improvement	No side effects observed	(25–27)
27 months, female	EAS	25 mg thrice daily (≈5 mg/kg) to 100 mg thrice daily	2 months	Clinical improvement	No side effects observed	(34)
36 years, male	EAS	5–22 mg/kg daily	10 months	Clinical improvement	Hashimoto's thyroiditis, gynecomastia, impotence, 'inhibition of cortisol synthesis'	(26, 27)
45 years, female	ACC		2 months	Clinical improvement	No side effects observed	(26, 27)
38 years, female	AA		6 weeks	Clinical improvement	Nausea	(26, 27)
42 years, male	EAS		12 months	Clinical improvement	Nausea, gynecomastia	(26, 27)
63 years, female	EAS		4 months	Clinical improvement	Adrenal crisis	(26, 27)
55 years, female	EAS		10 weeks	Clinical improvement	No side effects observed	(26, 27)
NR	NR	NR	<1 month	–	Hypotension	(26, 27)
NR	NR	NR	<1 month	–	*Pneumocystis carinii* pneumonia	(26, 27)
NR	NR	NR	<1 month	–	Severe nausea, prostration	(26, 27)
NR	NR	NR	<1 month	–	Nausea, 'inhibition of cortisol biosynthesis'	(26, 27)
14 years, female	NCS	400 mg daily	8 months (with interruptions)	Clinical improvement	Endometrial hyperplasia, transient rash, Hashimoto's thyroiditis	(32)
51 years, male	CD	400–2000 mg daily (≈25 mg/kg)	18 months	Clinical improvement	Severe hypokalaemia, adrenal crisis	(31)
43 years, male	ACC	800 mg, dose reduction to 400 mg daily	2 weeks	Mental abnormalities disappeared within 24 h	Hypoglycaemic episodes, increase in eosinophils	(28)
32 years, female	ACC	400 mg daily	2 months	Mental abnormalities improved within 24 h	No side effects observed	(26, 27)
Female	ACC	30 mg/kg daily, dose reduction to 20 mg/kg per KG	4 months	Clinical improvement, tumour regression	Vaginal bleeding, hypoglycaemia, water retention	(29)
62 years, male	ACC	400 mg daily	9 months	Initial improvement of hypokalaemic alkalosis and diabetes, but after 9 months clinical hypercortisolism recurred due to tumour growth	NR	(30)

AA, adrenal adenoma; ACC, adrenocortical carcinoma; CD, Cushing's disease; CS, Cushing's syndrome; EAS, ectopic ACTH syndrome; NCS, normocortisolaemic Cushing's syndrome; NR, not reported.

course of the treatment, the patient developed severe hypokalaemia, and spironolactone therapy was initiated. It was suggested that hypokalaemia resulted from stimulation of the mineralocorticoid receptor by cortisol, while GRs were blocked by mifepristone. The patient also experienced one episode of adrenal insufficiency, manifested by weakness, orthostatic hypotension and hypoglycaemia, which resolved after administration of i.v. dexamethasone. During treatment with RU 486, plasma ACTH and cortisol levels were fluctuating but remained elevated over a period of about 8 months. Then the ACTH and cortisol levels decreased, probably due to the delayed effects of radiotherapy, and mifepristone therapy was tapered down over the following 10 months.

The remaining two cases described in the literature were peculiar cases of transient hypercortisolism. One was a 14-year-old girl suffering from a so-called normocortisolaemic Cushing's syndrome, showing typical clinical features of hypercortisolism (central obesity, purple striae and reduced bone density) but normal cortisol levels (32). Investigators reported an increased amount of GR sites per cell. Treatment with RU 486 resulted in improvement of obesity and striae

but was without effect on bone. The treatment had to be interrupted several times because of vaginal bleeding. After 8 months of treatment, massive amorphous material was found in the distended uterus. Curettage followed and showed endometrial hyperplasia (33). The Cushingoid features continued to resolve gradually after withdrawal of RU 486. The other case was a 27-month-old baby girl in whom an ACTH-depending Cushing's syndrome was suspected but no tumour could be detected (34). Treatment with RU 486 caused significant improvement of central obesity, blood pressure and blood glucose levels. Plasma and urinary cortisol and, to a lesser extent, ACTH decreased. Treatment with RU 486 was stopped after 2 months. Interestingly, no clinical nor biochemical relapse occurred so that the cause of Cushing's syndrome remains elusive.

Side effects in short-term use

Termination of unwanted pregnancies with a single 600 mg dose of mifepristone followed by a prostaglandin analogue is generally well tolerated (35). The most frequent side effects include abdominal pain, cramping, nausea, vomiting and headache, and it is difficult to discriminate these symptoms from sensations that occur during spontaneous abortion. Some of the reported side effects are more likely associated with the prostaglandin used than with mifepristone. The abdominal pain, for example, is significantly less when using the mifepristone–prostaglandin combination compared with abortive regimens using prostaglandins alone (36). There were also several serious cardiovascular events, including a fatal acute myocardial infarction, that were attributed to the prostaglandin component of the treatment. The prostaglandin analogue used in these cases, sulprostone i.m., has been withdrawn from the market (14).

Only very few women do not abort after treatment with mifepristone plus prostaglandin. In these rare cases, however, possible teratogenic effects of the drugs administered would be of great importance. In contrast to prostaglandins, mifepristone had no teratogenic effects in animal studies (37). Rabbits, however, showed cephalic deformities that were explained by mechanical damage due to uterine contractions, resulting from the decrease in progesterone activity (36).

The doses of RU 486 needed to exhibit antiglucocorticoid effects are significantly higher than those needed for antiprogestin activity. Thus, in women receiving a single dose of mifepristone for termination of pregnancy, no clinically relevant antiglucocorticoid side effects have been reported (27).

Side effects in long-term use

Chronic administration of mifepristone has been tested in the patients with Cushing's syndrome described above previously, but these were only reports of individual cases. Larger studies have been performed in patients with unresectable meningioma, endometriosis, myoma and breast cancer. As these trials aimed at progesterone receptor blockade and not GR blockade, much lower doses were administered, which probably facilitated the availability of RU 486. Treatment duration varied from several weeks or months up to 14 years and was longest in patients with meningioma. Information on safety of long-term treatment with mifepristone is mainly provided by these pilot studies (Table 2).

Antiglucocorticoid side effects

Daily doses of mifepristone ranged from 5 to 100 mg in myoma and endometriosis studies, and from 200 to 400 mg in meningioma and breast cancer (38). These rather low doses had been chosen to avoid antiglucocorticoid effects while achieving full antiprogestin activity. However, repeated administration of even these low doses resulted in an activation of the HPA axis, which was demonstrated by elevated plasma ACTH and cortisol levels (20, 23, 38).

Spitz and Grunberg reported 28 patients with unresectable meningioma who received continuous treatment with 200 mg mifepristone daily for up to 13 years (39–41). Patients received concomitant dexamethasone therapy for the first 14 days. The most common side effect was fatigue, which was

Table 2 Side effects of long-term treatment with mifepristone depending on the blocked receptor and the doses administered.

Receptor	Daily dose	Potential side effects
PR	>5 mg	Amenorrhoea
	>10 mg	Endometrial hyperplasia
GR	>50 mg	Increase in cortisol, ACTH, adrenal androgens
	>100–200 mg	Mild to moderate fatigue/nausea
	>200–400 mg	Adrenal insufficiency (severe nausea, severe fatigue and other symptoms)
	>200 mg	Gynecomastia (due to elevated oestradiol levels derived from adrenal androgens)
	>200 mg (isolated cases)	Hypokalaemia (due to MR activation by cortisol?)
	>400 mg (isolated cases)	Hypothyroidism
AR	>200 mg	Gynecomastia, decrease *in libido*

Dose designations are estimated based on the results from long-term trials, exact doses at which the listed side effects occur may vary between individuals. PR, progesterone receptor; GR, glucocorticoid receptor; AR, androgen receptor; MR, mineralocorticoid receptor.

generally mild. Clinically relevant adrenal insufficiency only occurred in one patient who was already on glucocorticoid replacement for known hypopituitarism. Her symptoms resolved after increasing the exogenous steroid replacement. Lamberts, however, who investigated the effects of daily administration of mifepristone (200 mg) in ten patients with meningioma reported that in four patients prednisone therapy had to be initiated in order to overcome the side effects (20). De Keizer and colleagues, who treated two women with meningioma with 200–400 mg mifepristone daily for up to 14 years, combined mifepristone therapy from the start with concomitant glucocorticoid administration to prevent adrenal insufficiency (42). In the myoma and endometriosis studies, however, where much lower doses of mifepristone were administered (5–100 mg), antiglucocorticoid side effects seemed to be of minor importance, as no episodes of adrenal insufficiency were reported. In summary, clinical adrenal insufficiency must be considered a possible side effect of long-term treatment with mifepristone, but is a rare complication in patients with an intact HPA axis. The drug-induced compensatory hypersecretion of ACTH and cortisol seems to prevent the risk of peripheral cortisol deficiency. Some patients with progesterone-dependent diseases, however, may benefit from concomitant glucocorticoid therapy to better tolerate long-term treatment with mifepristone.

In the 18 patients with Cushing's syndrome described above previously, there were five events of adrenal insufficiency (presumed that the reported episodes of severe nausea, prostration and marked hypotension were indicative of acute adrenal insufficiency). Thus, the rate of adrenal insufficiency related to the GR blockade seems to be higher in patients with Cushing's syndrome than in patients with meningioma, myoma or other progesterone-dependent diseases. Several factors may contribute to this problem. First, the doses used were markedly higher. Secondly, the HPA axis is altered in these patients, and its response to GR blockade is more difficult to predict. In particular, hypothalamic CRH secretion is typically severely impaired in Cushing's syndrome hampering the adaptation to deficient glucocorticoid action. In addition, there are no biochemical markers for assessment of glucocorticoid insufficiency during treatment with RU 486, as measurement of plasma ACTH and plasma or urinary cortisol is not reliable, and the balance between desired antiglucocorticoid action and overtreatment is difficult to maintain.

Endometrial hyperplasia

A problem in long-term treatment with mifepristone is the complex influence of this drug on the endometrium. On one hand, mifepristone exhibits antiproliferative effects, of what is taken advantage in its use in myoma and endometriosis. On the other hand, mifepristone is associated with frequent development of endometrial hyperplasia.

In several studies, treatment with 5–50 mg mifepristone led to a marked reduction in myoma volume, with significant relief from pain and bleeding (38, 43, 44). It is supposed that blockade of progesterone-dependent growth factors, reduced blood supply due to vascular changes and decreased inhibition of oestrogen receptor gene transcription by the progesterone receptor A isoform are some of the mechanisms contributing to the antiproliferative activity of mifepristone (44).

Concerning endometrial hyperplasia, we have already mentioned detection of extensive hyperplasia in an adolescent girl with Cushing's syndrome after 8 months of treatment with RU 486 (33). In the meningioma study of Spitz *et al.*, the incidence of endometrial hyperplasia was reported to be about 10% (39). In women suffering from myoma, Eisinger reported a rate of endometrial hyperplasia of 25% after 6 months of treatment with 10 mg mifepristone daily (43). The mechanisms involved in these proliferative effects are not completely understood, and the histological changes differ from classical forms of endometrial hyperplasia (45). When low doses of RU 486 (5–50 mg daily) are administered, hyperplasia seems to be the result of unopposed oestradiol action on the endometrium due to progesterone receptor blockade. With higher doses, activation of the HPA axis may also play a role (44). It has been shown that the drug-induced rise in plasma ACTH is followed by an increase in not only plasma cortisol, but also adrenal androgens and oestradiol. The increased oestradiol levels may derive from peripheral aromatization of adrenal androgens and may also contribute to proliferation of the endometrium (20, 44, 46, 47).

So far, no case of endometrial carcinoma has been reported in relation to long-term treatment with mifepristone, and the risk seems to be rather low (43). However, regular vaginal ultrasound for monitoring of endometrial hyperplasia is recommended in women receiving long-term treatment with mifepristone.

Effects on biochemical parameters

Occasionally, long-term administration of mifepristone has been associated with low serum potassium levels, a slight increase in serum creatinine levels or moderate elevation of hepatic enzymes (43, 44, 48).

Depending on the dose and treatment duration, long-term administration of mifepristone may also be associated with alterations in thyroid homeostasis. Thyrotrophin (TSH) levels may increase significantly but in most cases remain within the normal range. Since glucocorticoids suppress pituitary TSH secretion, increased TSH levels might be related to central antiglucocorticoid effects of mifepristone. Direct effects within the thyroid gland itself, leading to a compensatory increase in TSH levels, were also suggested (49).

In individual cases, development of Hashimoto's thyroiditis has been reported (26, 27, 32).

Other side effects

Other side effects reported during long-term treatment with RU 486 include anorexia, weight loss, dizziness, amenorrhoea, hot flushes and transient thinning of the hair (36). Some men complained of gynecomastia and a decrease in libido. These latter side effects were probably related to binding of mifepristone to the androgen receptor and to elevated oestradiol levels.

Another adverse event reported was a grand mal seizure with impaired consciousness in a woman with breast cancer. At first, the grand mal seizure was thought to be caused by cerebral metastases, but no metastases were detected with computed tomography. After withdrawal of mifepristone and initiation of dexamethasone therapy, the patient significantly improved within 3 days (46).

The daily mifepristone doses administered in the patients with Cushing's syndrome ranged from 400 to 2000 mg. Besides this patient group, comparable doses were administered only in a group of 11 healthy male volunteers (50). Subjects were planned to receive RU 486 at a daily dose of 10 mg/kg over a period of 14 days. However, the study had to be revised because of a high incidence of adverse events. One subject developed acute adrenal insufficiency after 10 days of treatment with RU 486 and had to be treated with dexamethasone. Eight out of eleven subjects developed a generalized exanthema after 9–10 days of treatment. In all cases, the rash spontaneously resolved after withdrawal of mifepristone. This high incidence of skin rashes was not observed in other studies. In women receiving single-dose administration of 600 mg mifepristone, the rate of rashes was below 1% (14). In patients with Cushing's syndrome, who received comparable doses of mifepristone, there was only one case of transient rash (32). It was suggested that the hypercortisolism in these patients may have had a protective effect against such a hypersensitivity reaction (50).

Monitoring

General recommendations for monitoring of patients on long-term treatment with mifepristone include annual vaginal ultrasound in women and annual control of TSH and thyroid hormones in women and men (39).

Adrenal insufficiency can only be assessed by clinical observation, as cortisol and ACTH levels are either elevated or within the normal range. As the GRs are blocked, high cortisol levels may cause overstimulation of the mineralocorticoid receptors. Thus, in some cases, serum potassium levels and blood pressure values may be of little help in assessment of adrenal insufficiency. Extreme weakness and fatigue, severe nausea and hypoglycaemic episodes are indicative of peripheral cortisol deficiency, and then glucocorticoids should be given immediately.

Patients with Cushing's syndrome should be monitored with particular attention to clinical signs of adrenal insufficiency, and the dose of RU 486 should be increased only gradually.

Conclusions

The long-term use of mifepristone as an antiprogestin in myoma, meningioma and other progesterone-dependent diseases is generally well tolerated. In the rare cases with clinically relevant antiglucocorticoid side effects, concomitant glucocorticoid therapy can be initiated. Management of patients with Cushing's syndrome, however, seems to be more demanding. As there are no biochemical markers for adrenal insufficiency during treatment with RU 486, it requires careful clinical observation to establish where the desired antiglucocorticoid action ends and overtreatment starts. The most common starting dose in Cushing's syndrome, 400 mg daily, was deduced from the observation that mifepristone-induced blockade of the GR is dose dependent and becomes apparent only at doses of at least 4–6 mg/kg. Yet, this was derived from studies with single doses. Repeated administration of lower doses also produces antiglucocorticoid effects, as the long-term studies in meningioma, myoma and breast cancer have shown. Hence, doses below 400 mg/day might also be used successfully in the treatment of Cushing's syndrome and may be associated with fewer side effects.

In patients with Cushing's syndrome in whom long-term treatment with mifepristone was, on the whole, well tolerated, improvement of clinical features was impressive. Mifepristone, therefore, remains an interesting treatment option for Cushing's syndrome caused by ectopic ACTH production or adrenocortical carcinoma that cannot be controlled by surgery alone. It may be particularly useful in conditions in which a rapid onset of antiglucocorticoid effects is required, e.g. in acute cortisol-induced psychosis. Regrettably, mifepristone is currently not easily available for treatment of Cushing's syndrome outside of clinical trials, as the disposability of the 'abortion pill' is limited by legal restrictions. Well-designed clinical trials in patients with Cushing's syndrome are urgently needed to better appreciate the therapeutic potential of mifepristone in hypercortisolism.

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References

1 Ulmann A, Teutsch G & Philibert D. RU 486. *Scientific American* 1990 **262** 42–48.
2 Bertagna X, Bertagna C, Luton JP, Husson JM & Girard F. The new steroid analog RU 486 inhibits glucocorticoid action in man. *Journal of Clinical Endocrinology and Metabolism* 1984 **59** 25–28.
3 Kettel LM. Clinical applications of the antiprogestins. *Clinical Obstetrics and Gynecology* 1995 **38** 921–934.
4 Foldesi I, Falkay G & Kovacs L. Determination of RU 486 (mifepristone) in blood by radioreceptorassay; a pharmacokinetic study. *Contraception* 1996 **54** 27–32.
5 Kekkonen R, Heikinheimo O, Mandelin E & Lahteenmaki P. Pharmacokinetics of mifepristone after low oral doses. *Contraception* 1996 **54** 229–234.
6 Lähteenmäki P, Heikinheimo O, Croxatto H, Spitz IM, Shoupe D, Birgerson L & Luukkainen T. Pharmacokinetics and metabolism of RU 486. *Journal of Steroid Biochemistry* 1987 **27** 859–863.
7 Heikinheimo O, Kontula K, Croxatto H, Spitz I, Luukkainen T & Lahteenmaki P. Plasma concentrations and receptor binding of RU 486 and its metabolites in humans. *Journal of Steroid Biochemistry* 1987 **26** 279–284.
8 Heikinheimo O, Kekkonen R & Lahteenmaki P. The pharmacokinetics of mifepristone in humans reveal insights into differential mechanisms of antiprogestin action. *Contraception* 2003 **68** 421–426.
9 Heikinheimo O. Clinical pharmacokinetics of mifepristone. *Clinical Pharmacokinetics* 1997 **33** 7–17.
10 Kawai S, Nieman LK, Brandon DD, Udelsman R, Loriaux DL & Chrousos GP. Pharmacokinetic properties of the antiglucocorticoid and antiprogesterone steroid RU 486 in man. *Journal of Pharmacology and Experimental Therapeutics* 1987 **241** 401–406.
11 Sartor O & Cutler GB Jr. Mifepristone: treatment of Cushing's syndrome. *Clinical Obstetrics and Gynecology* 1996 **39** 506–510.
12 Bamberger CM & Chrousos GP. The glucocorticoid receptor and RU 486 in man. *Annals of the New York Academy of Sciences* 1995 **761** 296–310.
13 Cadepond F, Ulmann A & Baulieu EE. RU 486 (mifepristone): mechanisms of action and clinical uses. *Annual Review of Medicine* 1997 **48** 129–156.
14 Sitruk-Ware R & Spitz IM. Pharmacological properties of mifepristone: toxicology and safety in animal and human studies. *Contraception* 2003 **68** 409–420.
15 Raux-Demay MC, Pierret T, Bouvier D'yvoire M, Bertagna X & Girard F. Transient inhibition of RU 486 antiglucocorticoid action by dexamethasone. *Journal of Clinical Endocrinology and Metabolism* 1990 **70** 230–233.
16 Laue L, Chrousos GP, Loriaux DL, Barnes K, Munson P, Nieman L & Schaison G. The antiglucocorticoid and antiprogestin steroid RU 486 suppresses the adrenocorticotropin response to ovine corticotropin releasing hormone in man. *Journal of Clinical Endocrinology and Metabolism* 1988 **66** 290–293.
17 Laue L, Gallucci W, Loriaux DL, Udelsman R & Chrousos GP. The antiglucocorticoid and antiprogestin steroid RU 486: its glucocorticoid agonist effect is inadequate to prevent adrenal insufficiency in primates. *Journal of Clinical Endocrinology and Metabolism* 1988 **67** 602–606.
18 Healy DL, Chrousos GP, Schulte HM, Williams RF, Gold PW, Baulieu EE & Hodgen GD. Pituitary and adrenal responses to the antiprogesterone and anti-glucocorticoid steroid RU 486 in primates. *Journal of Clinical Endocrinology and Metabolism* 1983 **57** 863–865.
19 Gaillard RC, Riondel A, Muller AF, Herrmann W & Baulieu EE. RU 486: a steroid with antiglucocorticosteroid activity that only disinhibits the human pituitary–adrenal system at a specific time of day. *PNAS* 1984 **81** 3879–3882.
20 Lamberts SW, Koper JW & de Jong FH. The endocrine effects of long-term treatment with mifepristone (RU 486). *Journal of Clinical Endocrinology and Metabolism* 1991 **73** 187–191.
21 Garrel DR, Moussali R, de Oliveira A, Lesiege D & Lariviere F. RU 486 prevents the acute effects of cortisol on glucose and leucine metabolism. *Journal of Clinical Endocrinology and Metabolism* 1995 **80** 379–385.
22 Gaillard RC, Poffet D, Riondel AM & Saurat JH. RU 486 inhibits peripheral effects of glucocorticoids in humans. *Journal of Clinical Endocrinology and Metabolism* 1985 **61** 1009–1011.
23 Bertagna X, Escourolle H, Pinquier JL, Coste J, Raux-Demay MC, Perles P, Silvestre L, Luton JP & Strauch G. Administration of RU 486 for 8 days in normal volunteers: antiglucocorticoid effect with no evidence of peripheral cortisol deprivation. *Journal of Clinical Endocrinology and Metabolism* 1994 **78** 375–380.
24 Bertagna X, Bertagna C, Laudat MH, Husson JM, Girard F & Luton JP. Pituitary–adrenal response to the antiglucocorticoid action of RU 486 in Cushing's syndrome. *Journal of Clinical Endocrinology and Metabolism* 1986 **63** 639–643.
25 Nieman LK, Chrousos GP, Kellner C, Spitz IM, Nisula BC, Cutler GB, Merriam GR, Bardin CW & Loriaux DL. Successful treatment of Cushing's syndrome with the glucocorticoid antagonist RU 486. *Journal of Clinical Endocrinology and Metabolism* 1985 **61** 536–540.
26 Chrousos GP, Laue L, Nieman L, Udelsman R, Kawai S & Loriaux DL. *Clinical Applications of RU 486, a Prototype Glucocorticoid and Progestin Antagonist* New York: Raven Press, 1989.
27 Chrousos GP, Laue L, Nieman LK, Kawai S, Udelsman RU, Brandon DD & Loriaux DL. Glucocorticoids and glucocorticoid antagonists: lessons from RU 486. *Kidney International. Supplement* 1988 **26** S18–S23.
28 van der Lely AJ, Foeken K, Van Der Mast RC & Lamberts SW. Rapid reversal of acute psychosis in the Cushing syndrome with the cortisol-receptor antagonist mifepristone (RU 486). *Annals of Internal Medicine* 1991 **114** 143–144.
29 Contreras P. Adrenal cancer: tumor regression with ketoconazole or mifepristone (RU 486). *In vivo* and *in vitro* evidence supporting tumoral hormone dependency. Proceedings of the 69th Annual Endocrine Society Meeting, Indianapolis, p 23, 1987.
30 Donckier JE, Michel LA, Berbinschi A, de Coster PM, de Plaen JE, Ketelslegers JM & Buysschaert M. Late recurrence of operated adrenocortical carcinoma: atrial natriuretic factor before and after treatment with mitotane. *Surgery* 1989 **105** 690–692.
31 Chu JW, Matthias DF, Belanoff J, Schatzberg A, Hoffman AR & Feldman D. Successful long-term treatment of refractory Cushing's disease with high-dose mifepristone (RU 486). *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 3568–3573.
32 Newfield RS, Kalaitzoglou G, Licholai T, Chilton D, Ashraf J, Thompson EB & New MI. Normocortisolemic Cushing's syndrome initially presenting with increased glucocorticoid receptor numbers. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 14–21.
33 Newfield RS, Spitz IM, Isacson C & New MI. Long-term mifepristone (RU 486) therapy resulting in massive benign endometrial hyperplasia. *Clinical Endocrinology* 2001 **54** 399–404.
34 Beaufrere B, de Parscau L, Chatelain P, Morel Y, Aguercif M & Francois R. RU 486 administration in a child with Cushing's syndrome. *Lancet* 1987 **2** 217.
35 Goldberg JR, Plescia MG & Anastasio GD. Mifepristone (RU 486): current knowledge and future prospects. *Archives of Family Medicine* 1998 **7** 219–222.
36 Spitz IM & Bardin CW. Mifepristone (RU 486) – a modulator of progestin and glucocorticoid action. *New England Journal of Medicine* 1993 **329** 404–412.
37 Deraedt R, Vannier B & Fournex R. Toxicological study on RU 486. In: *The Antiprogestin Steroid RU 486 and Human Fertility Control*. pp 105–126, 1985. Eds EE Baulieu & SJ Segal, New York: Plenum Press 1992.
38 Koide SS. Mifepristone. Auxiliary therapeutic use in cancer and related disorders. *Journal of Reproductive Medicine* 1998 **43** 551–560.
39 Spitz IM, Grunberg SM, Chabbert-Buffet N, Lindenberg T, Gelber H & Sitruk-Ware R. Management of patients receiving long-term treatment with mifepristone. *Fertility and Sterility* 2005 **84** 1719–1726.
40 Grunberg SM, Weiss MH, Russell CA, Spitz IM, Ahmadi J, Sadun A & Sitruk-Ware R. Long-term administration of mifepristone (RU 486): clinical tolerance during extended treatment of meningioma. *Cancer Investigation* 2006 **24** 727–733.

