CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-896/S-006

ADMINISTRATIVE DOCUMENTS

DUPLICATE

Roche

August 14, 2000

Food and Drug Administration
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research
1451 Rockville Pike, Woodmont II Building
Rockville, MD 20852

SUPPL NEW CORRESP
X R

Ladies and Gentlemen:

Re: NDA 20-896 - Xeloda® (capecitabine) Tablets
Patent Information Update

Pursuant to revised 21 USC 505(b) and 21 CFR 314, Hoffmann-La Roche Inc. herewith submits updated Patent Information for Xeloda® (capecitabine) Tablets, approved under NDA 20-896.

The United States Patent and Trademark Office has granted a 796 days extension of the term of US Patent No. 4,966,891, covering the above drug product. The new expiration date of the patent is January 13, 2011.

The submission updates the patent information previously submitted in NDA 20-896, October 27, 1997 and the September 20, 1999 Supplemental NDA.

It is our understanding that the above information will be included in the next revision of the Approved Prescription Drug Products List (Orange Book).

If you have any questions regarding this submission, please feel free to contact the undersigned.

Sincerely,

HOFFMANN-LA ROCHE INC.

Murad Husain
Program Director
Drug Regulatory Affairs
Phone: 973-235-4578
Fax: 973-562-3700Attachment

HLR No.: 2000- 1982
MH/emd

Desk-copy (Fedex): US Food and Drug Administration
Center for Drug Evaluation and Research
Division of Data Management and Services
Drug Information Services Team
HFD-93 Room #235
Nicholson Lane Research Center
5516 Nicholson Lane, Building A
Kensington, MD 20895

cc: Patent Law Department

REVISED PATENT ATTACHMENT

First US Patent Number: 5,472,949

Expiration Date: December 14, 2013

Type of Patent-Indicate all that apply (check applicable boxes):

1.	Drug Substance (Active Ingredient)	[X]	Y	[ ]	N
2.	Drug Product (Composition/Formulation)	[X]	Y	[ ]	N
3.	Method of Use	[X]	Y	[ ]	N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that is covered by patent:

Method of treating tumors.

Name of Patent Owner: Hoffmann-La Roche Inc.

US Agent (if patent owner or applicant does not reside or have place of business in the US):

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 5,472,949 covers the composition, formulation and/or method of use of Xeloda® (capecitabine). This product is:

[X] currently approved under the Federal Food, Drug, and Cosmetic Act.

OR

[ ] the subject of this application for which approval is being sought.)

Second US Patent Number: 4,966,891

Expiration Date: January 13, 2011

Type of Patent-Indicate all that apply:

1.	Drug Substance (Active Ingredient)	[X]	Y	[ ]	N
2.	Drug Product (Composition/Formulation)	[X]	Y	[ ]	N
3.	Method of Use	[X]	Y	[ ]	N

If patent claims method(s) of use, please specify approved uses or uses for which approval is being sought that is covered by patent:

Method of treating carcinoma.

Name of Patent Owner: Hoffmann-La Roche Inc.

US Agent (if patent owner or applicant does not reside or have place of business in the US):

The following declaration statement is required if the above listed patent has Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 4,966,891 covers the composition, formulation and/or method of use of Xeloda® (capecitabine). This product is:

[X] currently approved under the Federal Food, Drug, and Cosmetic Act.)

OR

[ ] the subject of this application for which approval is being sought.)

By: _____
Name: Patricia S. Rocha-Tramaloni
Date: August 2, 2000
Title: Senior Counsel
Telephone Number: (973)235-2441

101132

EXCLUSIVITY SUMMARY FOR NDA # 20-896 SUPPL #006

Trade Name XELODA Tablets Generic Name capcitabine
Applicant Name: HL Roche HFD-150
Approval Date If Known ___4-30-01_____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /_X__/

b) Is it an effectiveness supplement?