41 Grunberg SM, Weiss MH, Spitz IM, Ahmadi J, Sadun A, Russell CA, Lucci L & Stevenson LL. Treatment of unresectable meningiomas with the antiprogesterone agent mifepristone. *Journal of Neurosurgery* 1991 **74** 861–866.
42 de Keizer RJ & Smit JW. Mifepristone treatment in patients with surgically incurable sphenoid-ridge meningioma: a long-term follow-up. *Eye* 2004 **18** 954–958.
43 Eisinger SH, Bonfiglio T, Fiscella K, Meldrum S & Guzick DS. Twelve-month safety and efficacy of low-dose mifepristone for uterine myomas. *Journal of Minimally Invasive Gynecology* 2005 **12** 227–233.
44 Spitz IM. Progesterone antagonists and progesterone receptor modulators: an overview. *Steroids* 2003 **68** 981–993.
45 Chabbert-Buffet N, Meduri G, Bouchard P & Spitz IM. Selective progesterone receptor modulators and progesterone antagonists: mechanisms of action and clinical applications. *Human Reproduction Update* 2005 **11** 293–307.
46 Klijn JG, de Jong FH, Bakker GH, Lamberts SW, Rodenburg CJ & Alexieva-Figusch J. Antiprogestins, a new form of endocrine therapy for human breast cancer. *Cancer Research* 1989 **49** 2851–2856.
47 Heikinheimo O, Ranta S, Grunberg S & Spitz IM. Alterations in sex steroids and gonadotropins in post-menopausal women subsequent to long-term mifepristone administration. *Steroids* 2000 **65** 831–836.
48 Murphy AA, Morales AJ, Kettel LM & Yen SS. Regression of uterine leiomyomata to the antiprogesterone RU 486: dose–response effect. *Fertility and Sterility* 1995 **64** 187–190.
49 Heikinheimo O, Ranta S, Grunberg S, Lahteenmaki P & Spitz IM. Alterations in the pituitary–thyroid and pituitary–adrenal axes – consequences of long-term mifepristone treatment. *Metabolism* 1997 **46** 292–296.
50 Laue L, Lotze MT, Chrousos GP, Barnes K, Loriaux DL & Fleisher TA. Effect of chronic treatment with the glucocorticoid antagonist RU 486 in man: toxicity, immunological, and hormonal aspects. *Journal of Clinical Endocrinology and Metabolism* 1990 **71** 1474–1480.

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CONTRACEPTION

PLASMA LEVELS OF ANTIPROGESTIN RU 486 FOLLOWING ORAL ADMINISTRATION TO NON-PREGNANT AND EARLY PREGNANT WOMEN

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ABSTRACT

RU 486 is a synthetic steroid which acts as an antiprogestin at the receptor level. The clinical usefulness of the compound for menstrual regulation and termination of early pregnancy is currently being evaluated. The aim of the present study was to determine the plasma levels of RU 486 following the oral administration of the compound to 42 pregnant and 10 non-pregnant women. The levels of RU 486 were measured by a radioimmunoassay method which uses chromatography on Sephadex LH 20 columns. The identity of the compound assayed as RU 486 was confirmed, but the presence of small amounts of two highly cross-reacting metabolites (monodemethyl and didemethyl RU 486) in the analyzed fractions could not be excluded. Following the ingestion of a single tablet containing 25 and 50 mg of the compound, a peak plasma value of approximately 3.5 to 4.0 μmol/l in both the pregnant and non-pregnant subjects was reached one to two hours later. The half-lives of elimination were about 20 hours in both the pregnant and the non-pregnant women. Following the repeated oral administration of 50, 100 or 200 mg of RU 486 daily for four days, maximum plasma levels of 2.9, 4.5 and 5.4 μmol/l, respectively, were found. Thus, the increase in plasma levels was not directly proportional to the increase in the dose. No accumulation of RU 486 in the plasma was found, even when the duration of treatment was prolonged to six days. The data partly explain the reported lack of relation between ingested dose and frequency of induced abortion and they may be useful for designing future studies on the use of the compound to prevent implantation, induce menstruation or terminate an early pregnancy.

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INTRODUCTION

RU 486 is a progesterone antagonist which acts at the receptor level (1). Clinical studies have shown that oral administration of the compound resulted in termination of an early pregnancy in the majority of cases. However, the frequency of incomplete abortion was too high for the treatment to compete with the surgical alternative, i.e. vacuum aspiration (2,3).

In the study by Kovacs et al. (3) different amounts of RU 486, from 50 to 200 mg daily for four days, were used. Within this dose range the frequency of complete abortion was the same, about 60 %. Even when the dose was further increased (4), or the duration of treatment was prolonged to seven days (5), the success rate did not increase significantly. In the only study in which a high frequency of complete abortion (94 %) was reported, the RU 486 treatment was supplemented by a small dose of the prostaglandin E_2 analogue, 16-phenoxy-PGE_2 methyl sulfonylamide, administered on the fourth day of RU 486 administration (6,7).

It is not clear why the treatment with RU 486 alone has proved ineffective, despite the compound's great affinity for progesterone receptors (1) and despite the fact that progesterone is a key hormone in the maintenance of human pregnancy. One reason may be that the different dose schedules used so far have not been optimal. They were arbitrarily chosen and were not based on pharmacokinetic studies performed in the pregnant female. The only pharmacokinetic data reported to date were obtained in rat, monkey and in three male volunteers (8).

The aim of the present study was to determine the plasma levels of RU 486 following the oral administration of different amounts of the compound to non-pregnant and early pregnant women. Some preliminary results of this study have been published (6).

SUBJECTS AND METHODS

Two categories of women were included in the study:

Group I: Ten non-pregnant women receiving a single oral dose of RU 486.

Group II: Forty-two pregnant women receiving either a single oral dose of RU 486 (Group IIA, n=10) or repeated doses of RU 486 to induce an abortion (Group IIB, n=32).

All the subjects fasted for two hours before and two hours after oral administration of the drug.

The study was approved by the Ethics Committee at Karolinska Hospital. Informed consent was obtained from each subject before she was included in the study.

Non-pregnant subjects

Group I. In the pharmacokinetic studies, 10 non-pregnant subjects who had regular menstrual cycles and used no hormonal contraceptives, received a single oral dose of 25 or 50 mg RU 486 between days 20 to 22 of the menstrual cycle. Each treatment subgroup consisted of five women. Blood samples were collected at 0, 0.5, 1, 2, 8, 12, 24, 48, 72, 96 and 120 hours.

Pregnant subjects

Group IIA. In the pharmacokinetic studies 10 early pregnant patients (up to 56 days of amenorrhoea) admitted to the hospital for legal abortion were given a single oral dose of 25 or 50 mg RU 486. Each treatment group consisted of five patients. Blood samples were collected at 0, 0.5, 1, 2, 8, 12, 24, 48, 72, 96 and 120 hours. At the end of the study period the pregnancy was terminated by vacuum aspiration.

Group IIB. The group in which an abortion was induced consisted of 32 early pregnant women with amenorrhoea of up to 49 days. Different amounts of RU 486 were administered orally twice daily for four to six days. The following total daily doses of RU 486 were used: 50 mg (8 subjects), 100 mg (11 subjects), or 200 mg (6 subjects) for four days, and 50 mg (7 subjects) for six days. Blood samples were collected in the morning of each treatment day immediately prior to the first tablet intake on that day and at the same time one week after the start of treatment.

In two of the patients who were treated with a total dose of 50 mg (25 mg given twice daily), repeated blood samples were collected during a 12-hour period between the second and third doses of RU 486.

Radioimmunoassay of RU 486

The levels of RU 486 in peripheral plasma were measured by radioimmunoassay using an antiserum, standard and tracer ([6,7-^{3}H] RU 486; 1.87 GBq/nmol) donated by the Roussel Uclaf Co., Romainville, France.

A phosphate buffer (0.1 mol/l; pH 7.2) was used which contained 9 g sodium chloride, 1 g sodium azide, 1 g gelatin, and 0.25 ml Triton X 100 per litre.

Standard solutions of RU 486 were prepared in which the lower concentrations were obtained by halving the higher ones. The range of concentrations was 29 to 1860 fmol/0.2 ml. Standard curve tubes were prepared by mixing the standard solutions (0.2 ml buffer for B_0 tubes) with tracer (approximately 6000 cpm in 0.05 ml buffer) and antiserum (0.05 ml of a 1:8000 dilution), and incubating the mixture at 60°C for 10 minutes and 30°C for 30 minutes (9). The bound and free fractions were separated by charcoal (0.5 ml of a 0.5 % suspension; 30 min at 0°C) after centrifugation (3000 g for 10 min). The radioactive supernatant was mixed with 1 ml of ethanol and counted in a "Permablend III" solution which contained 5.5 g of Permablend III per 1 l of toluene (Packard Instrument Co., Downers Grove, Il 60515, USA). For the

calculation of results, a logit-log transformation was used.

Plasma samples (0.1 ml) were diluted to 5 ml and 0.2 ml of this solution (containing 4 µl plasma) was mixed with 0.2 ml of a tracer solution in buffer (approximately 3000 cpm) and equilibrated at room temperature for 10 minutes. The mixture was extracted by shaking with diethyl ether (5 ml) for 15 minutes. After the aqueous phase had been frozen in an ethanol-solid carbon dioxide mixture, ether was decanted and evaporated under nitrogen. The residue was dissolved in 0.5 ml of a toluene:ethanol (8:2 v/v) mixture and placed in a column (length 6 cm, inner diameter 1 cm) of Sephadex LH 20 (Pharmacia, Uppsala, Sweden). A 3 ml fraction consisting of the 7th to 9th ml of the eluate was collected and evaporated under nitrogen. The residue was dissolved in 1 ml of buffer, and 0.5 ml taken for recovery measurement. Duplicate aliquots of 0.1 (corresponding to 400 nl of plasma) were diluted with 0.1 ml of buffer and then further processed for assay as described for the standard curve tubes. The lowest reliably detectable concentration was 29 fmol/tube, i.e. 72.5 nmol/l plasma assuming no procedural losses due to extraction or chromatography. Since the recovery was 70.0 % +5.1 % (SD), the lowest detectable concentration in reality was 110 nmol/l on the average. When calculating the results a correction was made for the mass of tracer added for recovery measurements (10).

There were two reasons for the use of very low volumes of plasma in the assay. First, the concentrations of RU 486 were relatively high - in the order of magnitude of µmol/l. Secondly, higher volumes of plasma caused disturbances in the charcoal separation of the bound and free fractions. It was shown (the details will be published elsewhere) that if more than 10 µl plasma were assayed, unidentified ether extractable plasma constituents (probably lipids) significantly obstructed the binding of free RU 486 to charcoal and thus created a negative plasma blank. The effect of these plasma constituents was very marked when chromatography of ether extracts was not employed. Thus, when non-radioactive RU 486 was added to plasma and the plasma was extracted and assayed without performing chromatography, the recoveries were 2-15 % and showed an inverse relation to the volume of the plasma (from 150 µl down to 10 µl).

The precision of the method was demonstrated by the calculation of within-assay and between-assay variations. The coefficients of variation (for the average plasma content of 3.62 µmol/l) were 5.1 % and 14.7 %, respectively. The specificity was assessed by a parallelism test (11). This test did not indicate a lack of parallelism at the 95 % confidence level, when three volumes of a plasma pool (2.5, 5 and 10 µl) were assayed.

In tests of cross-reactions (at 50 % binding) of the antiserum with three metabolites of RU 486 (kindly provided by the Roussel Uclaf Co.), the following estimates were obtained: N-monodemethyl RU 486 ~ 125 %, N-didemethyl RU 486 ~ 125 %, propargyl alcohol RU 486 ~ 4 %. Because of the strong cross-reactions of the two first-named metabolites it was possible to ascertain by radioimmunoassay their presence in the chromatographic fraction used for the assay of plasma samples. It was found that the peaks of RU 486 and its two metabolites were incompletely

separated and that small but significant amounts of both metabolites were present in the fraction.

A limited test of radiochemical purity (12) was performed to ascertain whether a plasma pool from subjects treated with RU 486 contained significant amounts of impurities. The chromatographic peaks of radioactive RU 486 and of the immunoreactive material coincided nearly completely (details will be published elsewhere). Hence, the identity of the material assayed with RU 486 was fully confirmed, but the presence of small amounts of the two cross-reacting metabolites could not be excluded.

The results of this study are expressed in terms of the concentrations of pure RU 486, on the understanding that small amounts of its metabolites may have been present.

Statistical methods

Statistical analysis was performed after logarithmic transformation of the data (13). Hence, geometric means and corresponding 95 % confidence limits are reported. Student's t-tests and analyses of variance were used for comparison between groups. The areas under the curve were calculated as sums of partial areas according to the following formula:

$$\text{Partial area} = \text{time} \cdot \frac{\text{level a} + \text{level b}}{2} \quad \mu\text{mol.t.l}^{-1}$$

where time (t) is expressed in hours or days and levels a and b are the successive levels expressed in µmol/l.

Half-lives were calculated using conventional regression analysis.

RESULTS

Following treatment with 50 mg RU 486 daily for four days, a maximum mean plasma level of 2.9 µmol/l was reached. When the dose was increased to 100 and 200 mg daily for four days the corresponding levels were 4.5 and 5.4 µmol/l, respectively (Fig.1). No accumulation of the compound was observed with any of these doses. Three days after the end of therapy the plasma concentrations following 50 and 100 mg RU 486 had decreased to 1 µmol/l, while following 200 mg RU 486 the concentration was approximately 3 µmol/l. With 50 mg of RU 486 daily for six days the same plasma levels were observed during treatment as with the four-day treatment.

The areas under curve following treatment with three different doses of RU 486 were calculated in individual subjects between days two and four of treatment (Table I). The geometric means (and ranges) of individual areas for 50, 100 and 200 mg RU 486 daily were 5.9 (4.4-9.4), 8.7 (5.1-13.0), and 9.7 (5.7-16.0) $\mu mol.l^{-1}.d$, respectively. The difference was significant ($p < 0.05$) for 50 mg RU 486 versus 100 and 200 mg RU 486 daily, respectively.

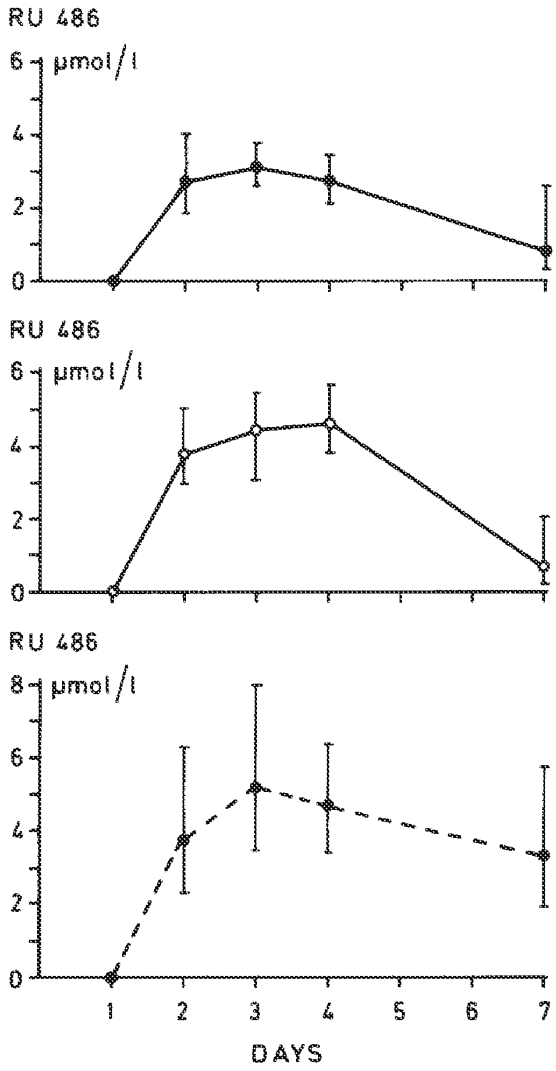

Fig 1. Geometric mean levels and 95 % confidence limits of RU 486 following oral administration to early pregnant patients. The treatment period was four days. Upper curve 50 mg, middle curve 100 mg and lower curve 200 mg daily.

Table I. Geometric means (and ranges) of areas under the curves (in $\mu mol.l^{-1}.d$) following the treatment of early pregnant women with three different doses of RU 486. The areas were calculated for the period between day two and four of drug administration. The significance of differences was assessed by a one-way analysis of variance and appropriate contrasts.

Daily dose (mg)	50	100	200
n	8	11	6
Geometric mean	5.9	8.7	9.7
Range	4.4-9.4	5.1-13.0	5.7-16.0

Significance of differences:

Group 50 mg vs. 100 mg: $p < 0.05$
50 mg vs. 200 mg: $p < 0.05$
100 mg vs. 200 mg: not significant at the 95 % confidence level

Table II. Geometric means (and ranges) of areas under elimination curves (in $\mu mol.l^{-1}.h$) following a single oral dose of 25 or 50 mg of RU 486 in early pregnant and non-pregnant women (n=5 each). The areas were calculated for the period between 2 and 12 hours after administration. The significance of the differences was assessed by the Student's t-test (n.s. = not significant at the 95 % confidence level).

Dose (mg)	Pregnant		Non-pregnant
25	15.6 (10.3-20.3)	n.s.	18.1 (11.5-25.0)
	$p < 0.001$		n.s.
50	28.7 (23.0-41.5)	n.s.	22.8 (16.4-37.8)

In the 12-hour period between the second and the third RU 486 doses in two of the eight patients treated with 25 mg RU 486 twice daily for four days, peak values of 3.4 and 4.7 µmol/l, respectively, were found two hours after tablet intake (Fig. 2).

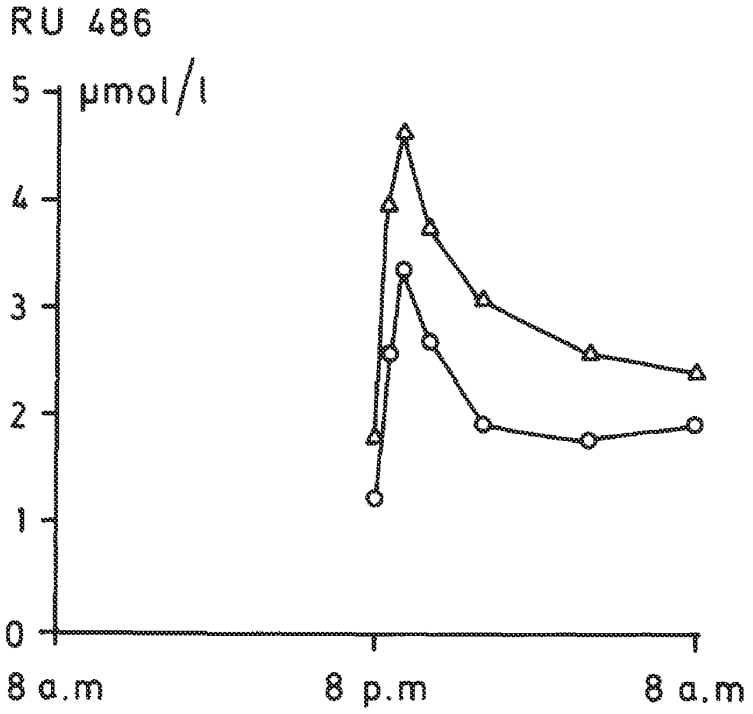

Fig. 2 Plasma levels of RU 486 between the second and third dose of 25 mg RU 486. The patients received the compound at 8 a.m. and 8 p.m. daily.

Following the administration of a single dose of 25 or 50 mg RU 486, a peak value of approximately 3.5 to 4.0 µmol/l was reached one to two hours after tablet intake in both pregnant and non-pregnant women (Figs. 3 and 4). The half-lives of elimination after a single dose of 25 mg RU 486 were 19.7 and 19.0 hours for pregnant and non-pregnant women, respectively. For 50 mg RU 486 the corresponding values were 17.3 and 22.7 hours. The differences observed between pregnant and non-pregnant women were not statistically significant.

The areas under the elimination curves between two and twelve hours following single doses of RU 486 were also calculated (Table II). The higher dose caused an increase in the area in both the pregnant and non-pregnant women, but the increase was significant only in the pregnant women.

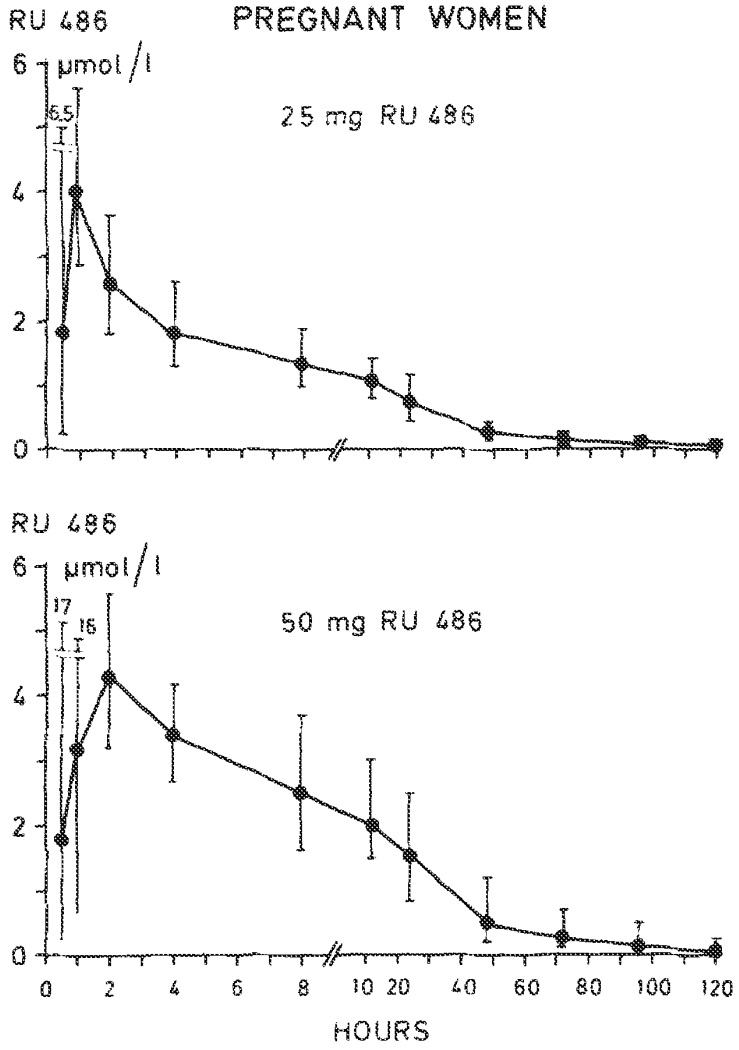

Fig. 3. Geometric means and 95 % confidence limits of RU 486 following a single dose of 25 mg or 50 mg to early pregnant women.

DISCUSSION

The aim of the study was to determine the plasma levels of RU 486 following the oral administration of the compound. The subjects participating in the study were either non-pregnant or early pregnant women. The non-pregnant volunteers received RU 486 orally during the secretory phase of the cycle (between cycle days 20 to 22); the early pregnant patients in the 6th to 8th week of pregnancy (duration of amenorrhoea up to 56 days).

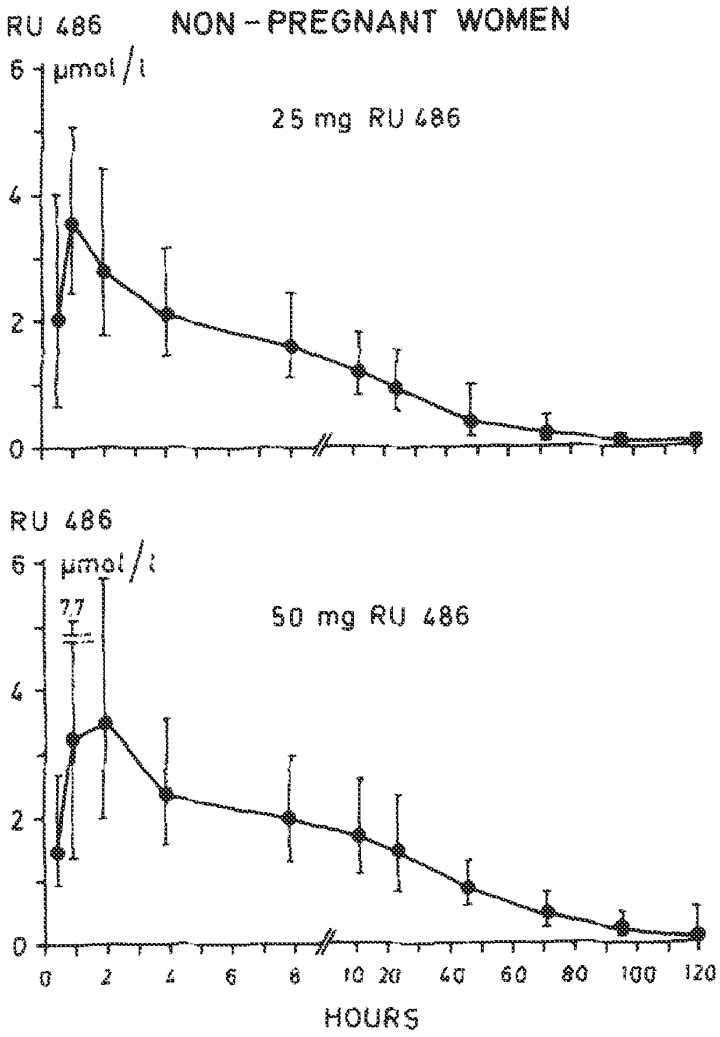

Fig. 4. Geometric means and 95 % confidence limits of RU 486 following a single dose of 25 mg or 50 mg to non-pregnant women.

The plasma concentration of RU 486 was determined by radioimmunoassay, the principles of which were described earlier by Salmon & Mouren (14). In order to increase its specificity, chromatography of plasma extracts was performed on Sephadex LH 20 prior to the radioimmunoassay proper. The specificity of the radioimmunoassay is of special importance, since it was shown by Salmon & Mouren (14) and confirmed in the present paper that two major metabolites of RU 486, its monodemethyl and didemethyl derivatives (8), exhibit a high degree of cross-reaction with the antibody available.

It was confirmed in the specificity studies mentioned in this investigation that the major compound assayed was identical with RU 486. The presence of this compound in the chromatographic fractions used for our assays was also confirmed by high performance liquid chromatograhy (15). At the same time, the presence of small amounts of the two major metabolites of RU 486 could not be excluded by the tests described in the present study. Investigations are being made to further improve the specificity of the radioimmunoassay.

A complete separation of the metabolites from the parent compound will make it possible to measure their concentrations and to establish a complete pharmacokinetic pattern for RU 486. This may be of particular interest in view of the observation that the main metabolites retain part of the biological activities of the parent molecule (8).

Following the oral administration of single doses of 25 and 50 mg RU 486 to non-pregnant and early pregnant women, peak plasma concentrations between 3.5 and 4.0 µmol/l were found after one to two hours. The half-lives were also the same in the two patient groups, about 20 hours. These results are similar to those reported by Deraedt et al. (8) in male volunteers receiving 100 mg RU 486 orally.

In early pregnant women the areas under the elimination curves were significantly higher for 50 mg than for 25 mg RU 486 following single doses of RU 486. The difference was less marked and not statistically significant in the non-pregnant subjects. The discrepancy may be due to chance as the number of subjects was small, but it may also reflect variations in the degree of absorption. In pregnant women with a reduced gastro-intestinal motility, the substance may be absorbed more completely than in non-pregnant women.

Following oral administration of a total daily dose of 50, 100 or 200 mg RU 486 for four days to early pregnant patients, maximum plasma levels of 2.9, 4.5 and 5.4 µmol/l, respectively, were found. The plasma levels were significantly higher following 100 mg RU 486 than following 50 mg RU 486. The differences in plasma levels following 100 and 200 mg RU 486 were less marked and not statistically significant. The results may indicate that the degree of absorption of the compound decreases with higher doses, even in pregnant women.

It has been reported that RU 486 is bound in human plasma to a hitherto unidentified protein (16). This finding suggests that a larger portion of RU 486 should be present in blood in a bound form and a smaller portion in an unbound (free) form. It should be noticed that, in the present study, the "total" circulating RU 486 was measured, i.e. the ether-extractable sum of the protein bound and unbound (free) portions.

It is frequently assumed that only the free fraction can interact with the receptor molecules and thus produce biological effects. An increase in the dose should result in an increase in the amount of both the "total" and the free RU 486 and, consequently, in a more pronounced effect.

As seen in the present study, the "total" and, consequently, the free levels of RU 486 did not increase proportionally to the dose. In the clinical dose-finding studies in early pregnant women the efficacy of the treatment was not dose-related within the dose range studied (3,4). There may be various explanations for this: 1) the degree of absorption is lower after higher doses, 2) the concentration of free RU 486 was insufficient to saturate the receptor even with the highest dose employed, or 3) the higher doses of RU 486 have agonistic effect. It is also possible that the saturation of the progesterone receptor in the uterus is not sufficient to induce an adequate endogenous release of $PGF_{2\alpha}$ that causes effective uterine contractions and complete expulsion of the conceptus (6).

It may be concluded from the present study that following oral administration in both non-pregnant and early pregnant women, no accumulation of the compound in plasma was seen with a dose up to 200 mg RU 486 daily for four days. Other studies are required to determine the plasma profiles of the main, partially bioactive metabolites of RU 486 and to assess the influence of RU 486 binding to plasma proteins on the efficacy of the drug for termination of early pregnancy and menstrual regulation.

ACKNOWLEDGEMENTS

The present study was supported by the WHO Special Programme of Research in Human Reproduction, Geneva, Switzerland. The compound RU 486 was kindly supplied by the Roussel Uclaf Co., Romainville, France. We are indebted to Dr. Pekka Lähtenmääki of the Department of Medical Chemistry, University of Helsinki, Finland, for performing an HPLC analysis of a pooled chromatographic fraction prepared by us from the plasma of patients treated with 100 and 200 mg RU 486. Blood samples from patients treated with 100 and 200 mg RU 486 were kindly supplied by Dr. L. Kovacs of the Department of Obstetrics and Gynaecology, University Medical School, Szeged, Hungary. The assistance of Dr. Zoe Walsh who made linguistic corrections is gratefully acknowledged. We are also indebted to Drs. Paul F.A. Van Look and A. Ulmann who had many valuable suggestions during the preparation of the manuscript.

REFERENCES

1. Baulieu, E.E. RU 486: An antiprogestin steroid with contragestive activity in women. In: The Antiprogestin Steroid RU 486 and Human Fertility Control (Baulieu, E.E. and Segal, S.J., Editors). Plenum Press, New York, 1985, p. 1-25

2. Herrmann, W., Wyss, R., Riondel, A., Philibert, D., Teutsch, G., Sakiz, E. and Baulieu, E.E. Effet d'un stéroide antiprogesterone chez la femme: interruption du cycle menstruel et de la grossesse au début. C R Acad Sci 294:933-938 (1982)

3. Kovacs, L., Sas, M., Resch, B.A., Ugocsai, G., Swahn, M.L. Bygdeman, M. and Rowe, P.J. Termination of very early pregnancy by RU 486 - An antiprogestational compound. Contraception 29:399-410 (1984)

4. Sitruk-Ware, R., Billaud, L., Mowszowicz, I., Yaneva, H., Mauvais-Jarvis, P., Bardin, C.W. and Spitz, I.M. The use of RU 486 as an abortifacient in early pregnancy. In: The Antiprogestin Steroid RU 486 and Human Fertility Control (Baulieu, E.E. and Segal, S.J., Editors). Plenum Press, New York, 1985, p. 243-248

5. Birgerson, L., Odlind, V. and Johansson, E. Clinical effects of RU 486 administered for seven days in early pregnancy. In: The Antiprogestin Steroid RU 486 and Human Fertility Control (Baulieu, E.E. and Segal, S.J., Editors). Plenum Press, New York, 1985, p. 235-241

6. Swahn, M.L., Cekan, S.Z., Wang, G., Lundström, V. and Bygdeman, M. Pharmacokinetic and clinical studies of RU 486 for fertility regulation. In: The Antiprogestin Steroid RU 486 and Human Fertility Control (Baulieu, E.E. and Segal, S.J., Editors). Plenum Press, New York, 1985, p. 249-258

7. Bygdeman, M. and Swahn, M.L. Progesterone receptor blockage. Effect on uterine contractility and early pregnancy. Contraception 32:45-51 (1985)

8. Deraedt, R., Bonnat, C., Busigny, M., Chatelet, P., Cousty, C., Mouren, M., Philibert, D., Pottier, J. and Salmon, J. Pharmacokinetics of RU 486. In: The Antiprogestin Steroid RU 486 and Human Fertility Control (Baulieu, E.E. and Segal, S.J., Editors). Plenum Press, New York, 1985, p. 103-122

9. Brenner, P.F., Guerrero, R., Cekan, S.Z. and Diczfalusy, E. Radioimmunoassay method for six steroids in human plasma. Steroids 22:775-794 (1973)

10. Cekan, S.Z. Correction for variation in amounts of labeled ligand in radioimmunoassays with chromatography. Clin Chem 28:1248-1249 (1982)

11. Cekan, S.Z. and Brodin, U. A simple statistical test of parallelism in immunoassays. Anal Letters 13(B5):371-379 (1980)

12. Cekan, S.Z. and de Gomez, M.S. A method to assess radiochemical purity of compounds measured by radioimmunoassay. Anal Letters 12(B6):589-602 (1979)

13. Gaddum, J.H. Lognormal distributions. Nature 156:463-466 (1945)

14. Salmon, J. and Mouren, M. Radioimmunoassay of RU 486. In:The Antiprogestin Steroid RU 486 and Human Fertility Control (Baulieu, E.E. and Segal, S.J., Editors). Plenum Press, New York, 1985, p. 99-101

15. Heikinheimo, O., Tevilin, M. and Lähteenmääki, P. High performance liquid chromatography in the assay of RU 486 and its metabolites. Acta Endocrinol 109: Suppl 270, 154 (1985)

16. Moguilewsky, M. and Philibert, D. Biochemical profile of RU 486. In: The Antiprogestin Steroid RU 486 and Human Fertility Control (Baulieu, E.E. and Segal, S.J.). Plenum Press, New York, 1985, p. 87-97

Electronic Patent Application Fee Transmittal

Application Number:	12199114
Filing Date:	27-Aug-2008
Title of Invention:	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Filer:	Alexander Reed Trimble/Shemekia Brown
Attorney Docket Number:	85178-756824(004110US)

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	2253	1	635	635

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	2801	1	465	465
		Total in USD ($)		**1100**

Electronic Acknowledgement Receipt	
EFS ID:	13852755
Application Number:	12199114
International Application Number:	
Confirmation Number:	5376
Title of Invention:	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	20350
Filer:	Alexander Reed Trimble/Shemekia Brown
Filer Authorized By:	Alexander Reed Trimble
Attorney Docket Number:	85178-756824(004110US)
Receipt Date:	27-SEP-2012
Filing Date:	27-AUG-2008
Time Stamp:	13:34:00
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Credit Card
Payment was successfully received in RAM	$1100
RAM confirmation Number	13492
Deposit Account	201430
Authorized User	TRIMBLE, ALEXANDER
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

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Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	85178-756824_RCE.pdf	187051 971b9aa2fb51220576ed78075c9b48953a7f6243	no	1
Warnings:					
This is not a USPTO supplied RCE SB30 form.					
Information:					
2	Extension of Time	85178-756824_EXT.pdf	157829 aa7eba5c2d2a3164e996584836feaa7615017b5d	no	1
Warnings:					
Information:					
3		85178-756824_AMD1.pdf	7229608 ec8176484df8f41b3b8c4304747d7bb6a3140b13	yes	66

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment After Final	1	1
Claims	2	3
Applicant Arguments/Remarks Made in an Amendment	4	66

Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	32958 9319a02990833c802330d2eb200436e129f79049	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	7607446		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 12/199,114	Filing Date 08/27/2008	☐ To be Mailed

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
AMENDMENT	**09/27/2012**	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 8	Minus	** 20	= 0	X $30 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $125 =	0	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)					
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/HENRIETT K. DENDY/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/199,114	08/27/2008	Joseph K. Belanoff	85178-756824(004110US)	5376

20350 7590 04/04/2012

KILPATRICK TOWNSEND & STOCKTON LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
HUI, SAN MING R	
ART UNIT	**PAPER NUMBER**
1628	

NOTIFICATION DATE	DELIVERY MODE
04/04/2012	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Docket@kilpatricktownsend.com
ipefiling@kilpatricktownsend.com
jlhice@kilpatrick.foundationip.com

Office Action Summary	Application No.	Applicant(s)	
	12/199,114	BELANOFF, JOSEPH K.	
	Examiner	Art Unit	
	SAN-MING HUI	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2012*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-8* is/are pending in the application.

5a) Of the above claim(s) *8* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-7* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed 1/24/2012 has been entered. Claims 1-8 are pending. Claim 8 is withdrawn from further consideration as it is directed to non-elected subject matter.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Medical Encyclopedia of Medline (http:// http://www.nlm.nih.gov/medlineplus/ency/article/003430.htm, 10/2005) in view of US 6,964,953 ('953) and Sarkar, European Journal of Obstetrics and Gynecology and Reproductive Biology, 2002;101:113-120.

Medical Encyclopedia teaches Therapeutic drug levels are usually performed to look for the presence and the amount of specific drug in the blood. With most medications, a certain level of drug is needed in the blood stream to obtain the desired therapeutic effect. (see page one of the article).

Medical Encyclopedia does not expressly teach the optimization of mifepristone level in patients with Acute stress disorder.

'953 teaches glucocorticoid antagonist, such as mifepristone, as useful in

Treating Acute Stress Disorder (see claims 1, 5, and 15 for example). '953 teaches the dosage of the glucocorticoid receptor antagonists as 1 to 10 mg per kilogram (see claim 6). For an average adult who weighs 75kg, it is about 75 – 750mg. '953 teaches the course of therapy is 30 days (see claim 16).

Sarkar teaches the serum concentration of various dosages of mifepristone administered. For medium dose (100-200mg of mifepristone), the serum concentration can reach to 4.5 and 5.4 µmol/l (1933.2 ng/ml to 2276.88ng/ml). For a higher dose (400-600mg), the serum concentration gets even higher. (see pages 114-115).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the serum level of mefipristone in patients suffering from Acute Stress Disorder.

One of ordinary skill in the art would have been motivated to optimize the serum level of mefipristone in patients suffering from Acute Stress Disorder. Adjusting the therapeutic serum levels to obtain a therapeutic effect is well-known in the art. Since both the serum concentration and the dosage of mifepristone useful in treating the Acute Stress Disorder are both well-known. Adjusting the serum level of mifepristone would be seen as equivalent to adjusting the dosage of mifepristone to effectively treat Acute Stress Disorder would be reasonably expected to be successful.

Response to Arguments

Applicant's arguments filed 1/24/2012 averring the serum level as unpredictable and being displaced a nonlinear pharmacokinetics have been fully considered but they are not persuasive. The examiner notes that it is well-known that mifepristone and the

serum level are positively correlated, i.e., increasing the dose will increase the serum level. Therefore, one of ordinary skill in the art would readily see that adjusting the serum level is essentially the same as adjusting the dosage of mifepristone. Since the dosages of mifepristone for treating various disorders are known and the common dosage are corresponding to the serum level of more than 1300ng/ml, regardless of the pharmacokinetics of mifepristone, one of ordinary skill in the art would have been motivated to employ the herein claimed dosages of mifepristone, and thereby achieve the serum levels of mifepristone to be more than 1300ng/ml.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAN-MING HUI whose telephone number is (571)272-0626. The examiner can normally be reached on Mon - Fri from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

San-ming Hui
Primary Examiner
Art Unit 1628

/San-ming Hui/
Primary Examiner, Art Unit 1628

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12199114	BELANOFF, JOSEPH K.
	Examiner	**Art Unit**
	SAN-MING HUI	1628

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/28/2011	07/28/2011	03/27/2012						
	1	÷	✓	✓						
	2	÷	✓	✓						
	3	÷	✓	✓						
	4	÷	✓	✓						
	5	÷	✓	✓						
	6	÷	✓	✓						
	7	÷	✓	✓						
	8	÷	N	N						

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	4289	mifepristone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/03/27 17:02
L2	13442	post adj traumatic	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/03/27 17:02
L3	450	L1 and L2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/03/27 17:02
L4	2	L1 same L2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/03/27 17:02
L5	448	L1 and L2 and dosage	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/03/27 17:02
L6	7230	post adj traumatic adj stress	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/03/27 17:02
L7	94	L1 and L6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/03/27 17:02
L8	1517	514/178.ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2012/03/27 17:02

EAST Search History (Interference)

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12199114	BELANOFF, JOSEPH K.
	Examiner	Art Unit
	SAN-MING HUI	1628

SEARCHED			
Class	Subclass	Date	Examiner
514	182, 178	7/27/11	SH
514	178, 182	3/27/12	SH

SEARCH NOTES		
Search Notes	Date	Examiner
EAST adn inventor search in PALM	7/27/11	SH
EAST and inventor search in PALM	3/27/12	SH

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

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KILPATRICK TOWNSEND & STOCKTON LLP

By: _____

PATENT
Attorney Docket No.: 85178-756824
Family ID No.: 004110US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 5376
Joseph K. Belanoff	Examiner: San Ming R Hui
Application No.: 12/199,114	Technology Center/Art Unit: 1628
Filed: August 27, 2008	
For: OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS	
Customer No.: 20350	AMENDMENT B

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Office Action mailed August 3, 2011, please enter the following amendments and remarks. A petition for a **three-month extension of time** is filed concurrently herewith.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 4 of this paper.

Amendments to the Claims:

The following is a complete list of claims indicating the changes incorporated by the present amendment and replacing all prior versions of the claims. Any claims canceled herein and all deletions made in claims that are not canceled herein are done so without prejudice to being re-instituted at a later date in this or a related application.

Listing of Claims:

1. (Original) A method for optimizing levels of mifepristone in a patient suffering from a mental disorder amenable to treatment by mifepristone, the method comprising:

treating the patient with seven or more daily doses of mifepristone over a period of seven or more days;

testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/mL; and

adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

2. (Original) The method of claim 1, wherein the mental disorder is a member selected from the group consisting of a stress disorder, delirium, mild cognitive impairment (MCI), dementia, psychosis and psychotic major depression.

3. (Original) The method of claim 2, wherein the stress disorder is a member selected from the group consisting of Acute Stress Disorder, Post-Traumatic Stress Disorder and Brief Psychotic Disorder with Marked Stressor(s).

4. (Original) The method of claim 1, wherein each of the seven or more daily doses of mifepristone are administered orally.

5. (Original) The method of claim 1, wherein the patient is treated with 28 or more daily doses over a period of 28 or more days.

6. (Original) The method of claim 1, wherein the testing is performed by a plasma sampling collection device suitable for detecting mifepristone serum levels.

7. (Original) The method of claim 1, wherein the adjusting step comprises increasing the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

8. (Withdrawn) A kit for treating a mental disorder amenable to treatment by mifepristone, the kit comprising:

seven daily doses of mifepristone; and

a plasma sampling collection device suitable for detecting mifepristone serum levels.

REMARKS

Upon entry of the present amendment, claims 1-8 are pending in the above-referenced patent application and are currently under examination. Claim 8 is withdrawn. Reconsideration of the application is respectfully requested.

I. OBVIOUSNESS OVER MEDICAL ENCYCLOPEDIA OF MEDLINE, THE '953 PATENT AND SARKAR

Claims 1-7 are rejected under 35 USC § 103(a) as allegedly being obvious over Medical Encyclopedia of Medline (http://www.nlm.nih.gov/medlineplus/ency/article/003430.htm, October 2005, "Medical Encyclopedia") in view of U.S. Patent No. 6,964,953 and Sarkar, European Journal of Obstetrics and Gynecology and Reproductive Biology 2002, 101, 113-120. Applicants respectfully traverse the rejection in view of the comments below.

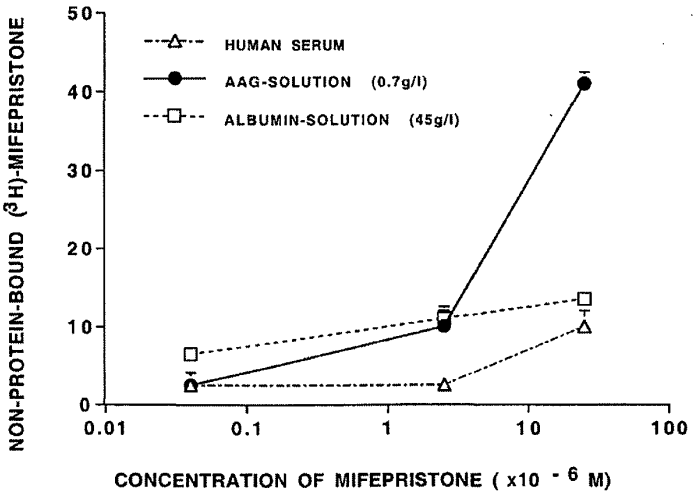
A claim is considered obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains" (35 USC § 103(a)). The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to the determination of obviousness as laid down in *Graham*. The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. One of the rationales addressed by the court in KSR supports a finding of obviousness when the prior art reference (or combination of references) (1) teaches or suggests the claim elements; (2) provides some suggestion or motivation to combine the references; and (3) provides a reasonable expectation of success (MPEP § 2143). As discussed in detail below, none of the cited references satisfies all three requirements under MPEP § 2143.

The Examiner alleges it would have been obvious to optimize the serum level of mifepristone in patients suffering from acute stress disorder because Medical Encyclopedia describes that a certain level of a drug is needed in the blood stream to obtain the desired therapeutic effect, the '953 patent describes administration of mifepristone to treat acute stress disorder, and Sarkar

describes the serum concentration of various dosages of mifepristone administered. Applicants disagree because (1) mifepristone exhibits nonlinear serum pharmacokinetics, and (2) in view of mifepristone's nonlinear serum pharmacokinetics, the combination of references fails to describe the surprising discovery of a mifepristone serum level of 1300 ng/mL as the dividing line between a mifepristone serum level with an effectiveness greater than the placebo, and a mifepristone serum level providing an effectiveness comparable to the placebo.

Mifepristone Exhibits Nonlinear Serum Pharmacokinetics

At the time the present invention was filed, it was known in the art that mifepristone exhibits nonlinear serum pharmacokinetics in humans (see *Contraception* 2003, 68, 421-426, Exhibit A, Abstract). Mifepristone serum kinetics are regulated by the serum transport protein α 1-acid glycoprotein (AAG). The binding of mifepristone to AAG limits the tissue availability of mifepristone because as the concentration of mifepristone is increased, the AAG first becomes saturated with mifepristone. At some critical point, the AAG is saturated and additional mifepristone is not bound to AAG. See Figure 4 of Exhibit A shown below, for example, showing the percentage of serum non-protein-bound mifepristone (dark line with circles) and the rapid increase in non-protein-bound mifepristone above the saturation concentration:



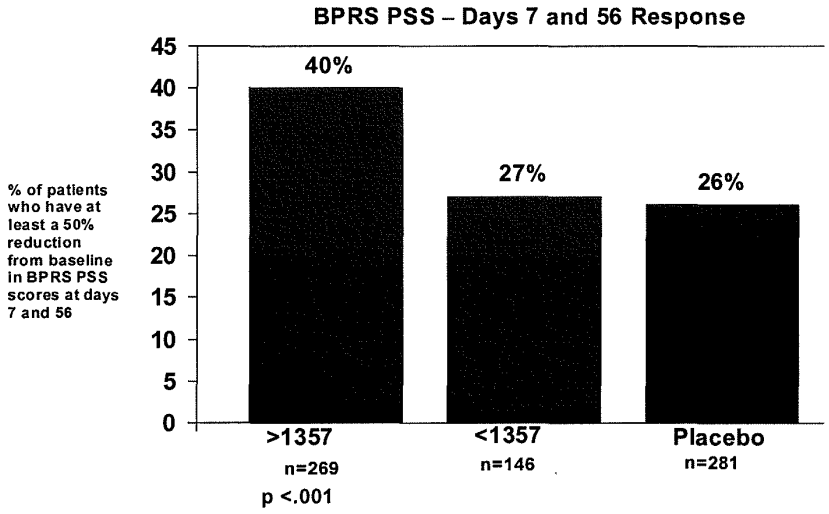
Thus, as Exhibit A describes, mifepristone exhibits nonlinear serum pharmacokinetics at doses greater than 200 mg (see Abstract of Exhibit A). Because the doses of the present invention are greater than 200 mg and the mifepristone serum pharmacokinetics are nonlinear, it is surprising

that mifepristone serum levels above 1300 ng/mL provide an effective treatment for a variety of mental disorders, while mifepristone serum levels below 1300 ng/mL are no more effective than the placebo.

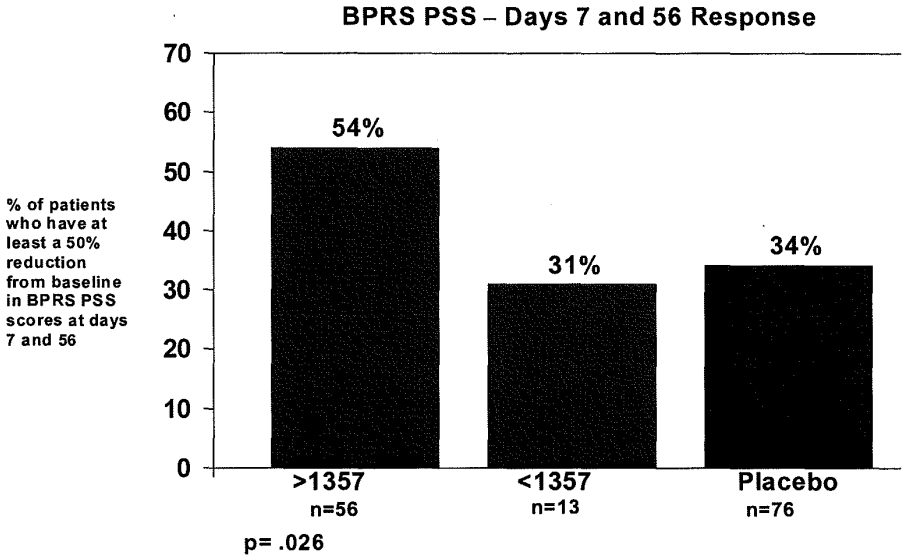
It is Unpredictable what Mifepristone Serum Concentration Would Provide an Effective Treatment for a Variety of Mental Disorders

Given the nonlinear serum pharmacokinetics for mifepristone known at the time the present application was filed, it is unpredictable what mifepristone serum concentration would provide an effective treatment for mental disorders. In view of the nonlinear behavior of mifepristone serum pharmacokinetics, the present invention surprisingly discovered that maintaining mifepristone serum levels above 1300 ng/mL provide an effective treatment for a variety of mental disorders, while mifepristone serum levels below 1300 ng/mL are no more effective than the placebo. Thus, maintaining blood serum levels of mifepristone above 1300 ng/mL in a patient suffering from a mental disorder amenable to treatment by mifepristone, the patient suffering from the mental disorder receives a mifepristone dose producing a efficacious mifepristone serum level.

As shown in Figure 2 of the application, reproduced below for the Examiner's convenience, for all dosage levels, 40% of the patients having mifepristone serum levels greater than 1357 ng/mL showed at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56. For patients having mifepristone serum levels less than 1357 ng/mL, only 27% of patients showed at least a 50% reduction from baseline in BPRS PSS scores, nearly identical to the 26% response rate of patients receiving the placebo.



Similarly, for patients receiving a 1200 mg dose of mifepristone, 54% of the patients showed at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56, versus 31% of patients having mifepristone serum levels of less than 1357 ng/mL. The placebo group showed only 34% of patients having at least a 50% reduction from baseline in BPRS PSS scores, comparable to those patients with a mifepristone serum level less than 1357 ng/mL. See Figure 5 of the application, reproduced below for the Examiner's convenience.



The combination of Medical Encyclopedia, the '953 patent and Sarkar only describe treatment of acute stress disorder with mifepristone and dosages of mifepristone that afford certain serum levels of mifepristone. The combination of references does not, however, describe the surprising discovery of a mifepristone serum level of 1300 ng/mL as the dividing line between a mifepristone serum level with an effectiveness greater than the placebo, and a mifepristone serum level providing an effectiveness comparable to the placebo.

Moreover, in relying on the combination of Medical Encyclopedia, the '953 patent and Sarkar, the Examiner is using the pending claims as a road-map, engaging in impermissible hindsight reconstruction. None of the cited references provides any motivation to select 1300 ng/mL as the dividing line between a mifepristone serum level with an effectiveness greater than the placebo, and a mifepristone serum level providing an effectiveness comparable to the placebo, in a patient suffering from a mental disorder, especially in view of the unpredictability provided by mifepristone's nonlinear serum pharmacokinetics.

Thus, Applicants respectfully submit the present invention is not obvious over the combination of Medical Encyclopedia, the '953 patent and Sarkar. Accordingly, Applicants respectfully request that the Examiner withdraw this aspect of the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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Contraception

Contraception 68 (2003) 421–426
Original research article

The pharmacokinetics of mifepristone in humans reveal insights into differential mechanisms of antiprogestin action

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Abstract

The pharmacokinetics of mifepristone is characterized by rapid absorption, a long half-life of 25–30 h, and high micromolar serum concentrations following ingestion of doses of ≥100 mg of the drug. The serum transport protein—α 1-acid glycoprotein (AAG)—regulates the serum kinetics of mifepristone in man. Binding to AAG limits the tissue availability of mifepristone, explaining its low volume of distribution and low metabolic clearance rate of 0.55 L/kg per day. In addition, the similar serum levels of mifepristone following ingestion of single doses exceeding 100 mg can be explained by saturation of the binding capacity of serum AAG. Mifepristone is extensively metabolized by demethylation and hydroxylation, the initial metabolic steps being catalyzed by the cytochrome P-450 enzyme CYP3A4. The three most proximal metabolites, namely, monodemethylated, didemethylated and hydroxylated metabolites of mifepristone, all retain considerable affinity toward human progesterone and glucocorticoid receptors. Also, the serum levels of these three metabolites are in ranges similar to those of the parent mifepristone. Thus, the combined pool of mifepristone—plus its metabolites—seems to be responsible for the biological actions of mifepristone. Recent clinical studies on pregnancy termination and emergency contraception have focused on optimization of the dose of mifepristone. In these studies it has become apparent that the doses efficient for pregnancy termination differ from those needed in emergency contraception—mifepristone is effective in emergency contraception at a dose of 10 mg, which results in linear pharmacokinetics. However, the ≥200 mg doses of mifepristone needed for optimal abortifacient effects of mifepristone result in saturation of serum AAG and thus nonlinear pharmacokinetics. In view of the pharmacokinetic data, it may be speculated that dosing of mifepristone for pregnancy termination and for emergency contraception could be reduced to approximately 100 mg and 2–5 mg, respectively. It remains to be seen whether the newly synthesized, more selective antiprogestins will prove more efficacious in the clinical arena.

Keywords: Metabolism; High performance-liquid chromatography; Radioimmunoassay; Emergency contraception; Medical abortion; Dose-response relationships

1. Introduction

Recent clinical studies on the use of mifepristone in medical termination of pregnancy and in emergency contraception have focused on optimization of mifepristone regimens. In termination of first-trimester pregnancy, a 200-mg dose of mifepristone, in combination with vaginally administered prostaglandin, is equally effective as a higher dose (600 mg) of mifepristone [1–3]. In these studies, the percentages of complete abortions have ranged 88–96% [1–3]. The results of preliminary studies have suggested that even a 100-mg dose of mifepristone might be equally effective [4]. However, in a randomized multicenter study arranged by the World Health Organization (WHO), 50 mg of mifepristone combined with vaginally administered prostaglandin was 1.6 times more likely to fail in termination of first trimester pregnancy when compared with a regimen containing 200 mg of mifepristone [5].

In emergency contraception, considerably lower doses of mifepristone are needed. In a randomized study arranged by the WHO, a 10-mg dose of mifepristone was equally effective as 50 mg or 600 mg doses, each preventing 84–86% of pregnancies [6]. In fact, the lowest effective dose of mifepristone in emergency contraception has not been characterized. The more than 10-fold difference in the doses of

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doi:10.1016/S0010-7824(03)00077-5

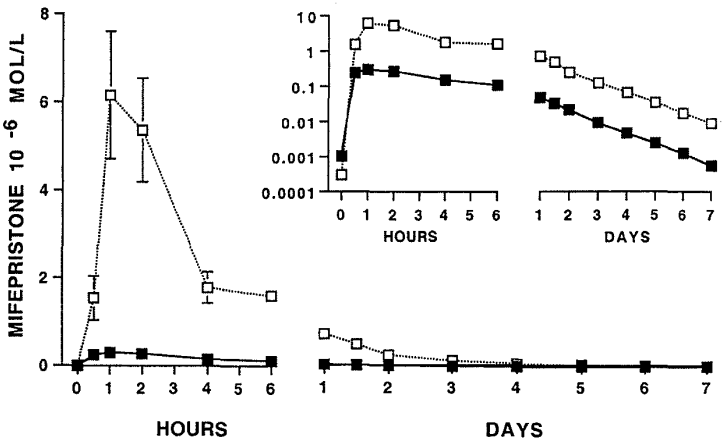

Fig. 1. Serum levels (mean ± SE) of mifepristone following administration of 2 mg (■) and 25 mg (□) to five female volunteers. The data are depicted on both linear (lower) and semilogarithmic (upper) scales. Redrawn from Kekkonen et al. [17].

mifepristone required for optimal clinical effects in emergency contraception and in pregnancy termination suggests that different biological mechanisms mediate these clinical effects of mifepristone.

The antiglucocorticoid effects of mifepristone are in sharp contrast with its antiprogestagenic effects in pregnancy termination or in emergency contraception. Early studies by Bertagna et al. [7] and Gaillard et al. [8] showed that activation of the hypothalamic-pituitary-adrenal (HPA) axis in response to mifepristone is clearly a dose-dependent phenomenon, and significant increases in the circulating concentrations of adrenocorticotropic hormone and cortisol are seen following administration of ≥200 mg of the drug. Moreover, more pronounced activation of the HPA axis is seen as the dose of mifepristone is increased [7,8].

The differences in the clinical effects of mifepristone are also related to its pharmacokinetics—the high efficacy of mifepristone in emergency contraception is seen in the dose range that results in linear kinetics of the drug in serum. However, the doses required for termination of pregnancy or activation of the HPA axis result in saturation level, non linear kinetics of mifepristone. In this article we review the pharmacokinetics of mifepristone in humans, with special emphasis on the relationships between its pharmacokinetics and clinical efficacy.

2. Pharmacokinetics of mifepristone

2.1. Assay systems for mifepristone

Various assay methods such as radioimmunoassay (RIA) [9], radioreceptorassay (RRA) [10,11] and assays based on high-performance liquid chromatography (HPLC) have been used to measure serum mifepristone levels [12–14]. It soon became apparent that mifepristone is extensively metabolized, and due to the cross-reacting metabolites, direct RIA and RRA failed to distinguish the parent mifepristone from its metabolites [15]. However, the micromolar serum levels of mifepristone—seen following ingestion of doses currently used in clinical practice—allowed us to develop methods based on HPLC for detailed analysis of the pharmacokinetics and metabolism of mifepristone [16]. Column chromatography can be used to separate the metabolites from the parent mifepristone, which can then be measured specifically either by RIA or HPLC [13].

2.2. Absorption and distribution of mifepristone

Following oral ingestion, mifepristone is rapidly absorbed and the time to peak serum levels (t_{max}) is approximately 1–2 h [11–13]. Also, when analyzed by specific RIA or HPLC, the t_{max} values have been similar within the dose range of 200–600 mg of mifepristone [16,17]. Peak concentrations (C_{max}) rise according to the dose of mifepristone within the dose range of 2–25 mg [17]. However, at higher doses of 100–800 mg, C_{max} values do not differ significantly, most likely as a result of saturation of the serum binding capacity for mifepristone [16]. The bioavailability has been estimated to be 40% following oral intake of 100 mg of mifepristone [18]. Unfortunately, attempts to bypass the first-pass metabolism by means of vaginal administration resulted in low serum levels of mifepristone [19].

2.3. Serum levels of mifepristone

The pharmacokinetics of mifepristone have been studied following single oral doses ranging 2–800 mg. Following ingestion of 2 and 25 mg doses, the levels of mifepristone, as well as the areas under the concentration curves (AUCs), rise according to the dose (Fig. 1) [17]. However, following

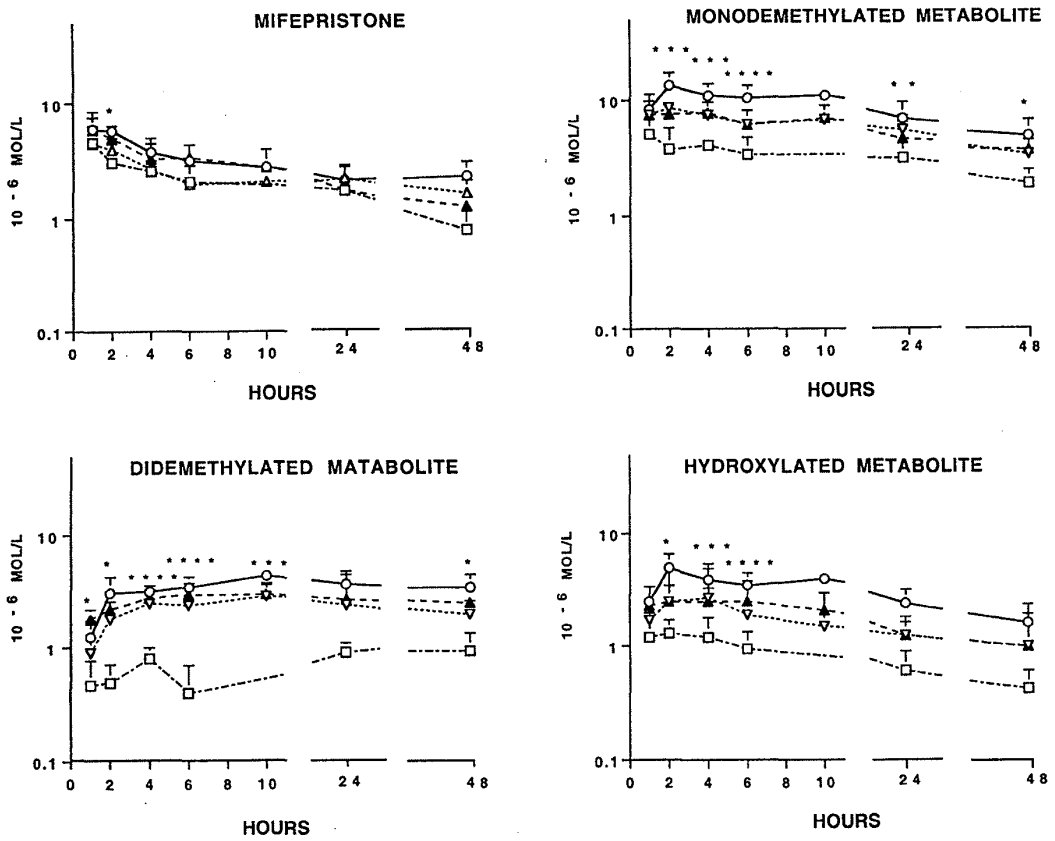

Fig. 2. Serum levels (mean ± SE) of mifepristone and its monodemethylated, hydroxylated and didemethylated metabolites following administration of single doses of 100, 400, 600 and 800 mg to female volunteers. Statistically significant differences in the serum levels between the groups ingesting 100 and 800 mg are indicated by asterisks (*$p < 0.05$; **$p < 0.01$; ***$p < 0.005$; ****$p < 0.001$). Redrawn from Heikinheimo et al. [16].

intake of single doses of 100, 400, 600 and 800 mg, the concentrations of mifepristone have all been observed to be at ~2.5 μmol/L at 24 h (Fig. 2) [16] despite the nearly 10-fold difference in the dose ingested.

When administered repeatedly, a similar phenomenon in the plateau levels is seen when the daily dose of mifepristone exceeds 100 mg [20]. Figure 3 shows the individual and mean levels of mifepristone in a group of six women given 50 mg twice a day for 7 days. The individual levels of mifepristone were similar among the subjects, and the individual half-lives of mifepristone varied from 26–48 h. The micromolar serum concentrations of mifepristone also persist during prolonged daily treatment with 200 mg for up to 20 months [21].

2.4. Serum binding characteristics of mifepristone

In human serum, 94–99% of mifepristone is protein bound [10,16]. Early studies by Moguilewsky and Philibert [22] indicated that human serum, unlike rat serum, contains a high-affinity binding protein for mifepristone, which was soon identified as α 1-acid glycoprotein (AAG). The highly significant correlations between serum levels of mifepristone and AAG suggested that AAG has a great impact on the pharmacokinetics of mifepristone in man [16,23]. Studies involving centrifugal ultrafiltration dialysis showed that a serum concentration of mifepristone of 2.5 μmol/L represents saturation of AAG binding capacity (Fig. 4) [16]. In addition, albumin appears to have a high-capacity role in the serum transport of mifepristone [16].

Thus, in humans, serum AAG appears to limit the tissue availability of mifepristone. However, mifepristone exceeding the binding capacity of AAG may be more susceptible to excretion or possibly diffusion into peripheral tissues [24]. In accordance with the low volume of distribution, tissue mifepristone levels have been observed to be in the same range or lower than serum levels following intake of 200 mg of mifepristone prior to hysterectomy [24].

2.5. Metabolism of mifepristone in humans

The elimination phase half-life of mifepristone ($t_{1/2}$) has been reported to vary between 24 and 48 h when analyzed

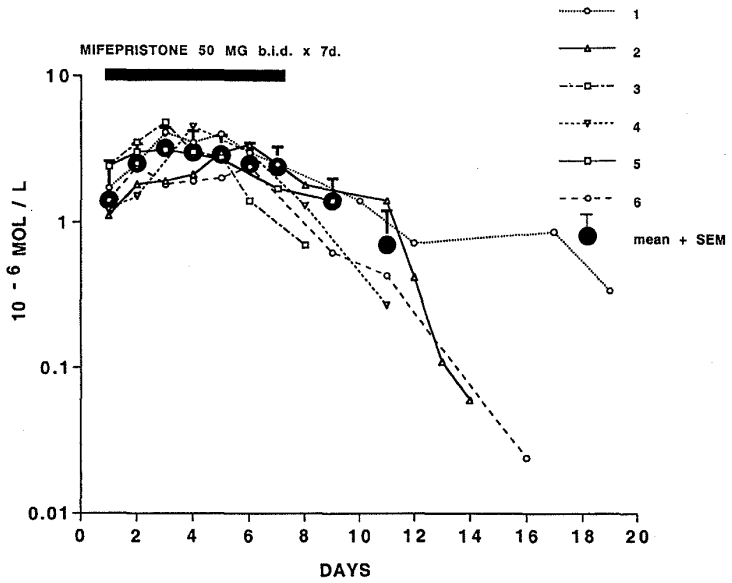

Fig. 3. Individual and mean (±SE) levels of mifepristone during intake of 50 mg twice a day for 7 days in six female volunteers. Redrawn from Heikinheimo [20].

by HPLC [14,20]. However, investigators employing either RIA or RRA have reported $t_{1/2}$ values between 54 and 90 h [11,25], this most likely a result of the presence of cross-reacting metabolites of mifepristone.

The metabolism of mifepristone is initiated by rapid demethylation and hydroxylation in humans, rats and monkeys [18]. The enzyme CYP3A4 has been shown to be the primary cytochrome P-450 enzyme responsible for the oxidative metabolism of mifepristone in human liver microsomes [26]. Following oral intake of 100 mg or more, constant serum levels of mifepristone, but increasing concentrations of the monodemethylated, didemethylated and hydroxylated metabolites of mifepristone are found, with serum levels of the monodemethylated metabolite exceeding those of the parent compound [16,27]. Following administration of mifepristone at doses over 400 mg, the concentrations of the didemethylated and hydroxylated metabolites also exceed those of the parent compound (Fig. 2) [16]. Peak levels of the monodemethylated and hydroxylated metabolites are reached by 2–4 h. The time course of the didemethylated metabolite is somewhat different, with peak levels being measured only after 10 h following ingestion of mifepristone.

The demethylated and hydroxylated metabolites are further metabolized and excreted into bile. In humans, only a very small fraction of mifepristone can be detected in urine [18].

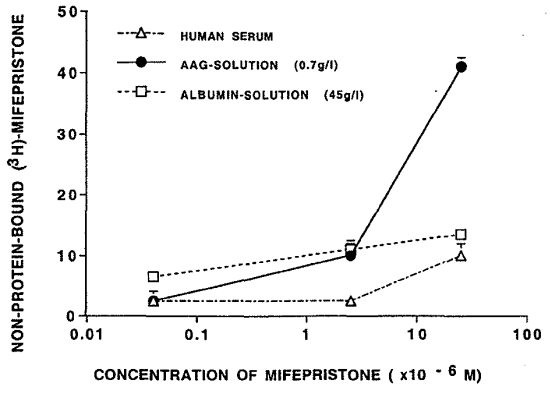

Fig. 4. Percentage of serum non-protein–bound mifepristone (mean ± SE) in human serum, in phosphate-buffered saline (PBS) containing human alpha 1-acid glycoprotein (AAG), and in PBS containing human albumin. Redrawn from Heikinheimo et al. [16].

3. Binding of mifepristone and its metabolites to hPR and hGR

Tables 1 and 2 summarize the relative binding affinities (RBAs) of mifepristone, the monodemethylated, hydroxylated and didemethylated metabolites, as well as those of reference steroids, to the human progesterone receptor (hPR) and glucocorticoid receptor (hGR) [15]. The relatively high receptor-binding affinities of mifepristone's metabolites in combination with the high serum levels of the metabolites suggest that some of the biological effects of mifepristone may be mediated via both the parent compound as well as the pool of metabolites.

The efficacy of mifepristone in pregnancy termination

Table 1
Relative binding affinities (RBAs) of mifepristone and its three metabolites to the human uterine progesterone receptor

Compound	RBA %
ORG-2058	374
Mifepristone	100
Progesterone	43
Monodemethylated metabolite	21
Hydroxylated metabolite	15
Didemethylated metabolite	9

cannot be improved by increasing the dose beyond 200 mg [1–3]. Thus, based on the similar serum concentrations of mifepristone, but increasing levels of the metabolites following intake of ≥100 mg of mifepristone (Fig. 2), it may be speculated that the lower affinities of the metabolites towards hPR (Table 1) imply minor importance of these metabolites in the abortifacient action of mifepristone.

In comparison with hPR, the RBAs of the monodemethylated, hydroxylated and didemethylated metabolites toward hGR (Table 2) are more pronounced. The antiglucocorticoid effects of mifepristone increase in a dose-dependent manner following ingestion of doses of ≥200 mg [7,8]. Thus, based on the similar serum levels of parent mifepristone but increasing levels of the metabolites, it may be speculated that the metabolites are important in the antiglucocorticoid actions of mifepristone.

4. Pharmacokinetics vs. clinical effects of mifepristone

Understanding the pharmacokinetics of mifepristone has aided the design of studies aimed at optimizing mifepristone regimens. In several randomized multicenter studies, it has become clear that a 200-mg dose, but not a 50-mg dose, of mifepristone in combination with prostaglandin is effective in pregnancy termination [1–3,5]. In fact, even a 100-mg dose of mifepristone might be acceptably effective [4]. In view of the saturation stage pharmacokinetics of mifepristone following intake of doses of 100 mg and more, the efficacy of the 100 mg dose is not surprising. Thus, for termination of pregnancy, the saturation stage serum kinetics of mifepristone appear important. It may be speculated that the abortifacient properties—decidual bleeding, increased uterine contractility and sensitivity to prostaglandins—require complete saturation of the uterine progesterone receptors.

Table 2
Relative binding affinities (RBAs) of mifepristone and its three metabolites to the human placental glucocorticoid receptor

Compound	RBA %
Mifepristone	100
Monodemethylated metabolite	61
Hydroxylated metabolite	48
Didemethylated metabolite	45
Dexamathasone	23
Cortisol	9

When women with complete and incomplete termination of pregnancy following administration of a single dose of 600 mg of mifepristone were compared, the serum levels of mifepristone and those of the three metabolites were indistinguishable [28]. It therefore appears that individual uterine sensitivity to progesterone withdrawal, and not differences in the pharmacokinetics of mifepristone, dictate the eventual clinical outcome of each subject.

In emergency contraception, mifepristone doses in the range of 10–600 mg behave similarly, inhibiting 84–85% of pregnancies [6]. Therefore, the mechanism by which mifepristone acts as an emergency contraceptive is clearly different from its ability to start a cascade resulting in termination of pregnancy. Continuous daily administration of 2 mg of mifepristone or more inhibits ovulation in women [29,30]; this inhibition occurs most likely via central mechanisms [29,30]. As inhibition or delay of ovulation also appears to be a major mechanism of action in emergency contraception [31], 10 mg of mifepristone, and thus linear range serum levels of the drug, are sufficient for the presumed ovulation inhibition. It may be speculated that an even lower dose than 10 mg of mifepristone might be effective in emergency contraception. As the endometrium appears to be very sensitive to the effects of mifepristone [32,33], possible actions on the endometrium might complement the efficacy of mifepristone in emergency contraception.

Mifepristone has several pharmacokinetic features that make it very useful in both termination of pregnancy and in emergency contraception. It is rapidly absorbed and the bioavailability of mifepristone is sufficient for clinical use. The long $t_{1/2}$ of mifepristone allows effective single-dose treatment, and thus controlled distribution for both clinical indications. It may be argued that identification of the minimal effective dose, which may be approximately 100 mg for pregnancy termination and 2–5 mg for emergency contraception, is important. It remains to be seen whether some of the newly synthesized antiprogestins with higher selectivity will be clinically superior to mifepristone.

Acknowledgments

Our studies have been carried out with financial support from The Population Council (New York City, NY, USA). Dr. Heikinheimo is a recipient of a Finnish Medical Foundation Clinical Fellowship grant.

References

[1] World Health Organization. Task force on post-ovulatory methods of fertility regulation. Termination of pregnancy with reduced doses of mifepristone. BMJ 1993;307:532–7.

[2] World Health Organization. Task force on post-ovulatory methods of fertility regulation. Comparison of two doses of mifepristone in combination with misoprostol for early medical abortion: a randomised trial. Br J Obstet Gynecol 2000;107:524–30.
[3] World Health Organization. Task force on post-ovulatory methods of fertility regulation. Medical abortion at 57 to 63 days' gestation with a lower dose of mifepristone and gemeprost. A randomized controlled trial. Acta Obstet Gynecol Scand 2001;80:447–51.
[4] Creinin M, Pymar H, Schwartz J. Mifepristone 100 mg abortion regimens. Obstet Gynecol 2001;98:434–9.
[5] World Health Organization. Task force on post-ovulatory methods of fertility regulation. Lowering the doses of mifepristone and gemeprost for early abortion: a randomised controlled trial. Br J Obstet Gynecol 2001;108:738–42.
[6] World Health Organization. Task force on post-ovulatory methods of fertility regulation. Comparison of three single doses of mifepristone as emergency contraception: a randomized trial. Lancet 1999;353: 697–702.
[7] Bertagna X, Bertagna C, Luton J-P, Husson J-M, Girard F. The new steroid analog RU 486 inhibits glucocorticoid action in man. J Clin Endocrinol Metab 1984;59:25–8.
[8] Gaillard R, Riondel A, Müller AF, Herrmann W, Baulieu E-E. RU 486: a steroid with antiglucocorticosteroid activity that only disinhibits the human pituitary-adrenal system at a specific time of day. Proc Natl Acad Sci USA 1984;81:3879–82.
[9] Salmon J, Mouren M. Radioimmunoassay of RU 486. In: Baulieu E-E, Segal S, editors. The antiprogestin steroid RU 486 and human fertility control. New York: Plenum Press, 1985. p. 99–101.
[10] Kawai S, Nieman L, Brandon D, Udelsman R, Loriaux L, Chrousos G. Pharmacokinetic properties of the antiglucocorticoid and antiprogesterone steroid RU 486 in man. J Pharmacol Exp Ther 1987;241: 401–6.
[11] Földesi I, Falkay G, Kovács L. Determination of RU486 (mifepristone) in blood by radioreceptorassay; a pharmacokinetic study. Contraception 1996;54:27–32.
[12] Swahn ML, Wang G, Aedo AR, Cekan S, Bygdeman M. Plasma levels of antiprogestin RU 486 following oral administration to nonpregnant and early pregnant women. Contraception 1986;34:469–81.
[13] Heikinheimo O, Tevilin M, Shoupe D, Croxatto H, Lähteenmäki P. Quantitation of RU 486 in human plasma by HPLC and RIA after column chromatography. Contraception 1986;34:613–23.
[14] He CH, Shi YE, Ye ZH, Zhang GG, Jiang NX, Van Look PF, et al. Pharmacokinetic study of orally administered RU 486 in non-pregnant women. Contraception 1989;40:449–60.
[15] Heikinheimo O, Kontula K, Croxatto H, Spitz I, Luukkainen T, Lähteenmäki P. Plasma concentrations and receptor binding of RU 486 and its metabolites in humans. J Steroid Biochem 1987;26:279–84.
[16] Heikinheimo O, Lähteenmäki PL, Koivunen E, Shoupe D, Croxatto H, Luukkainen T, et al. Metabolism and serum binding of RU 486 in women after various single doses. Hum Reprod 1987;2:379–85.
[17] Kekkonen R, Heikinheimo O, Mandelin E, Lähteenmäki P. Pharmacokinetics of mifepristone after low oral doses. Contraception 1996; 54:229–34.
[18] Deraedt R, Bonnat C, Busigny M, et al. Pharmacokinetics of RU 486. In: Baulieu E-E, Segal S, editors. The antiprogestin steroid RU 486 and human fertility control. New York: Plenum Press, 1985. p. 103–22.
[19] Heikinheimo O, Croxatto H, Salvatierra A, Chang C, Luukkainen T, Lähteenmäki P. Intravaginal administration of RU486 in humans and rats: inadequate absorption in humans. Hum Reprod 1987;2:645–8.
[20] Heikinheimo O. Pharmacokinetics of the antiprogesterone RU486 in women during multiple dose administration. J Steroid Biochem 1989; 32:21–5.
[21] Heikinheimo O, Ranta S, Grunberg S, Spitz I. Alterations in the pituitary- thyroid and pituitary-adrenal axes—consequences of long-term mifepristone treatment. Metabolism 1997;46:292–6.
[22] Moguilewsky M, Philibert D. Biochemical profile of RU 486. In: Baulieu E-E, Segal S, editors. The antiprogestin steroid RU 486 and human fertility control. New York: Plenum Press, 1985. p. 87–97.
[23] Grimaldi B, Barre J, Tillement J-P. Les rôles respectifs des liasons aux protéines sanguines et tissulaires de la mifépristone (RU486) dans sa distribution quantitative dans l'organisme. C R Acad Sci Paris, t.315, Série III, 1992:93–9.
[24] Heikinheimo O, Haukkamaa M, Lähteenmäki P. Distribution of RU 486 and its demethylated metabolites in humans. J Clin Endocrinol Metab 1989;68:270–5.
[25] Liu JH, Garzo VG, Yen SSC. Pharmacodynamics of the antiprogesterone RU486 in women after oral administration. Fertil Steril 1988; 50:245–9.
[26] Jang GR, Wrighton SA, Benet LZ. Identification of CYP3A4 as the principal enzyme catalyzing mifepristone (RU 486) oxidation in human liver microsomes. Biochem Pharmacol 1996;52:753–61.
[27] Shi YE, Ye ZH, He CH, Zhang GQ, Xu JQ, Van Look PF, et al. Pharmacokinetic study of RU 486 and its metabolites after oral administration of single doses to pregnant and non-pregnant women. Contraception 1993;48:133–49.
[28] Heikinheimo O, Ylikorkala O, Turpeinen U, Lähteenmäki P. Pharmacokinetics of the antiprogesterone RU486: no correlation to clinical performance of RU486. Acta Endocrinol 1990;123:298–304.
[29] Ledger W, Sweeting V, Hillier H, Baird D. Inhibition of ovulation by low-dose mifepristone (RU 486). Hum Reprod 1992;7:945–50.
[30] Croxatto H, Salvatierra AM, Croxatto H, Fuentealba B. Effects of continuous treatment with low dose mifepristone throughout one menstrual cycle. Hum Reprod 1993;8:201–7.
[31] Croxatto HB, Devoto L, Durand M, Ezcurra E, Larrea F, Nagle C, et al. Mechanism of action of hormonal preparations used for emergency contraception: a review of literature. Contraception 2001;63: 111–21.
[32] Batista M, Cartledge T, Zellmer A, Nieman L, Merriam G, Loriaux L. Delayed endometrial maturation induced by daily administration of the antiprogestin RU 486: a potential new contraceptive strategy. Am J Obstet Gynecol 1992;167:60–5.
[33] Gemzell-Danielsson K, Westlund P, Johannisson E, Swahn M-L, Bygdeman M, Seppälä M. Effect of low weekly doses of mifepristone on ovarian function and endometrial development. Hum Reprod 1996;11:256–64.

Electronic Patent Application Fee Transmittal

Application Number:	12199114
Filing Date:	27-Aug-2008
Title of Invention:	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Filer:	Alexander Reed Trimble/Shemekia Brown
Attorney Docket Number:	019904-004110US

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	2253	1	635	635

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**635**

Electronic Acknowledgement Receipt	
EFS ID:	11911104
Application Number:	12199114
International Application Number:	
Confirmation Number:	5376
Title of Invention:	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	20350
Filer:	Alexander Reed Trimble/Shemekia Brown
Filer Authorized By:	Alexander Reed Trimble
Attorney Docket Number:	019904-004110US
Receipt Date:	24-JAN-2012
Filing Date:	27-AUG-2008
Time Stamp:	17:51:00
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The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		85178-756824_EXT_AMD_ExA.PDF	1076306 e5e8285d28ce2ca1e42d05ad7aa3961d7ec11105	yes	15

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Extension of Time	1	1
	Amendment/Req. Reconsideration-After Non-Final Reject	2	2
	Claims	3	4
	Applicant Arguments/Remarks Made in an Amendment	5	15

Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31114 3b218380e5986fc85570d4d2c258bc5cdc14dc26	no	2
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<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/22 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2009 *(Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)*	Docket Number (Optional) 85178-756824
Application Number 12/199,114	Filed Aug 27, 2008
For OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS	
Art Unit 1628	Examiner HUI, SAN MING R

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):

		Fee	Small Entity Fee	
☐	One month (37 CFR 1.17(a)(1))	$150	$75	$____
☐	Two months (37 CFR 1.17(a)(2))	$560	$280	$____
☒	Three months (37 CFR 1.17(a)(3))	$1270	$635	$635
☐	Four months (37 CFR 1.17(a)(4))	$1980	$990	$____
☐	Five months (37 CFR 1.17(a)(5))	$2690	$1345	$____

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check in the amount of the fee is enclosed.

☒ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☐ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number _____ .

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

☐ assignee of record of the entire interest. See 37 CFR 3.71
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 52,301

☐ attorney or agent under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34. _____ .

/Alexander R. Trimble/	01/24/12
Signature	Date
Alexander R. Trimble	415-273-4718
Typed or printed name	Telephone Number

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☐ Total of _____ forms are submitted.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/199,114	08/27/2008	Joseph K. Belanoff	019904-004110US	5376

20350 7590 08/03/2011

KILPATRICK TOWNSEND & STOCKTON LLP
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EXAMINER	
HUI, SAN MING R	
ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
08/03/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Docket@kilpatricktownsend.com
ipefiling@kilpatricktownsend.com
jlhice@kilpatrick.foundationip.com

Office Action Summary	Application No.	Applicant(s)
	12/199,114	BELANOFF, JOSEPH K.
	Examiner	Art Unit
	SAN-MING HUI	1628

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) 8 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-7 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of the invention of group I, claims 1-7, in the reply filed 5/18/2011 is acknowledged. The traversal is on the ground(s) that there will not be serious burden. This is not found persuasive because the search fields for both patentably distinct inventions are diverse and not significantly overlapped. Therefore searching and examining all of the inventions encompassed by the claims would impose serious burden to the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claim 8 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/18/2011.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Medical Encyclopedia of Medline (http:// http://www.nlm.nih.gov/medlineplus/ency/article/003430.htm, 10/2005) in view of US

6,964,953 (‘953) and Sarkar, European Journal of Obstetrics and Gynecology and Reproductive Biology, 2002;101:113-120.

Medical Encyclopedia teaches Therapeutic drug levels are usually performed to look for the presence and the amount of specific drug in the blood. With most medications, a certain level of drug is needed in the blood stream to obtain the desired therapeutic effect. (see page one of the article).

Medical Encyclopedia does not expressly teach the optimization of mifepristone level in patients with Acute stress disorder.

‘953 teaches glucocorticoid antagonist, such as mifepristone, as useful in Treating Acute Stress Disorder (see claims 1, 5, and 15 for example). '953 teaches the dosage of the glucocorticoid receptor antagonists as 1 to 10 mg per kilogram (see claim 6). For an average adult who weighs 75kg, it is about 75 – 750mg. ‘953 teaches the course of therapy is 30 days (see claim 16).

Sarkar teaches the serum concentration of various dosages of mifepristone administered. For medium dose (100-200mg of mifepristone), the serum concentration can reach to 4.5 and 5.4 μmol/l (1933.2 ng/ml to 2276.88ng/ml). For a higher dose (400-600mg), the serum concentration gets even higher. (see pages 114-115).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to optimize the serum level of mefipristone in patients suffering from Acute Stress Disorder.

One of ordinary skill in the art would have been motivated to optimize the serum level of mefipristone in patients suffering from Acute Stress Disorder. Adjusting the

therapeutic serum levels to obtain a therapeutic effect is well-known in the art. Since both the serum concentration and the dosage of mifepristone useful in treating the Acute Stress Disorder are both well-known. Adjusting the serum level of mifepristone would be seen as equivalent to adjusting the dosage of mifepristone to effectively treat Acute Stress Disorder would be reasonably expected to be successful.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAN-MING HUI whose telephone number is (571)272-0626. The examiner can normally be reached on Mon - Fri from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

San-ming Hui
Primary Examiner
Art Unit 1628

/San-ming Hui/
Primary Examiner, Art Unit 1628

Notice of References Cited	Application/Control No. 12/199,114	Applicant(s)/Patent Under Reexamination BELANOFF, JOSEPH K.	
	Examiner SAN-MING HUI	Art Unit 1628	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,964,953	11-2005	Belanoff, Joseph K.	514/178
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Sarkar, European Journal of Obstetrics and Gynecology and Reproductive Biology, 2002;101:113-120
	V	Medical Encyclopedia of Medline (http:// http://www.nlm.nih.gov/medlineplus/ency/article/003430.htm, 10/2005
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12199114	BELANOFF, JOSEPH K.
	Examiner	**Art Unit**
	SAN-MING HUI	1628

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/28/2011	07/28/2011							
	1	÷	✓							
	2	÷	✓							
	3	÷	✓							
	4	÷	✓							
	5	÷	✓							
	6	÷	✓							
	7	÷	✓							
	8	÷	N							

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12199114	BELANOFF, JOSEPH K.
	Examiner	Art Unit
	SAN-MING HUI	1628

SEARCHED			
Class	Subclass	Date	Examiner
514	182, 178	7/27/11	SH

SEARCH NOTES		
Search Notes	Date	Examiner
EAST adn inventor search in PALM	7/27/11	SH

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1467	514/178.ccls.	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/07/27 14:37
S1	3899	mifepristone	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/07/25 11:55
S2	12557	post adj traumatic	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/07/25 11:55
S3	424	S1 and S2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/07/25 11:55
S4	2	S1 same S2	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/07/25 11:55
S5	422	S1 and S2 and dosage	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/07/25 11:56
S6	6681	post adj traumatic adj stress	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/07/25 11:56
S7	84	S1 and S6	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2011/07/25 11:56

EAST Search History (Interference)

<This search history is empty>

7/27/2011 2:37:47 PM
C:\Users\shui\Documents\EAST\Workspaces\12-199114.wsp

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on May 16, 2011.

KILPATRICK TOWNSEND & STOCKTON LLP

By: Patricia Andrus

PATENT
Attorney Docket No.: 85178-756824
Family ID No.: 004110US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No. 5376
Joseph K. Belanoff	Examiner: San Ming R Hui
Application No.: 12/199,114	Technology Center/Art Unit: 1628
Filed: August 27, 2008	
For: OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS	
Customer No.: 20350	AMENDMENT A & RESPONSE TO RESTRICTION REQUIREMENT

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Restriction Requirement mailed March 31, 2011, Applicants elect, with traverse, the invention of Group 1, drawn to a method of optimizing the levels of mifepristone, classified in class 514, subclass 182. Applicants' election is made with traverse, believing that the full scope of the invention could be searched and examined without undue burden on the Patent Office. Accordingly, Applicants submit that the requirement under 35 U.S.C. § 121 has been met.

CONCLUSION

In view of the foregoing, Applicants believe the pending claims in this Application are in condition for substantive review on the merits. Favorable consideration is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

Alexander R. Trimble
Reg. No. 52,301

KILPATRICK TOWNSEND & STOCKTON LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415-576-0300
Attachments
ART:art
63296813 v1

Electronic Acknowledgement Receipt

EFS ID:	10119209
Application Number:	12199114
International Application Number:	
Confirmation Number:	5376
Title of Invention:	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	20350
Filer:	Alexander Reed Trimble/Patricia Andrews
Filer Authorized By:	Alexander Reed Trimble
Attorney Docket Number:	019904-004110US
Receipt Date:	18-MAY-2011
Filing Date:	27-AUG-2008
Time Stamp:	15:36:43
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Response to Election / Restriction Filed	85178-75624.PDF	66394 7b54732c5a5d518701b160d9a905b72338e65b29	no	2

Warnings:

Information:

Total Files Size (in bytes):	66394

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Document code: WFEE

United States Patent and Trademark Office
Sales Receipt for Accounting Date: 05/25/2011

KWANZER SALE #00000001 Mailroom Dt: 05/18/2011 201430 12199114
01 FC : 2251 65.00 DA

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/199,114	08/27/2008	Joseph K. Belanoff	019904-004110US	5376

20350 7590 03/31/2011

KILPATRICK TOWNSEND & STOCKTON LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
HUI, SAN MING R	
ART UNIT	PAPER NUMBER
1628	

NOTIFICATION DATE	DELIVERY MODE
03/31/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

Docket@kilpatricktownsend.com
ipefiling@kilpatricktownsend.com
jlhice@kilpatrick.foundationip.com

Office Action Summary	Application No.	Applicant(s)	
	12/199,114	BELANOFF, JOSEPH K.	
	Examiner	Art Unit	
	SAN-MING HUI	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-8 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-7, drawn to a method of optimizing the levels of mifepristone, classified in class 514, subclass 182.

II. Claim 8, drawn to a kit comprising mifepristone, classified in class 424, subclass 401+.

The inventions are distinct, each from the other because of the following reasons:

Inventions II and I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the product as claimed can be used for materially different method such as pharmacokinetic study.

Restriction for examination purposes as indicated is proper because all these inventions listed in this action are independent or distinct for the reasons given above and there would be a serious search and/or examination burden if restriction were not required because at least the following reason(s) apply:

The search fields for the invention groups are diverse and not being overlapped. Therefore, searching for all of the inventions encompassed by the claims impose undue burden to the examiner.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention**.

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Because the above restriction/election requirement is complex, a telephone call to applicant's agent to request an oral election was not made. See M.P.E.P. Sec. 812.01.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAN-MING HUI whose telephone number is (571)272-0626. The examiner can normally be reached on Mon - Fri from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brandon Fetterolf can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

San-ming Hui
Primary Examiner
Art Unit 1628

/San-ming Hui/
Primary Examiner, Art Unit 1628

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	12199114	BELANOFF, JOSEPH K.
	Examiner	**Art Unit**
	SAN-MING HUI	1628

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☐ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	03/28/2011								
	1	÷								
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	8	÷								

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/199,114	08/27/2008	Joseph K. Belanoff	019904-004110US

CONFIRMATION NO. 5376

20350
TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

PUBLICATION NOTICE

OC000000034852628

Title:OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

Publication No.US-2009-0062248-A1
Publication Date:03/05/2009

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/199,114	08/27/2008	1614	500	019904-004110US	8	2

CONFIRMATION NO. 5376

UPDATED FILING RECEIPT

20350
TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

OC000000033133988

Date Mailed: 11/17/2008

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Joseph K. Belanoff, Woodside, CA;

Assignment For Published Patent Application

Corcept Therapeutics, Inc., Menlo Park, CA

Power of Attorney: The patent practitioners associated with Customer Number 20350

Domestic Priority data as claimed by applicant

This appln claims benefit of 60/969,027 08/30/2007

Foreign Applications

If Required, Foreign Filing License Granted: 09/08/2008

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/199,114**

Projected Publication Date: 03/05/2009

Non-Publication Request: No

Early Publication Request: No
** **SMALL ENTITY** **

Title

OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/199,114	08/27/2008	Joseph K. Belanoff	019904-004110US

CONFIRMATION NO. 5376

20350
TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

POA ACCEPTANCE LETTER

OC000000033133969

Date Mailed: 11/17/2008

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 11/07/2008.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/ctuazon/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on November 7, 2008.

TOWNSEND and TOWNSEND and CREW LLP

By: Patricia Andrus

PATENT
Attorney Docket No.: 019904-004110US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 5376
Joseph K. Belanoff	Examiner:
Application No.: 12/199,114	Art Unit: 1614
Filed: August 27, 2008	TRANSMITTAL LETTER – RESPONSE TO NOTICE OF MISSING PARTS
For: OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS	
Customer No.: 20350	

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to the Notice to File Missing Parts of Nonprovisional Application, dated 09/11/2008, enclosed are the following to be made of record in the above-identified application:

1) Executed Declaration

2) Power of Attorney and Certificate of Assignee Under 37 C.F.R. § 3.73(b)

Please charge Deposit Account No. 20-1430 for the following fees:

Small Entity:	(a)	Filing Fee	$0
	(b)	Search Fee	$0
	(c)	Examination Fee	$0
	(d)	Application Size Fee	$0
	(e)	Excess Claims Fees (§ 1.16(b), (c)):	
		- = x =	
		- = x =	
	(f)	Multiple Dependent Claims	
	(g)	Missing Parts Surcharge	$65
		TOTAL FEES TO BE CHARGED	$65

The Commissioner is hereby authorized to charge any additional fees associated with this paper or during the pendency of this application, or credit any overpayment, to Deposit Account No. 20-1430. This Transmittal Letter is submitted in duplicate.

Respectfully submitted,

/Alexander R. Trimble/

Alexander R. Trimble
Reg. No. 52,301

Customer No. 20350

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: 415 576-0300
ART:pja

61685686 v1

Attorney Docket No.: 019904-004110US
Client Ref. No.:

PTO/SB/01A (07-07)

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

As the below named inventor(s), I/we declare that:

This declaration is directed to:

☐ The attached application, or

☒ Application No. 12/199,114, filed on August 27, 2008,

☐ as amended on _____ (if applicable);

I/we believe that I/we am/are the original and first inventor(s) of the subject matter which is claimed and for which a patent is sought;

I/we have reviewed and understand the contents of the above-identified application, including the claims, as amended by any amendment specifically referred to above;

I/we acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me/us to be material to patentability as defined in 37 CFR 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the national or PCT International filing date of the continuation-in-part application.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

All statements made herein of my/our own knowledge are true, all statements made herein on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and may jeopardize the validity of the application or any patent issuing thereon.

FULL NAME OF INVENTOR(S)

Inventor one: Joseph K. Belanoff Date: NOV 4, 2008

Signature: _____ Citizen of: United States

Inventor two: _____ Date: _____

Signature: _____ Citizen of: _____

☐ Additional inventors or a legal representative are being named on _____ additional form(s) attached hereto.

61543962 v1

Application Data Sheet

Application Information

Application number::	
Filing Date::	08/27/08
Application Type::	Regular
Subject Matter::	Utility
Suggested classification::	
Suggested Group Art Unit::	
CD-ROM or CD-R??::	
Number of CD disks::	
Number of copies of CDs::	
Sequence Submission::	
Computer Readable Form (CRF)?::	
Number of copies of CRF::	
Title::	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
Attorney Docket Number::	019904-004110US
Request for Early Publication::	No
Request for Non-Publication::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	6
Small Entity?::	Yes
Latin name::	
Variety denomination name::	
Petition included?::	No
Petition Type::	
Licensed US Govt. Agency::	

Contract or Grant Numbers One::	
Secrecy Order in Parent Appl.::	No

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Joseph
Middle Name::	K.
Family Name::	Belanoff
Name Suffix::	
City of Residence::	Woodside
State or Province of Residence::	CA
Country of Residence::	US
Street of Mailing Address::	1 Southgate Drive
City of Mailing Address::	Woodside
State or Province of mailing address::	CA
Country of mailing address::	US
Postal or Zip Code of mailing address::	94062

Correspondence Information

Correspondence Customer Number::	20350

Representative Information

Representative Customer Number::	20350

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::
This Application	An Appn claiming benefit under 35 USC 119(e) of	60/969,027	08/30/07

Foreign Priority Information

Country:: Application number:: Filing Date::

Assignee Information

Assignee Name::

Street of mailing address::

City of mailing address::

State or Province of mailing address::

Country of mailing address::

Postal or Zip Code of mailing address::

Submitted by:

Signature _____ Date _____

Printed Name Alexander R. Trimble Registration Number 52,301

PTO/SB/81 (07-08)

POWER OF ATTORNEY OR REVOCATION OF POWER OF ATTORNEY WITH A NEW POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS		
	Application Number	12/199,114
	Filing Date	August 27, 2008
	First Named Inventor	Belanoff, Joseph K.
	Title	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
	Art Unit	1614
	Examiner Name	
	Attorney Docket	019904-004110US

I hereby revoke all previous powers of attorney given in the above-identified application.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith: **20350**

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

I further authorize any of the above-identified practitioners to execute a Statement Under 37 CFR 3.73(b) on my/our behalf to certify the chain of title and establish my/our ownership in the application identified above.

Please recognize or change the correspondence address for the above-identified application to:

☒ The address associated with the above-mentioned Customer Number:

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the:

☐ Applicant/Inventor.

OR

☐ Assignee of record of the entire interest. See 37 CFR 3.71.

Statement under 37 CFR 3.73(b) (Form PTO/SB/96 submitted herewith or filed on _____.

SIGNATURE of Applicant or Assignee of Record

Signature		Date	NOV. 4, 2008
Name	Joseph K. Belanoff	Telephone	650-327-3270
Title and Company	CEO, Concept Therapeutics		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

61543968 v1

Attorney Docket No. 019904-004110US

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Joseph K. Belanoff

Application No./Patent No.: 12/199,114 Filed/Issue Date: August 27, 2008

Entitled: OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

Corcept Therapeutics, Inc. (Name of Assignee), a corporation (Type of Assignee: corporation, partnership, university, government agency, etc.)

states that it is:

1. ☒ the assignee of the entire right, title, and interest; or
2. ☐ an assignee of less than the entire right, title and interest. (The extent (by percentage) of its ownership interest is _____%)

in the patent application/patent identified above by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.
2. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.
3. From: _____ To: _____
   The document was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

[signature]	NOV. 4, 2008
Signature	Date
Joseph K. Belanoff	650-327-3270
Printed or Typed Name	Telephone Number
CEO	
Title	

61543971 v1

Attorney Docket No.: 019904-004110US

ASSIGNMENT OF PATENT APPLICATION

SOLE

WHEREAS, Joseph K. Belanoff of 1 Southgate Drive, Woodside, CA 94062, hereinafter referred to as "Assignor," is the inventor of the invention described and set forth in the below-identified application for United States Letters Patent:

Title of Invention: OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

Date(s) of execution of Declaration: NOV. 4, 2008

Filing Date: August 27, 2008

Application No.: 12/199,114; and

WHEREAS, Corcept Therapeutics, Inc., a corporation of the state of Delaware, located at 149 Commonwealth Drive, Menlo Park, CA 94025, hereinafter referred to as "ASSIGNEE," is desirous of acquiring an interest in the invention and application and in any U.S. Letters Patent and Registrations which may be granted on the same;

For good and valuable consideration, receipt of which is hereby acknowledged by Assignor, Assignor has assigned, and by these presents does assign to Assignee all right, title and interest in and to the invention and application and to all foreign counterparts (including patent, utility model and industrial designs), and in and to any Letters Patent and Registrations which may hereafter be granted on any patent application claiming priority from the same in the United States and all countries throughout the world, and to claim the priority from the application as provided by the Paris Convention. The right, title and interest is to be held and enjoyed by Assignee and Assignee's successors and assigns as fully and exclusively as it would have been held and enjoyed by Assignor had this Assignment not been made, for the full term of any Letters Patent and Registrations which may be granted thereon, or of any division, renewal, continuation in whole or in part, substitution, conversion, reissue, prolongation or extension thereof.

Assignor further agrees that Assignor will, without charge to Assignee, but at Assignee's expense, (a) cooperate with Assignee in the prosecution of U.S. Patent applications and foreign counterparts on the invention and any improvements, (b) execute, verify, acknowledge and deliver all such further papers, including applications and instruments of transfer, and (c) perform such other acts as Assignee lawfully may request to obtain or maintain Letters Patent and Registrations for the invention and improvements in any and all countries, and to vest title thereto in Assignee, or Assignee's successors and assigns.

IN TESTIMONY WHEREOF, Assignor has signed his/her name on the date indicated.

Dated: NOV 4, 2008

Joseph K. Belanoff

SIGNATURE WITNESSED BY:

Dated: NOV 4, 2008

Signature of Witness

MARK STREM

Printed Name

Dated: NOV 4, 2008

Signature of Witness

ANNE LE DOUX

Printed Name

61543960 v1

Electronic Patent Application Fee Transmittal

Application Number:	12199114
Filing Date:	27-Aug-2008
Title of Invention:	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Filer:	Alexander Reed Trimble/Patricia Andrews
Attorney Docket Number:	019904-004110US

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Late filing fee for oath or declaration	2051	1	65	65
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**65**

Electronic Acknowledgement Receipt	
EFS ID:	4250890
Application Number:	12199114
International Application Number:	
Confirmation Number:	5376
Title of Invention:	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	20350
Filer:	Alexander Reed Trimble/Patricia Andrews
Filer Authorized By:	Alexander Reed Trimble
Attorney Docket Number:	019904-004110US
Receipt Date:	07-NOV-2008
Filing Date:	27-AUG-2008
Time Stamp:	13:27:45
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$65
RAM confirmation Number	9603
Deposit Account	201430
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees) Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		019904-004110us.pdf	305281 00df255907cf76a5b542c1b9772e2cf38c3efcd3	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Response to Pre-Exam Formalities Notice	1	2
	Oath or Declaration filed	3	6
	Power of Attorney	7	8
	Assignee showing of ownership per 37 CFR 3.73(b).	9	11

Warnings:

Information:

2	Fee Worksheet (PTO-06)	fee-info.pdf	30888 441ee976c6d1765a9ccc6f4c282b6408ae707f28	no	2

Warnings:

Information:

Total Files Size (in bytes):	336169

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/199,114	08/27/2008	1614	435	019904-004110US	8	2

CONFIRMATION NO. 5376

20350
TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

FILING RECEIPT

OC000000031951597

Date Mailed: 09/11/2008

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Applicant(s)

Joseph K. Belanoff, Woodside, CA;

Assignment For Published Patent Application

Corcept Therapeutics, Inc., Menlo Park, CA

Power of Attorney: None

Domestic Priority data as claimed by applicant

This appln claims benefit of 60/969,027 08/30/2007

Foreign Applications

If Required, Foreign Filing License Granted: 09/08/2008

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/199,114**

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No
** **SMALL ENTITY** **

Title

OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

Preliminary Class

514

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where

the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/199,114	08/27/2008	Joseph K. Belanoff	019904-004110US

CONFIRMATION NO. 5376

20350
TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

FORMALITIES LETTER

OC000000031951598

Date Mailed: 09/11/2008

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

Items Required To Avoid Abandonment:

An application number and filing date have been accorded to this application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items and pay any fees required below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The oath or declaration is missing.
  A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.
  Note: If a petition under 37 CFR 1.47 is being filed, an oath or declaration in compliance with 37 CFR 1.63 signed by all available joint inventors, or if no inventor is available by a party with sufficient proprietary interest, is required.

The applicant needs to satisfy supplemental fees problems indicated below.

The required item(s) identified below must be timely submitted to avoid abandonment:

- To avoid abandonment, a surcharge (for late submission of filing fee, search fee, examination fee or oath or declaration) as set forth in 37 CFR 1.16(f) of $**65** for a small entity in compliance with 37 CFR 1.27, must be submitted with the missing items identified in this notice.

SUMMARY OF FEES DUE:

Total additional fee(s) required for this application is $**65** for a small entity
- $**65** Surcharge.

Replies should be mailed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/fasrat/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

Application Data Sheet

Application Information

Application number::	
Filing Date::	08/27/08
Application Type::	Regular
Subject Matter::	Utility
Suggested classification::	
Suggested Group Art Unit::	
CD-ROM or CD-R??::	
Number of CD disks::	
Number of copies of CDs::	
Sequence Submission::	
Computer Readable Form (CRF)?::	
Number of copies of CRF::	
Title::	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
Attorney Docket Number::	019904-004110US
Request for Early Publication::	No
Request for Non-Publication::	No
Suggested Drawing Figure::	
Total Drawing Sheets::	6
Small Entity?::	Yes
Latin name::	
Variety denomination name::	
Petition included?::	No
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PATENT APPLICATION

OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

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OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 60/969,027, filed August 30, 2007, the disclosure of which is incorporated herein in its entirety.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0002] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK.

[0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

[0004] It has been surprisingly discovered that administration of the same dose of mifepristone can produce widely varying blood serum levels in different patients. The varied blood serum levels can result in some patients not receiving an efficacious dose of mifepristone. For the same dose of mifepristone, the blood serum levels can differ by as much as 800% from one patient to another. Thus, a method for ensuring that the blood serum levels of mifepristone remain in an efficacious and safe range is needed.

BRIEF SUMMARY OF THE INVENTION

[0005] In one embodiment, the present invention provides a method for optimizing levels of mifepristone in a patient suffering from a mental disorder amenable to treatment by mifepristone, the method comprising: treating the patient with seven or more daily doses of mifepristone over a period of seven or more days; testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/mL; and

adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

[0006] In some embodiments, the mental disorder is a member selected from the group consisting of a stress disorder, delirium, mild cognitive impairment (MCI), dementia, psychosis and psychotic major depression. In other embodiments, the stress disorder is a member selected from the group consisting of Acute Stress Disorder, Post-Traumatic Stress Disorder and Brief Psychotic Disorder with Marked Stressor(s).

[0007] In another embodiment, each of the seven or more daily doses of mifepristone are administered orally. In other embodiments, the patient is treated with 28 or more daily doses over a period of 28 or more days.

[0008] In a further embodiment, the testing is performed by a plasma sampling collection device suitable for detecting mifepristone serum levels.

[0009] In other embodiments, the adjusting step comprises increasing the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

[0010] In a second embodiment, the present invention provides a kit for treating a mental disorder amenable to treatment by mifepristone, the kit comprising: seven daily doses of mifepristone; and a plasma sampling collection device suitable for detecting mifepristone serum levels.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] **Figure 1** shows a comparison of patients receiving Corlux vs. placebo on primary endpoint (OC) for all studies. Of the patients receiving Corlux, 35% of the patients showed at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56, versus 26% of patients receiving the placebo.

[0012] **Figure 2** shows a comparison of patients with plasma levels >1357 ng/mL vs. <1357 ng/mL vs. placebo (OC) for all studies. Of the patients having plasma levels of greater than 1357 ng/mL, 40% of the patients showed at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56, versus 27% of patients having plasma levels of less than 1357 ng/mL and 26% of patients receiving the placebo.

[0013] **Figure 3** shows a comparison of patients with plasma levels >1661ng/ml vs. placebo (OC) for all studies. Of the patients having plasma levels of greater than 1661 ng/mL, 44% of the patients showed at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56, versus 29% of patients having plasma levels of less than 1661 ng/mL and 26% of patients receiving the placebo.

[0014] **Figure 4** shows a comparison of patients receiving Corlux vs. placebo on primary endpoint (OC) for the 1200mg group. Of the patients receiving the 1200 mg dose of Corlux, 47% of the patients showed at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56, versus 34% of patients receiving the placebo.

[0015] **Figure 5** shows a comparison of patients with plasma levels >1357ng/ml vs. placebo (OC) for the 1200mg group. Of the patients in the 1200 mg group having plasma levels of greater than 1357 ng/mL, 54% of the patients showed at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56, versus 31% of patients having plasma levels of less than 1357 ng/mL and 34% of patients receiving the placebo.

[0016] **Figure 6** shows a comparison of patients with plasma levels >1661ng/ml vs. placebo (OC) for the 1200mg group. Of the patients in the 1200 mg group having plasma levels of greater than 1661 ng/mL, 58% of the patients showed at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56, versus 39% of patients having plasma levels of less than 1661 ng/mL and 34% of patients receiving the placebo.

DETAILED DESCRIPTION OF THE INVENTION

I. Introduction

[0017] Administration of the same dose of mifepristone can produce widely varying mifepristone blood serum levels in different patients. For the same dose, the blood serum levels can differ by as much as 800% from one patient to another. For those patients with lower blood serum levels, the effectiveness of mifepristone treatment can suffer significantly. The present invention provides a method for optimizing the blood serum levels of mifepristone so that the blood serum levels remain in an efficacious range and the patient receives the necessary treatment.

[0018] The method of the present invention optimizes blood serum levels of mifepristone in a patient suffering from a mental disorder amenable to treatment by mifepristone by first

treating the patient with mifepristone. The treatment can be for any appropriate period of time, such as seven or more daily doses over a period of seven or more days. Following treatment for an appropriate period of time, the serum levels of the patient are tested to determine whether the blood levels of mifepristone are greater than 1300 ng/mL. The daily dose of the patient is then adjusted in order to achieve mifepristone blood levels of greater than 1300 ng/mL.

II. Definitions

[0019] The term "amenable to treatment by mifepristone" refers to a condition that is known to be treated by glucocorticoid antagonists such as mifepristone. Conditions such as mental disorders (discussed below) are amenable to treatment by mifepristone.

[0020] The term "mental disorder" refers to disorders of the mind that can be treated with a glucocorticoid antagonist such as mifepristone. Mental disorders amenable to treatment by the methods of the present invention include, but are not limited to, a stress disorder, delirium, mild cognitive impairment (MCI), dementia, psychosis and psychotic major depression.

[0021] The term "stress disorder" refers to a psychiatric condition precipitated by exposure to a traumatic or stressful event. Stress disorders include Acute Stress Disorder, Post-Traumatic Stress Disorder, and Brief Psychotic Disorder with Marked Stressor(s).

[0022] The term "Acute Stress Disorder" refers to a psychiatric condition in its broadest sense, as defined in American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Washington, D.C., 2000 ("DSM-IV-TR"). The DSM-IV-TR defines "Acute Stress Disorder" as characterized by anxiety, dissociative, and other symptoms occurring within 1 month after exposure to an extreme traumatic stressor. The DSM-IV-TR sets forth a generally accepted standard for diagnosing and categorizing Acute Stress Disorder.

[0023] The term "Brief Psychotic Disorder with Marked Stressor(s)" refers to a psychiatric condition in its broadest sense, as defined in DSM-IV-TR. The DSM-IV-TR defines "Brief Psychotic Disorder with Marked Stressor(s)" as a sudden but brief onset of psychotic symptoms developing shortly after and apparently in response to one or more stressful events. The DSM-IV-TR sets forth a generally accepted standard for diagnosing and categorizing Brief Psychotic Disorder with Marked Stressor(s).

[0024] The term "delirium" refers to a psychiatric condition in its broadest sense, as defined in American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, Washington, D.C., 2000 ("DSM-IV-TR"). The DSM-IV-TR defines "delirium" as a disturbance of consciousness, developing over a short period of time, accompanied by a change in cognition that cannot be better accounted for by a preexisting or evolving dementia. The DSM-IV-TR sets forth a generally accepted standard for diagnosing and categorizing delirium.

[0025] The term "dementia" refers to a psychiatric condition in its broadest sense, as defined in American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Washington, D.C., 1994 ("DSM-IV"). The DSM-IV defines "dementia" as characterized by multiple cognitive deficits that include impairments in memory and lists various dementias according to presumed etiology. The DSM-IV sets forth a generally accepted standard for such diagnosing, categorizing and treating of dementia and associated psychiatric disorders.

[0026] The term "mild cognitive impairment (MCI)" refers to a category of memory and cognitive impairment that is typically characterized by a clinical dementia rating (CDR) of 0.5 (*see, e.g.*, Hughes *et al.*, *Brit. J. Psychiat.* 140:566-572, 1982) and further characterized by memory impairment, but not impaired function in other cognitive domains. Memory impairment is preferably measured using tests such as a "paragraph test". A patient diagnosed with MCI often exhibits impaired delayed recall performance. MCI is typically associated with aging and generally occurs in patients who are 45 years of age or older.

[0027] The term "mifepristone" refers to a family of compositions also referred to as RU486, or RU38.486, or 17-beta-hydroxy-11-beta-(4-dimethyl-aminophenyl)-17-alpha-(1-propynyl)-estra-4,9-dien-3-one), or 11-beta-(4dimethylaminophenyl)-17-beta-hydroxy-17-alpha-(1-propynyl)-estra-4,9-dien-3-one), or analogs thereof, which bind to the glucocorticoid receptor (GR), typically with high affinity, and inhibit the biological effects initiated/ mediated by the binding of any cortisol or cortisol analogue to a GR receptor (as discussed within). Salts, hydrates and prodrugs of mifepristone are all within the scope of the present invention.

[0028] The term "Post-Traumatic Stress Disorder" refers to a psychiatric condition in its broadest sense, as defined in DSM-IV-TR. The DSM-IV-TR defines "Post-Traumatic Stress Disorder" as characterized by persistent re-experiencing of an extreme traumatic event. The

DSM-IV-TR sets forth a generally accepted standard for diagnosing and categorizing Post-Traumatic Stress Disorder.

[0029] The term "psychotic" as used herein refers to a psychiatric condition in its broadest sense, as defined in the DSM-IV (Kaplan, ed. (1995) supra) and described below. The term "psychotic" has historically received a number of different definitions, ranging from narrow to broadly described. A psychotic condition can include delusions or prominent hallucinations, including prominent hallucinations that the individual realizes are hallucinatory experiences, and those with hallucinations occurring in the absence of insight into their pathological nature. Finally, the term includes a psychotic condition characterized by a loss of ego boundaries or a gross impairment in reality testing. Unlike this definition, which is broad and based primarily on symptoms, characterization of psychosis in earlier classifications (e.g., DSM-II and ICD-9) were more inclusive and focused on the severity of functional impairment (so that a mental disorder was termed "psychotic" if it resulted in "impairment" that grossly interferes with the capacity to meet ordinary demands of life). Different disorders which have a psychotic component comprise different aspects of this definition of "psychotic." For example, in schizophreniform disorder, schizoaffective disorder and brief psychotic disorder, the term "psychotic" refers to delusions, any prominent hallucinations, disorganized speech, or disorganized or catatonic behavior. In psychotic disorder due to a general medical condition and in substance-induced psychotic disorder, "psychotic" refers to delusions or only those hallucinations that are not accompanied by insight. Finally, in delusional disorder and shared psychotic disorder, "psychotic" is equivalent to "delusional" (see DSM-IV, supra, page 273).

[0030] Objective tests can be also be used to determine whether an individual is psychotic and to measure and assess the success of a particular treatment schedule or regimen. For example, measuring changes in cognitive ability aids in the diagnosis and treatment assessment of the psychotic patient. Any test known in the art can be used, such as the so-called "Wallach Test," which assesses recognition memory (see below, Wallach (1980) J. Gerontol. 35:371-375). Another example of an objective text which can be used to determine whether an individual is psychotic and to measure efficacy of an anti-psychotic treatment is the Stroop Color and Word Test ("Stroop Test") (see Golden, C. J., Cat. No. 30150M, In A Manual for Clinical and Experimental Uses, Stoelting, Wood Dale, Ill.) The Stroop Test is an objective neuropsychiatric test that can differentiate between individuals with psychosis and those without, and is described in detail below.

[0031] The term "psychosis" refers to a psychiatric symptom, condition or syndrome in its broadest sense, as defined in the DSM-IV (Kaplan, ed. (1995) supra), comprising a "psychotic" component, as broadly defined above. The term psychosis can refer to a symptom associated with a general medical condition, a disease state or other condition, such as a side effect of drug abuse (a substance-induced disorder) or as a side effect of a medication. Alternatively, the term psychosis can refer to a condition or syndrome not associated with any disease state, medical condition, drug intake or the like.

[0032] Psychosis is typically defined as a mental disorder or condition causing gross distortion or disorganization of a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others to the degree of interfering with his capacity to cope with the ordinary demands of everyday life.

[0033] The term "psychotic major depression," also referred to as "psychotic depression" (Schatzberg (1992) Am. J. Psychiatry 149:733-745), "psychotic (delusional) depression" (Ibid.), "delusional depression" (Glassman (1981) supra) and, "major depression with psychotic features" (see the DSM-III-R), refers to a distinct psychiatric disorder which includes both depressive and psychotic features. Individuals manifesting both depression and psychosis, i.e. psychotic depression, are herein referred to as "psychotic depressives." It has been long-recognized in the art as a distinct syndrome, as described, for example, by Schatzberg (1992) supra. Illustrative of this distinctness are studies which have found significant differences between patients with psychotic and nonpsychotic depression in glucocorticoid activity, dopamine-beta-hydroxylase activity, levels of dopamine and serotonin metabolites, sleep measures and ventricle to brain ratios. Psychotic depressives respond very differently to treatment compared to individuals with other forms of depression, such as "non-psychotic major depression." Psychotic depressives have a low placebo response rate and respond poorly to antidepressant therapy alone (without concurrent anti-psychotic treatment). Psychotic depressives are markedly unresponsive to tricyclic (anti-depressive) drug therapy (Glassman, et al. (1975) supra). While psychotic depressives can respond to electroconvulsive therapy (ECT), their response time is relatively slow and the ECT has a high level of related morbidity. Clinical manifestations and diagnostic parameters of "psychotic major depression" is described in detail in the DSM-IV (Kaplan, ed. (1995) supra). Thus, due to its unique pathophysiology, high rate of morbidity and response to treatment, there is great practical need to differentially diagnose and specifically treat psychotic major depression as compared to non-psychotic depression.

[0034] The term "optimizing" refers to the process of testing mifepristone blood levels and adjusting the dosage of mifepristone administered to the patient in need in order to achieve mifepristone blood levels above 1300 ng/mL.

[0035] The terms "treat", "treating" and "treatment" collectively refer to any indicia of success in the treatment or amelioration of an injury, pathology or condition, including any objective or subjective parameter such as abatement; remission; diminishing of symptoms or making the injury, pathology or condition more tolerable to the patient; slowing in the rate of degeneration or decline; making the final point of degeneration less debilitating; improving a patient's physical or mental well-being; or, in some situations, preventing the onset of dementia. The treatment or amelioration of symptoms can be based on objective or subjective parameters; including the results of a physical examination, neuropsychiatric exams, and/or a psychiatric evaluation.

[0036] The term "testing" refers to determining the mifepristone blood levels in a patient. The testing can be performed by any suitable instrument, such as a plasma sampling collection device capable of detecting mifepristone serum levels.

III. Method for Optimizing Mifepristone Levels

[0037] Administration of the same dose of mifepristone to different patients can produce widely varying blood serum levels, varying by up to 800% from one patient to another, resulting in decreased efficacy. The present invention provides a method for optimizing the blood serum levels of mifepristone so that the blood serum levels remain in an efficacious range and the patient receives the necessary treatment.

A. Patients in Need

[0038] Patients amenable to treatment with mifepristone according to the method of the present invention suffer from any mental disorder. Exemplary mental disorders include, but are not limited to, a stress disorder, delirium, mild cognitive impairment (MCI), dementia, psychosis and psychotic major depression.

[0039] Stress disorders treatable by the methods of the present invention include, but are not limited to, Acute Stress Disorder (ASD), Post-Traumatic Stress Disorder and Brief Psychotic Disorder with Marked Stressor(s).

[0040] Acute Stress Disorder (ASD) is characterized by a constellation of symptoms, lasting at least two days, that appear and resolve within one month of exposure to an extreme traumatic stressor. If symptoms appear or persist beyond one month after exposure to the traumatic stressor, the patient may be considered to suffer from Post-Traumatic Stress Disorder rather than ASD. ASD is a common precursor to Post-Traumatic Stress Disorder, and up to 80% of trauma survivors initially suffering from ASD will meet the diagnostic criteria for Post-Traumatic Stress Disorder six months later (see Brewin et al., Am J Psychiatry 156:360-6, 1999).

[0041] Patients develop ASD following exposure to an extreme traumatic stressor (DSM-IV-TR Criterion A). A person must respond to the stressor with intense fear, helplessness, or horror to be diagnosed with ASD. ASD may develop from direct experience of traumatic events, including violent crimes, physical trauma, combat, diagnosis with a life-threatening illness, and natural or manmade disasters. Patients may also develop ASD from witnessing or learning about traumatic events that happen to others, especially family members or close friends. Unexpected exposure to death, dead bodies, or body parts may also induce ASD.

[0042] A diagnosis of ASD requires that the person meet several other symptomatic criteria. The person must experience three or more dissociative symptoms in connection with the traumatic stressor (Criterion B). Dissociative symptoms include a subjective sense of numbing or detachment, a reduction in awareness of surroundings, derealization, depersonalization, and dissociative amnesia. Furthermore, ASD requires that the victim persistently re-experience the traumatic event, though recurrent images, thoughts, dreams, illusions, flashbacks, sense of reliving the event, or distress upon exposure to reminders of the event (Criterion C). The person must display marked avoidance of stimuli that arouse recollection of the trauma (Criterion D) and marked symptoms of anxiety or increased arousal (Criterion E). Finally, in addition to the time requirements described above, a diagnosis of ASD requires that the disturbance cause significant distress; or life impairment, and not be due to another psychiatric or physiological condition (Criteria F-H).

[0043] Like Acute Stress Disorder, Post-Traumatic Stress Disorder (PTSD) emerges following exposure to an extreme traumatic stressor, and is characterized by persistent reexperiencing of the traumatic event, avoidance of stimuli associated with the trauma, and anxiety or increased arousal. The types of traumatic stressors giving rise to PTSD, and the manifestations of PTSD symptoms, are identical to those described above for ASD, but for

three differences. First, the dissociative symptoms required for a diagnosis of ASD are not required for a diagnosis of PTSD, although dissociative symptoms may commonly be seen in PTSD patients. Secondly, PTSD need not arise within one month of exposure to the traumatic stressor, and may emerge months or years after the traumatic event. Thirdly, in contrast to the one month maximum duration of symptoms required for a diagnosis of ASD, symptoms must persist for at least one month in order for a diagnosis of PTSD to be made.

[0044] A Brief Psychotic Disorder is a short-term (between one day and one month) disturbance involving the sudden onset of at least one psychotic symptom, such as delusions, hallucinations, disorganized speech, or grossly disorganized or catatonic behavior. Brief Psychotic Disorders exclude those induced by a general medical condition. If psychotic symptoms develop shortly after, and apparently in response to, one or more severely stressful events, the disturbance is diagnosed as Brief Psychotic Disorder with Marked Stressor(s) (formerly labeled "brief reactive psychosis" in DSM-III-R). Brief Psychotic Disorder with Marked Stressor(s) is treatable by the glucocorticoid receptor antagonists of the present invention.

[0045] Delirium is characterized by disturbances of consciousness and changes in cognition that develop over a relatively short period of time. The disturbance in consciousness is often manifested by a reduced clarity of awareness of the environment. The patient displays reduced ability to focus, sustain or shift attention (DSM-IV-TR diagnostic Criterion A). Accompanying the disturbance in consciousness, delirium patients display a disturbance in cognition (e.g., memory impairment, disorientation, language difficulties) or perceptual disturbances (e.g., misinterpretations, illusions, or hallucinations) (Criterion B). To be considered delirium, these disturbances in consciousness, cognition, or perception should develop over a short period of time and tend to fluctuate during the course of the day (Criterion C).

[0046] Delirium may arise from a number of general medical conditions, including central nervous system disorders (e.g., trauma, stroke, encephalopathies), metabolic disorders (e.g., renal or hepatic insufficiency, fluid or electrolyte imbalances), cardiopulmonary disorders (e.g., congestive heart failure, myocardial infarction, shock), and systemic illnesses or effects (e.g., infections, sensory deprivation, and postoperative states). Glucocorticoid receptor antagonists are also effective to treat Substance-Induced Delirium (e.g., delirium induced by substance intoxication or withdrawal, medication side effects, and toxin exposure). Delirium

may arise from multiple simultaneous etiologies (e.g., a combination of a general medical condition and substance intoxication) and such delirium, as well as delirium of unknown or unclassified origin, may be treated with the glucocorticoid receptor antagonists of the present invention.

[0047] Mild cognitive impairment (MCI) is characterized as a mild impairment of cognition categorized as a CDR of 0.5 that is associated with deficits in a memory task test, such as a paragraph test. An MCI patient is fully oriented, but demonstrates mild consistent forgetfulness. Impairment in cognitive domains other than memory, such as problem solving and judgment is doubtful, if present at all, and, further, the MCI patient does not demonstrate impairment in functioning in the community or at home. A patient with MCI scores normally on standard tests of dementia.

[0048] There are various means to diagnose the onset of MCI and to assess the efficacy of treatment using the methods of the invention. These include the administration of psychiatric tests to determine the CDR, the administration of memory tests, and the administration of psychiatric tests for dementia, which are used to exclude a diagnosis of dementia. The results of these test may be considered in conjunction with other objective physical tests as described below. These means are also useful for assessing the efficacy of the methods of the invention in improving memory or decreasing or diminishing further impairment in memory or cognitive decline in a patient with MCI. Subjective and objective criteria can be used to measure and assess the success of a particular GR antagonist, pharmaceutical formulation, dosage, treatment schedule or regimen. The features (symptoms) of and criteria for diagnosing MCI are described, e.g., in Petersen et al., Arch. Neurol. 56:303-308, 1999.

[0049] The dementia treated in the methods of the invention encompasses a broad range of mental conditions and symptoms, as broadly described in the DSM-IV. While the practitioner can use any set of prescribed or empirical criteria to diagnose the presence of dementia as an indication to practice the methods of the invention, some illustrative diagnostic guidelines and examples of relevant symptoms and conditions are described below.

[0050] The DSM-IV states that dementias typically associated with Alzheimer's disease (dementia of the Alzheimer's type), "vascular dementia" (also known as multi-infarct dementia), or "dementia due to general medical conditions," e.g., human immunodeficiency virus (HIV-1) disease, head trauma, Parkinson's disease, or Huntington's disease (further

discussed, below). Dementias can also be "substance-induced persisting dementia," i.e., due to a drug of abuse, a medication, or toxin exposure, "dementia due to multiple etiologies," or a "dementia not otherwise specified" if the etiology is indeterminate.

[0051] Psychosis can be manifested as a mental illness in the form of a syndrome or as an element of a variety of disease processes. There are various means to diagnose these various forms of psychosis and assess the success of treatment. These means include classical psychological evaluations in addition to the various laboratory procedures described above. Such means are well-described in the scientific and patent literature, and some illustrative examples are provided below.

[0052] The psychosis ameliorated in the methods of the invention encompasses a broad range of mental conditions and symptoms, as broadly described in the DSM-IV (Kaplan, ed. (1995) supra). Psychosis can refer to a symptom associated with a general medical condition, a disease state or other condition, such as a side effect of drug abuse (a substance-induced disorder) or as a side effect of a medication. While the practitioner can use any set of proscribed or empirical criteria to diagnose the presence of a psychosis as an indication to practice the methods of the invention, some illustrative diagnostic guidelines and examples of relevant symptoms and conditions are described below.

[0053] Psychiatric conditions, such as psychosis, can be further diagnosed and evaluated using any of the many tests or criteria well-known and accepted in the fields of psychology or psychiatry.

[0054] The features (symptoms) of and criteria for diagnosing psychotic disorders, such as psychotic major depression, are further described DSM-IV, supra. While the practitioner can use any criteria or means to evaluate whether an individual is psychotic to practice the methods of the invention, the DSM-IV sets forth a generally accepted standard for such diagnosing, categorizing and treating of psychiatric disorders, including psychosis. Several illustrative examples of such criteria utilized in the methods of the invention are set forth below.

[0055] Psychosis is typically characterized as a mental disorder or condition causing gross distortion or disorganization of a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others to the degree of interfering with his capacity to cope with the ordinary demands of everyday life. In a condition or illness involving psychosis, delusions or hallucinations can be present. The content of the delusions

or hallucinations have many depressive themes. In psychotic major depression there can be "mood-congruent" psychotic features, including, for example, delusions of guilt, delusions one deserves punishment (e.g. because of a personal inadequacy or moral transgression), nihilistic delusions (e.g. of world or personal destruction), somatic delusions (e.g. having cancer), or delusions of poverty. Hallucinations, when present in psychotic major depression are usually transient and not elaborate and may involve voices that berate the patient for shortcomings or sins. More rarely, the content of the delusions or hallucinations has no apparent relationship to depressive themes. In this situation these "mood-incongruent" psychotic features include, for example, grandiose delusions.

[0056] Psychosis can also include bipolar I disorder with psychotic features, brief psychotic disorder, delusional disorder, shared psychotic disorder, substance induced psychotic disorder and psychotic disorder not otherwise specified.

B. Formulations of Mifepristone

[0057] Formulations of the present invention include mifepristone in combination with pharmaceutical excipients. Mifepristone is commercially available from a variety of sources such as Eurolabs Ltd. (London, England). Mifepristone can also be synthesized by one of skill in the art using known synthetic procedures.

[0058] The term "mifepristone" refers to a family of compositions also referred to as RU486, or RU38.486, or 17-beta-hydroxy-11-beta-(4-dimethyl-aminophenyl)-17-alpha-(1-propynyl)-estra-4,9-dien-3-one), or 11-beta-(4dimethylaminophenyl)-17-beta-hydroxy-17-alpha-(1-propynyl)-estra-4,9-dien-3-one), or analogs thereof, which bind to the GR, typically with high affinity, and inhibit the biological effects initiated/ mediated by the binding of any cortisol or cortisol analogue to a GR receptor. Chemical names for RU-486 vary; for example, RU486 has also been termed: 11B-[p-(Dimethylamino)phenyl]-17B-hydroxy-17-(1-propynyl)-estra-4,9-dien-3-one; 11B-(4-dimethyl-aminophenyl)-17B-hydroxy-17A-(prop-1-ynyl)-estra-4,9-dien-3-one; 17B-hydroxy-11B- (4-dimethylaminophenyl-1)-17A-(propynyl-1)-estra-4,9-diene-3-one; 17B-hydroxy- 11B-(4-dimethylaminophenyl-1)-17A-(propynyl-1)-E; (11B,17B)-11- [4-dimethylamino)- phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one; and 11B- [4-(N,N-dimethylamino) phenyl]-17A-(prop-1-ynyl)-D-4,9-estradiene-17B-ol-3-one. Salts, hydrates and prodrug forms of mifepristone are also useful in the formulations of the present invention.

[0059] Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of mifepristone suspended in diluents, such as water, saline or PEG 400; (b) capsules, sachets or tablets, each containing a predetermined amount of the active ingredient, as liquids, solids, granules or gelatin; (c) suspensions in an appropriate liquid; and (d) suitable emulsions. Tablet forms can include one or more of lactose, sucrose, mannitol, sorbitol, calcium phosphates, corn starch, potato starch, microcrystalline cellulose, gelatin, colloidal silicon dioxide, talc, magnesium stearate, stearic acid, and other excipients, colorants, fillers, binders, diluents, buffering agents, moistening agents, preservatives, flavoring agents, dyes, disintegrating agents, and pharmaceutically compatible carriers. Lozenge forms can comprise the active ingredient in a flavor, e.g., sucrose, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin or sucrose and acacia emulsions, gels, and the like containing, in addition to the active ingredient, carriers known in the art.

[0060] The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form. The composition can, if desired, also contain other compatible therapeutic agents. Preferred pharmaceutical preparations can deliver the compounds of the invention in a sustained release formulation.

C. Administration of Mifepristone

[0061] The formulations of the present invention provide serum levels of mifepristone of at least 1300 ng/mL. The mifepristone utilized in the pharmaceutical method of the invention is administered at the initial dosage of about 0.001 mg/kg to about 1000 mg/kg daily. A daily dose range of about 0.01 mg/kg to about 500 mg/kg, or about 0.1 mg/kg to about 200 mg/kg, or about 1 mg/kg to about 100 mg/kg, or about 10 mg/kg to about 50 mg/kg, can be used. The dosages, however, may be varied depending upon the requirements of the patient and the condition being treated. The dose administered to a patient, in the context of the present invention, should be sufficient to effect a beneficial therapeutic response in the patient over time. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of a particular compound in a

particular patient. Determination of the proper dosage for a particular situation is within the skill of the practitioner.

[0062] Generally, treatment is initiated with six daily doses, with the blood levels tested on the day of the seventh daily dose in order to determine whether the dose used is providing a mifepristone blood level of at least 1300 ng/mL. The testing is also performed to ensure the blood levels are below those afforded by an LD50 dose of about 1000mg/kg. If the mifepristone blood level is lower than 1300 ng/mL. Additional testing of mifepristone blood levels can be necessary in order to confirm a mifepristone blood level of at least 1300 ng/mL or to adjust the mifepristone daily dose higher. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired. In addition, the interval from initiation of treatment and testing for mifepristone blood levels can be as short as 1 daily dose, or up to 28 daily doses and longer.

[0063] Mifepristone can be administered for any period of time, such as 7 daily doses over a period of seven days. Mifepristone can also be administered using more daily doses over a longer period of time, such as via 28 daily doses over a period of 28 days. Longer times for administration of mifepristone are also within the scope of the present invention.

D. Assay for Testing Mifepristone Levels

[0064] Mifepristone levels can be determined by any method known in the art. Methods for detecting mifepristone levels include, but are not limited to, radio-immuno assay and mass spectrometry (MALDI, SELDI, LS/MS, LS/MS/MS, among others). Liquid chromatography mass spectrometry (LC/MS or LC-MS) separates compounds chromatographically before they are introduced to the ion source and mass spectrometer. It differs from GC/MS in that the mobile phase is liquid, usually a combination of water and organic solvents, instead of gas. Most commonly, an electrospray ionization source is used in LC/MS.

[0065] Tandem mass spectrometry (MS/MS) involves multiple steps of mass selection or analysis, usually separated by some form of fragmentation. A tandem mass spectrometer is one capable of multiple rounds of mass spectrometry. For example, one mass analyzer can isolate one peptide from many entering a mass spectrometer. A second mass analyzer then stabilizes the peptide ions while they collide with a gas, causing them to fragment by collision-induced dissociation (CID). A third mass analyzer then catalogs the fragments

produced from the peptides. Tandem MS can also be done in a single mass analyzer over time as in a quadrupole ion trap. There are various methods for fragmenting molecules for tandem MS, including collision-induced dissociation (CID), electron capture dissociation (ECD), electron transfer dissociation (ETD), infrared multiphoton dissociation (IRMPD) and blackbody infrared radiative dissociation (BIRD). One of skill in the art will appreciate that other assays for testing mifepristone levels are known to one of skill in the art.

[0066] In some embodiments, the assay can be performed as follows. Blood is collected from a patient in a vacutainer containing sodium heparin. The blood is centrifuged and the resulting plasma frozen at an appropriate temperature until assay. In some embodiments, the temperature is about -70 °C. In other embodiments, other blood components can be collected and stored. Prior to analysis, the plasma is thawed and a fraction of the plasma is mixed with an internal standard in a solvent such as acetonitrile, to obtain a fixed concentration of the standard. In some embodiments, the internal standard can be mifepristone-d_4. The concentration of the internal standard is selected in order to be greater than the expected concentration of mifepristone in the plasma. For example, the internal standard can have a concentration of 2000 ng/mL. One of skill in the art will appreciate that other internal standards, and other concentrations, are useful in the present invention.

[0067] Base is then added to the sample solution. The base can be any amine or ammonium base, such as ammonium hydroxide. One of skill in the art will appreciate that other bases are useful in the present invention.

[0068] Solvent is then added to the solution and the mifepristone (along with the internal standard) are extracted from the plasma. Solvents useful for the extraction of mifepristone include, but are not limited to, hexanes, pentanes, ethers (such as diethylether, tetrahydrofuran and methyl-t-butyl ether (MTBE)), ethyl acetate, chloroform and methylene chloride. One of skill in the art will appreciate that other solvents are useful in the present invention.

[0069] Following separation and concentration of the organic layer, the sample is reconstituted in a solvent mixture comprising water, acetonitrile and formic acid. The ratio of the solvent components can vary. In some embodiments, the solvent mixture is water:acetonitrile:formic acid (75:25:0.1, v/v/v). One of skill in the art will appreciate that other solvent mixtures are useful in the present invention.

[0070] The sample can then be analyzed by reverse-phase high pressure liquid chromatography (HPLC). In some embodiments, the reverse-phase HPLC is performed using a water:acetonitrile:formic acid (60:40:0.1) mobile phase (isocratic) at a flow rate of 0.3 mL/min. One of skill in the art will appreciate that other mobile phases and flow rates are useful in the present invention.

[0071] The reverse-phase HPLC column can be a phenyl column maintained at 50°C. Mifepristone elutes at 4.2 minutes. Following elution, the mobile phase can be nebulized using heated nitrogen in a Z-spray source/interface and the ionized compounds detected using a tandem quadrupole mass spectrometer. Mifepristone (molecular weight of 430 g/mol) can be detected at m/z 372.30. The internal standard mifepristone-d_4 can be detected at m/z 376.30. The ratio of the mifepristone peak height to the peak height for the internal standard can then be calculated.

[0072] The plasma concentration of mifepristone is then calculated by comparing the experimental ratio to a standard curve of mifepristone:mifepristone-d_4 peak height ratio v. mifepristone concentration. The standard curve is generated by first measuring the mifepristone:mifepristone-d_4 peak height ratios for mifepristone samples at 10, 20, 50, 100, 200, 500, 1000 and 2000 ng/mL where the mifepristone-d_4 internal standard has a concentration of 2000 ng/mL. The mifepristone:mifepristone-d_4 peak height ratios of these known solutions are then fit to a power equation (Mass Lynx by Micromass, Beverly, MA), against which future samples with unknown concentrations of mifepristone are compared.

[0073] The plasma levels of mifepristone derivatives such as RU42633, RU42698 and RU42848, among others, can also be determined using the assay described above.

E. Kits for Treating Mental Disorders with Mifepristone

[0074] The present invention provides kits. The kits of the present invention comprise seven daily doses and a plasma sampling collection device. The kits of the present invention can also comprise any other component necessary for a kit, such as a container.

[0075] Patient plasma can be collected by any known plasma collection device. Some plasma collection devices useful in the present invention include, but are not limited to, vacutainers. The plasma collection devices of the present invention can optionally comprise additives in the device, such as anticoagulants (EDTA, sodium citrate, heparin, oxalate), a gel

with intermediate density between blood cells and blood plasma, particles causing the blood to clot, a gel to separate blood cells from serum, thrombin and fluoride, among others.

[0076] The kits can also contain additional vessels used for further analysis of the plasma. For example, when the plasma is centrifuged, the centrifuged plasma can be transferred to a vessel, such as a cryostat tube. One of skill in the art will appreciate that other vessels and containers are useful in the present invention.

IV. Examples

Example 1: Determination of Mifepristone Plasma Level

[0077] This example provides a procedure for determining the plasma level of mifepristone in a patient.

[0078] Three (3) mL of blood was collected from a patient in a vacutainer containing sodium heparin. The blood was centrifuged and the resulting plasma frozen at -70 to -80°C until assay. For analysis, the plasma samples were warmed and prepared as follows:

1. Using a pipette, 50.0 µL of the sample was aliquoted into a 16 x 100-mm glass test tube. When a partial volume aliquot was needed, the aliquot was added to the tube and diluted to full volume with blank human plasma.
2. 20.0 µL of the internal standard, mifepristone-d_4 (5.00 µg/mL in acetonitrile), was added to the tube, resulting in 2000.0 ng/mL mifepristone-d_4 in plasma.
3. The tube was vortexed for approximately 1 minute.
4. 50.0 µL of 6% ammonium hydroxide was added to the tube.
5. The tube was vortexed for approximately 1 minute.
6. 2.00 mL of MTBE was added to the tube.
7. 2.00 mL of hexane was added to the tube.
8. The tube was vortexed for at least 15 minutes.
9. The tube was centrifuged for at least 10 minutes at 2500 RPM (575 x g).
10. The aqueous layer was frozen in a freezer set to maintain -70°C.
11. The upper organic layer was poured into a 13 x 100-mm polypropylene tube.
12. The organic layer was evaporated in a Turbovap set to 40°C.
13. 200.0 µL of a solution of water:acetonitrile:formic acid (75:25:0.1, v/v/v) was added to the tube.
14. The tube was vortexed for approximately 1 minute.
15. The tube was sonicated for approximately 1 minute.
16. The tube was vortexed for approximately 1 minute.

17. The sample was transferred to a labeled injection vial or well plate.
18. The vial or plate was capped and checked for air bubbles.

[0079] The sample was then analyzed by reverse-phase high pressure liquid chromatography using a water:acetonitrile:formic acid (60:40:0.1) mobile phase (isocratic) at a flow rate of 0.3 mL/min. The column was a phenyl column maintained at 50°C. Mifepristone elutes at 4.2 minutes. Following elution, the mobile phase was nebulized using heated nitrogen in a Z-spray source/interface and the ionized compounds detected using a tandem quadrupole mass spectrometer. Mifepristone (molecular weight of 430 g/mol) was detected at m/z 372.30. The internal standard mifepristone-d_4 was detected at m/z 376.30. The ratio of the mifepristone peak height to the mifepristone-d_4 peak height was calculated.

[0080] The plasma concentration of mifepristone was then calculated by comparing the experimental ratio to a standard curve of mifepristone:mifepristone-d_4 peak height ratio v. mifepristone concentration. The standard curve was generated by first measuring the mifepristone:mifepristone-d_4 peak height ratios for mifepristone samples at 10, 20, 50, 100, 200, 500, 1000 and 2000 ng/mL where the mifepristone-d_4 internal standard has a concentration of 2000 ng/mL. The mifepristone:mifepristone-d_4 peak height ratios of these known solutions were then fit to a power equation (Mass Lynx by Micromass, Beverly, MA), and the sample with unknown concentrations of mifepristone was compared.

Example 2: Phase III Trial with three dose levels of CORLUX™

[0081] This example provides a randomized, double-blind, placebo-controlled, parallel group study of the safety and efficacy of three dose levels of CORLUX™ (Mifepristone) plus an antidepressant vs. placebo plus an antidepressant in the treatment of psychotic symptoms in patients with major depressive disorder with psychotic features (PMD).

[0082] The study was a Phase III trial performed using several investigators at several different sites. The objectives were to demonstrate the efficacy and safety of three dose levels of CORLUX (mifepristone) combined with an antidepressant compared to placebo combined with an antidepressant in the treatment of psychotic symptoms in patients with Major Depressive Disorder with Psychotic Features (PMD).

[0083] The number of patients was less than 440. Patients eligible for randomization were male or nonpregnant female outpatients, and inpatients, if clinically required, with a diagnosis of Major Depressive Disorder with Psychotic Features (DSM-IV 296.24 or 296.34),

and a BPRS Positive Symptom subscale score of at least 12, a BPRS total score of at least 38, and a HAMD-24 score of at least 20.

[0084] CORLUX was used as the test drug at 300 (1x300mg tablet), 600 (2x300mg tablet), and 1200 mg (4x300mg tablet) once a day by mouth for the initial 7 days. Appropriate numbers of active and placebo tablets will be given to all dose groups so that each patient takes a total of 4 tablets at each daily dose. The reference drug was a placebo (1, 2, or 4 tablets matching CORLUX 300 mg tablets) once a day by mouth for the initial 7 days.

[0085] Up to 440 patients were randomly assigned to receive CORLUX 300, 600, or 1200 mg/day or placebo (in a 1:1:1:1 ratio) each day for 7 days. An antidepressant selected from a prescribed list was started simultaneously with the study drug, and continued to the end of the trial. BPRS and HAM-D assessments were performed at Screen and on Days 0, 7, 14, 28, 42, and 56, and at early termination when it occurred. Safety visits occurred at Days 21 and 35. The patients who are seen as outpatients made daily visits to the clinic setting to receive study medications for the first 7 days. If clinically necessary, a patient was treated as an inpatient.

[0086] In addition to the selected antidepressant, continuing benzodiazepines was allowed up to specified dose levels, but antipsychotics, mood stabilizers and additional antidepressants were not allowed during the entire study. If the patient was at imminent risk to him/herself and/or others and therefore could not be adequately treated within the study (e.g., required ECT, new or re-hospitalization for PMD, antipsychotics or mood stabilizers, or a second antidepressant), the patient underwent an early termination visit on the day that rescue therapy was started and completed final efficacy evaluations. If early termination occurred prior to day 35, the patient returned for a safety follow up visit at day 35.

[0087] The primary efficacy endpoint was the proportion of patients with at least a 50% reduction from baseline of the BPRS Positive Symptom Subscale (PSS) scores at Days 7 and 56. The secondary endpoints were: (1) the proportion of responders at days 7 and 28; and (2) the mean change from baseline to day 56 in the HAM-D-24 total score.

[0088] Adverse events, laboratory assessments including electrocardiograms, and physical examination were used to assess safety.

[0089] The criteria for assessing study efficacy objective was the proportion of patients with a reduction of at least 50% from baseline in BPRS Positive Symptom Subscale scores at Days 7 and 56.

Example 3: Phase III Trial for study of the efficacy and safety of CORLUX™

[0090] This example provides an international, double-blind, placebo-controlled study of the efficacy and safety of CORLUX™ (Mifepristone) vs. placebo in the treatment of psychotic symptoms in patients with Psychotic Major Depression (PMD).

[0091] The study was a Phase III trial performed using several investigators at several different international sites. The objective of the trial was to demonstrate the efficacy and safety of CORLUX (mifepristone) combined with an antidepressant compared to placebo combined with an antidepressant in the treatment of psychotic symptoms in patients with Major Depressive Disorder with Psychotic Features (PMD).

[0092] The number of patients was 220 evaluable subjects. Patients eligible for randomization were male or non-pregnant female outpatients, or inpatients, if necessary for patient well-being, with a diagnosis of Major Depressive Disorder with Psychotic Features (ICD-10 F32.3 or F33.3 or DSM-IV 296.24 or 296.34). At the screening and baseline visits, patients demonstrated the following severity of illness: BPRS Positive Symptom Subscale (PSS) score $\geq$ 12; BPRS total score $\geq$ 38, and HAMD-24 total score $\geq$ 20.

[0093] CORLUX was administered in a 600 mg dose once a day by mouth for the initial 7 days (administered as two 300mg tablets). Reference drug, dose, dosage regimen, route of administration: Matching placebo was administered once a day by mouth for the initial 7 days.

[0094] Up to 280 patients were randomly assigned (1:1 ratio) to receive either CORLUX 600 mg/day or placebo daily for 7 days. After the 7-day dosing period, patients were evaluated at Days 14, 21, 28, 35, 42 and 56. An antidepressant was administered simultaneously with study drug, and continued to the end of the trial (Day 56). BPRS and HAMD-24 assessments were performed at Screen and on Days 0, 7, 14, 28, 42 and 56, or at early termination. A safety visit occurred on Days 21 and 35, and at study termination on Day 56. Subjects treated on an outpatient basis made daily visits to the clinic to receive study medication for the first 7 days. Subjects were treated on an inpatient basis for as long as deemed clinically necessary by the investigator.

[0095] In addition to the selected antidepressant, concomitant benzodiazepine treatment was allowed up to specified dose levels. Antipsychotics, mood stabilizers and a second antidepressant were prohibited during the entire study. If the patient was at imminent risk to

him/herself and/or others and therefore could not be adequately treated within the study (i.e., required ECT, new or re-hospitalization for PMD, antipsychotics or mood stabilizers, or a second antidepressant), the patient underwent an early termination visit on the day that rescue therapy was started, and completed procedures listed for the day 56 termination visit, including final efficacy evaluations. If early termination occurred prior to day 35, the patient returned for a safety follow-up visit at regularly scheduled day 35.

[0096] The Primary efficacy endpoint was determined by the proportion of patients with ≥ 50% reduction from baseline on the BPRS-PSS at Days 7 and 28. Key secondary efficacy endpoints include (1) the proportion of patients with ≥ 50% reduction from baseline on the BPRS-PSS at Days 7 and 56; and (2) change from baseline on the HAMD-24 at Day 56.

[0097] Adverse events, laboratory assessments including electrocardiograms, and physical examination were used to assess safety.

Example 4: Treatment of Male Patient with PMD

[0098] A 50 year-old male, weighing 175 pounds, presents to physician with psychotic major depression (PMD). The physician prescribes 300 mg of mifepristone for seven daily doses over a period of seven days. One week later on the day of the seventh daily dose, three (3) mL of blood are collected from the patient and analyzed as described above in the specification. The dose of mifepristone is then adjusted, if necessary, to achieve mifepristone blood levels of greater than 1300 ng/mL. The mifepristone dose can be adjusted a single time to achieve mifepristone blood levels of greater than 1300 ng/mL. Alternatively, several adjustments to the mifepristone dose can be necessary to safely achieve mifepristone blood levels of greater than 1300 ng/mL.

[0099] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference.

WHAT IS CLAIMED IS:

1. A method for optimizing levels of mifepristone in a patient suffering from a mental disorder amenable to treatment by mifepristone, the method comprising:

treating the patient with seven or more daily doses of mifepristone over a period of seven or more days;

testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/mL; and

adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

2. The method of claim 1, wherein the mental disorder is a member selected from the group consisting of a stress disorder, delirium, mild cognitive impairment (MCI), dementia, psychosis and psychotic major depression.

3. The method of claim 2, wherein the stress disorder is a member selected from the group consisting of Acute Stress Disorder, Post-Traumatic Stress Disorder and Brief Psychotic Disorder with Marked Stressor(s).

4. The method of claim 1, wherein each of the seven or more daily doses of mifepristone are administered orally.

5. The method of claim 1, wherein the patient is treated with 28 or more daily doses over a period of 28 or more days.

6. The method of claim 1, wherein the testing is performed by a plasma sampling collection device suitable for detecting mifepristone serum levels.

7. The method of claim 1, wherein the adjusting step comprises increasing the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

8. A kit for treating a mental disorder amenable to treatment by mifepristone, the kit comprising:

seven daily doses of mifepristone; and

a plasma sampling collection device suitable for detecting mifepristone serum levels.

OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS

ABSTRACT OF THE DISCLOSURE

The present invention provides a method for optimizing levels of mifepristone in a patient suffering from a mental disorder amenable to treatment by mifepristone. The method comprises the steps of treating the patient with seven or more daily doses of mifepristone over a period of seven or more days; testing the serum levels of the patient to determine whether the blood levels of mifepristone are greater than 1300 ng/mL; and adjusting the daily dose of the patient to achieve mifepristone blood levels greater than 1300 ng/mL.

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Figure 1.

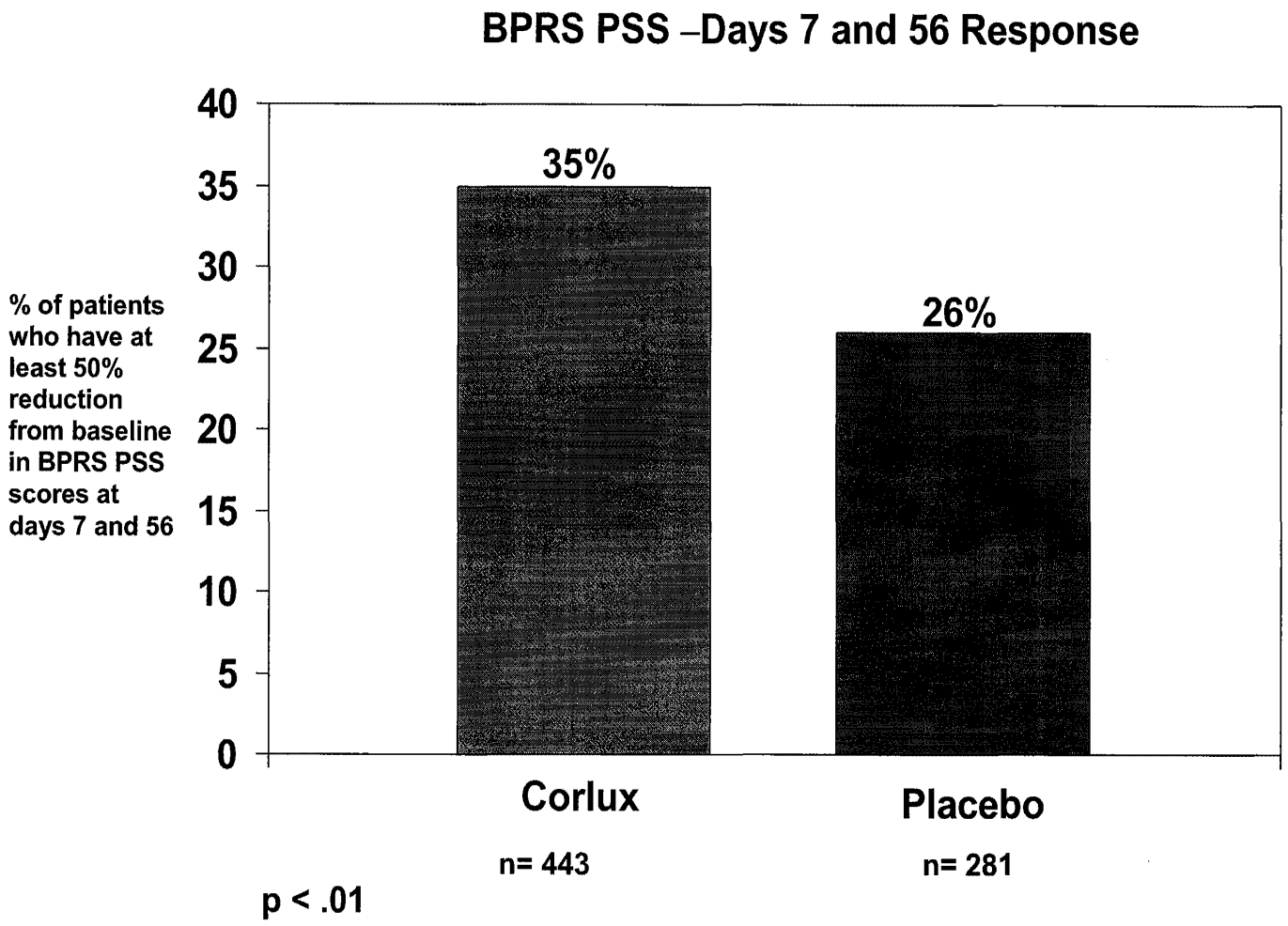
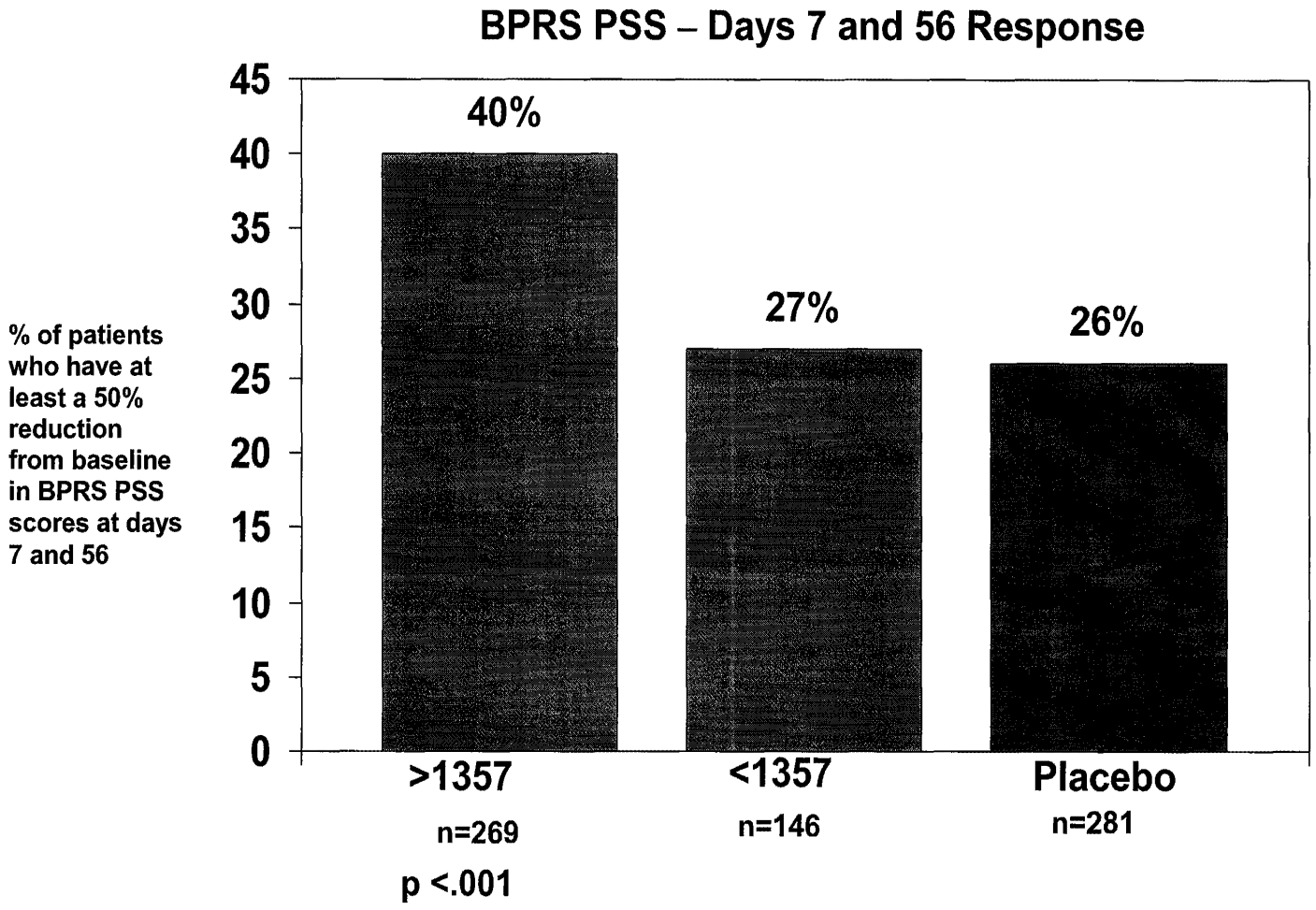

BPRS PSS –Days 7 and 56 Response
% of patients who have at least 50% reduction from baseline in BPRS PSS scores at days 7 and 56
40
35
30
25
20
15
10
5
0
35%
26%
Corlux
Placebo
n= 443
n= 281
p < .01

Figure 2.


BPRS PSS – Days 7 and 56 Response
% of patients who have at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56
45
40
35
30
25
20
15
10
5
0
40%
27%
26%
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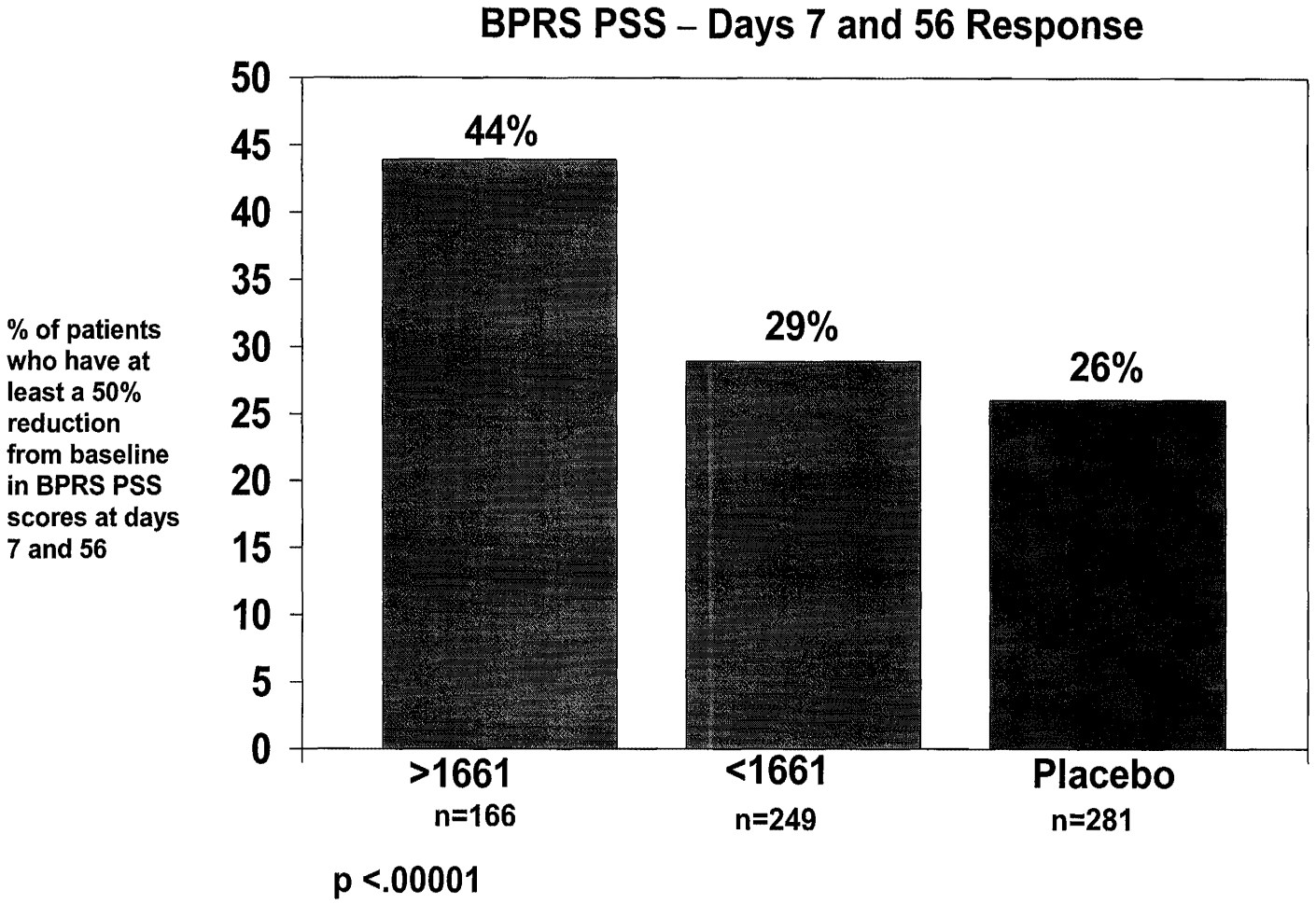
Placebo
n=281
p <.001

Figure 3.


BPRS PSS – Days 7 and 56 Response
% of patients who have at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56
50
45
40
35
30
25
20
15
10
5
0
44%
29%
26%
>1661
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Placebo
n=281
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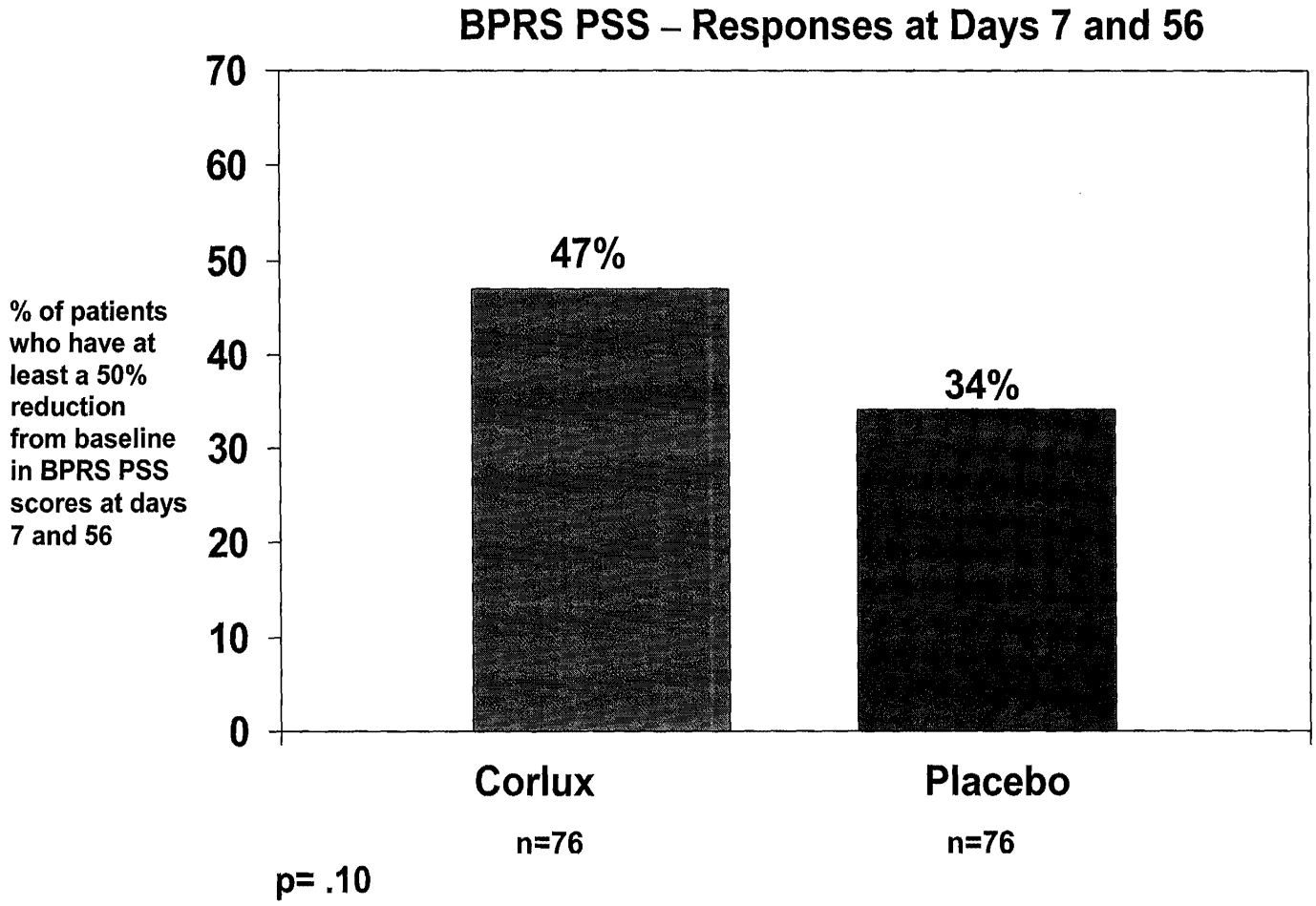
Figure 4.


BPRS PSS – Responses at Days 7 and 56
% of patients who have at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56
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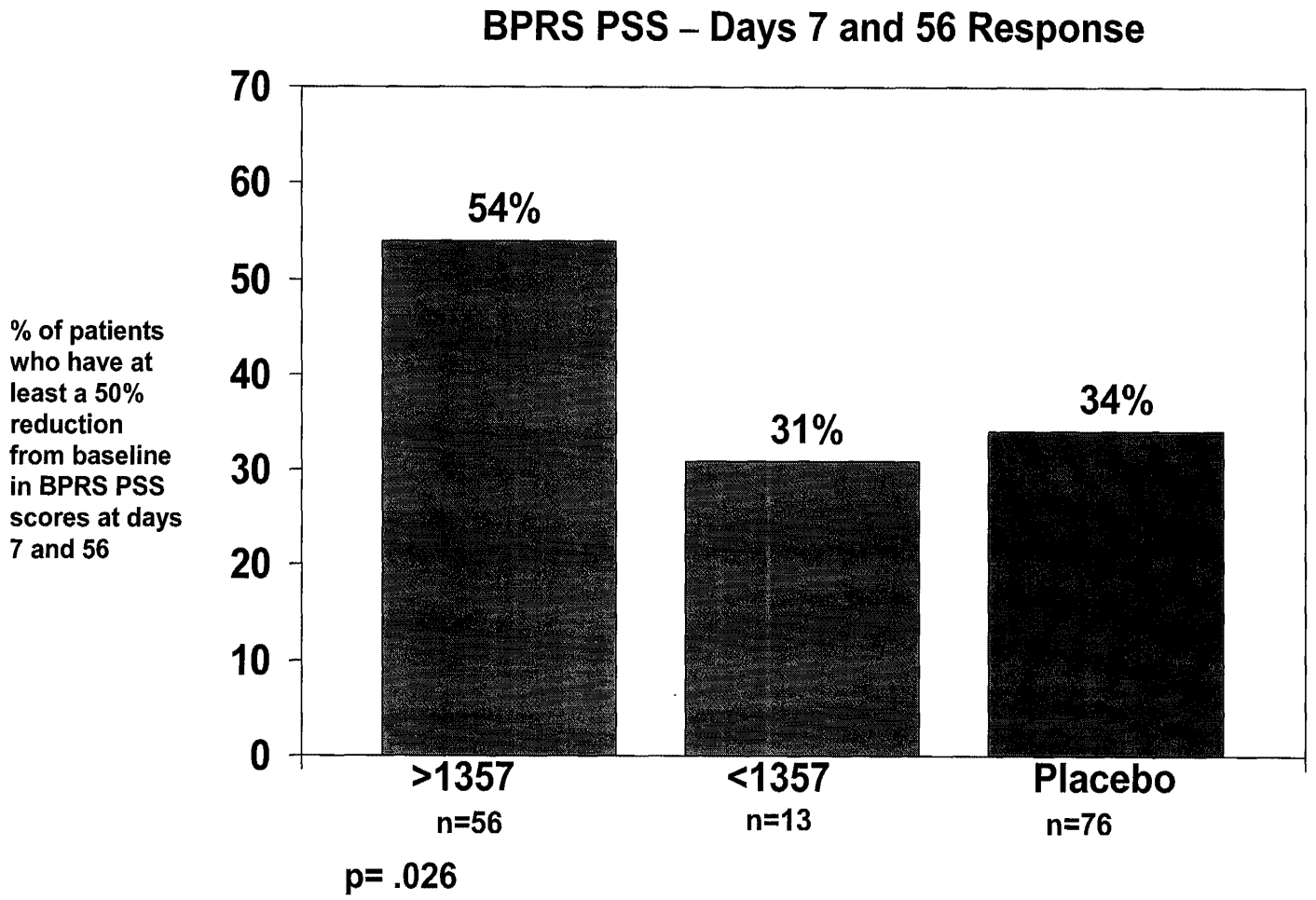
60
50
40
30
20
10
0
47%
34%
Corlux
Placebo
n=76
n=76
p= .10

Figure 5.


BPRS PSS – Days 7 and 56 Response
% of patients who have at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56
70
60
50
40
30
20
10
0
54%
31%
34%
>1357
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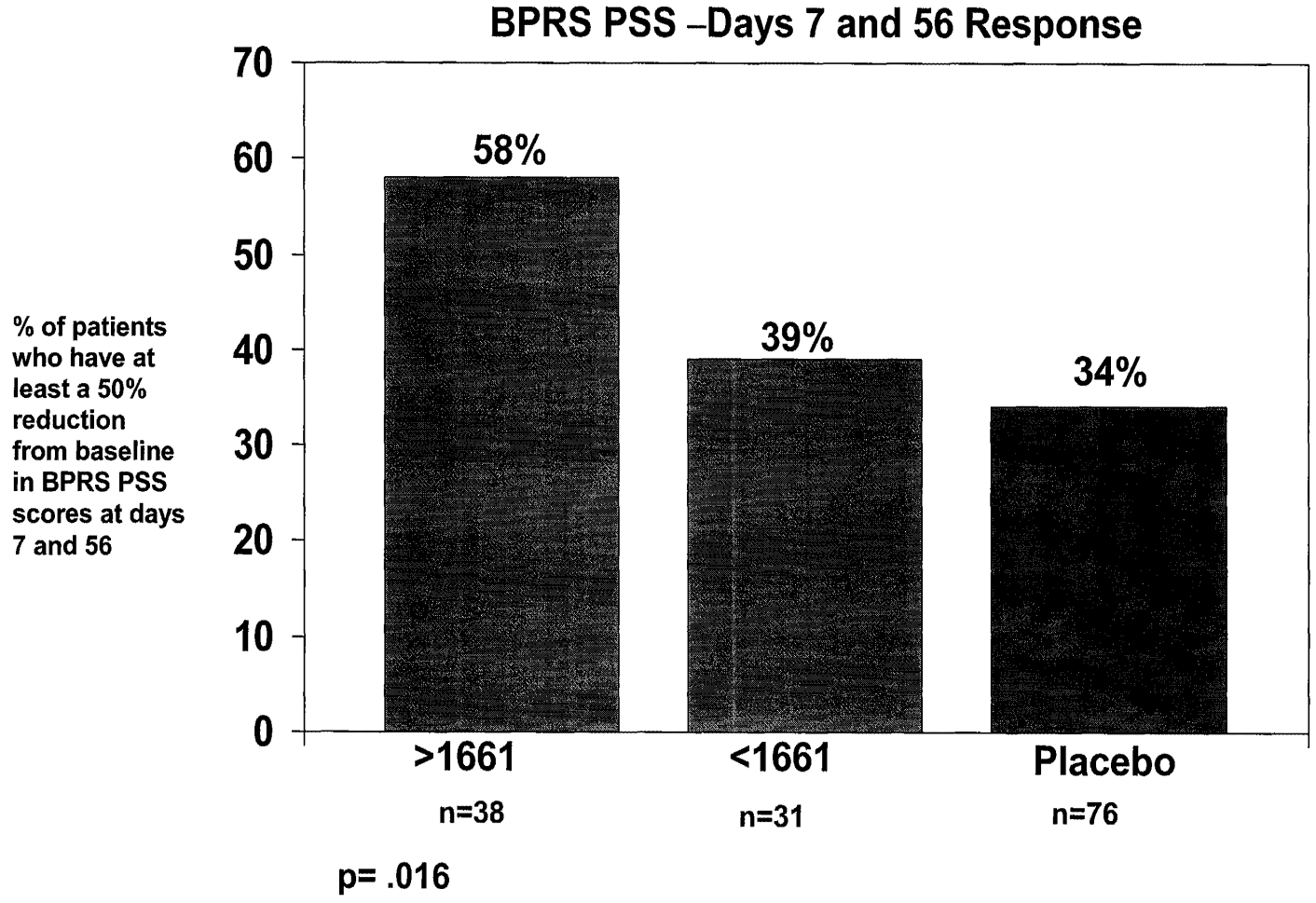
<1357
n=13
Placebo
n=76
p= .026

Figure 6.


BPRS PSS –Days 7 and 56 Response
% of patients who have at least a 50% reduction from baseline in BPRS PSS scores at days 7 and 56
70
60
50
40
30
20
10
0
58%
39%
34%
>1661
<1661
Placebo
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Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	OPTIMIZING MIFEPRISTONE LEVELS IN PLASMA SERUM OF PATIENTS SUFFERING FROM MENTAL DISORDERS TREATABLE WITH GLUCOCORTICOID RECEPTOR ANTAGONISTS
First Named Inventor/Applicant Name:	Joseph K. Belanoff
Filer:	Alexander Reed Trimble/Patricia Andrews
Attorney Docket Number:	019904-004110US
Filed as Small Entity	

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	75	75
Utility Search Fee	2111	1	255	255
Utility Examination Fee	2311	1	105	105
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
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EFS ID:	3846183
Application Number:	12199114
International Application Number:	
Confirmation Number:	5376
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First Named Inventor/Applicant Name:	Joseph K. Belanoff
Customer Number:	20350
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Receipt Date:	27-AUG-2008
Filing Date:	
Time Stamp:	14:13:24
Application Type:	Utility under 35 USC 111(a)

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Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$435
RAM confirmation Number	8389
Deposit Account	201430
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees) Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)					
File Listing:					
Document Number	**Document Description**	**File Name**	**File Size(Bytes)/ Message Digest**	**Multi Part /.zip**	**Pages (if appl.)**
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Information:					
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Information:					
		Total Files Size (in bytes):	2297055		

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PTO/SB/06 (12-04)
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PATENT APPLICATION FEE DETERMINATION RECORD
Substitute for Form PTO-875

Application or Docket Number
12/199,114

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	**75**		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	**255**		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	**105**		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	**8** minus 20 =		X$ 25		OR	X$50	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	**2** minus 3 =	*	X$105			X$210	
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $260 ($130 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			185			370	
			TOTAL	**435**		TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDI-TIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDI-TIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X =		OR	X =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X =		OR	X =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDI-TIONAL FEE ($)	OR	RATE ($)	ADDI-TIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X =		OR	X =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X =		OR	X =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))					N/A		OR	N/A	
					TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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