YES /__X_/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE-1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____N/A_____

_____N/A_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____N/A_____

_____N/A_____

Form OGD-011347 Revised 10/13/98
cc: Original NDA 20-896 Division File HFD-150 HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety? _____NO_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X__/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /__X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /__X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _20-896_____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /__X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /__X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /__X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

SO 14795

SO 14796

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /__X_/

Investigation #2 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

__SO 14795_____ _____

_ SO 14796_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for

the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # [_____] YES /__X_/	NO /___/ Explain: _____
	_____
Investigation #2	
IND # [_____] YES /_X__	NO /___/ Explain: _____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are

purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/

Maureen A. Pelosi, Project Manager /9-6-00

Concur: Alison Martin, MD Team Leader / 9-6-00
Concur: John Johnson,MD for R. Pazdur, MD, Div Director/9-6-00

cc: Original NDA 20-896 SE1-006
HFD-150/Division File
/Pelosi
HFD-93 Mary Ann Holovac

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____

/S/ 9-6-00

Signature of Preparer Date

Title: Project Manager

Concur: ALISON MARTIN: /S/ Date: 9-6-00

Concur: /S/ MD 9-6-00

Signature of Office or Division Director Date

for Richard Pazdur, MD

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20896	**Trade Name:**	XELODA (CAPECITABINE)TABS 150MG/500MG
Supplement Number:	6	**Generic Name:**	CAPECITABINE
Supplement Type:	SE1	**Dosage Form:**	TAB
Regulatory Action:	PN	**Proposed Indication:**	First-line chemotherapy in patients with advanced or metastatic colorectal cancer

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	
Studies Needed	
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Waiver was granted 9/23/99

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MAUREEN PELOSI

/S/ 9-7-00

Signature Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20896	**Trade Name:**	XELODA (CAPECITABINE)TABS 150MG/500MG
Supplement Number:	6	**Generic Name:**	CAPECITABINE
Supplement Type:	SE1	**Dosage Form:**	TAB
Regulatory Action:	PN	**Proposed Indication:**	metastatic colorectal cancer

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Waiver was granted 9/23/99

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, MAUREEN PELOSI

/S/ _____ 2/1/00

Signature Date

DEBARMENT CERTIFICATION

Hoffmann-La Roche Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Financial Disclosure Comments – See Medical Review

2 pages redacted from this section of the approval package consisted of draft labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached list.	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Dr. Don Maclean	Vice Presdident of Drug Regulatory Affaris
FIRM/ORGANIZATION Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, NJ 07110	
SIGNATURE	**DATE** September 17, 1999

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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CLINICAL TEAM LEADER REVIEW OF SNDA

NDA 20896 / S006

APPLICANT Hoffman La-Roche, Inc.

DRUG Xeloda (Capecitabine) Tablets

DATE RECEIVED September 20, 2000

PROPOSED INDICATION "as first-line treatment of patients with metastatic colorectal carcinoma"

REGULATORY HISTORY

On April 30, 1998 Xeloda received accelerated approval for "the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline may be contraindicated, e.g., patients who have received cumulative doses of 400 mg/m2 of doxirubicin or doxirubicin equivalents." Phase 4 commitments are pending. The Xeloda recommended dose is 2500 mg/m2 orally daily in two divided dose approximately 12 hours apart for 2 weeks followed by a one week rest period before the next cycle. Cycles are repeated every three weeks. This same Xeloda regimen was used in the two pivotal randomized controlled trials in advanced metastatic colorectal cancer.

REGULATORY CONSIDERATIONS

Efficacy Endpoints

For initial treatment of advanced metastatic colorectal cancer the efficacy endpoint used as the basis of approval by the FDA is survival. Secondary efficacy endpoints such as tumor response (tumor shrinkage), tumor response duration, time to tumor progression and progression free survival may be supportive, but alone are not sufficient for FDA approval.

Standard Treatment

Until recently the standard treatment for this condition was the combination of 5-FU (FU) and leucovorin (LV). In the past year the combination of FU + LV + Camptosar has been shown to produce better survival than FU + LV and has been approved by the FDA.

The two randomized controlled trials (RCTs) in this SNDA compared Xeloda with the standard at the time the trials were initiated (FU + LV). The basis of approval of Xeloda would be equivalent survival to FU + LV. Because Camptosar + FU + LV has been shown to be better than FU + LV, the question arises whether equivalent survival to an inferior regimen (FU + LV) is an adequate basis for approval of Xeloda.

The NCI Cancer Cooperative Groups have adopted the Camptosar + FU + LV regimen as their standard for future clinical trials. However, in practice many oncologists are said to continue using FU + LV as initial treatment because they do not like the toxicity of Camptosar. Many of them will use Camptosar after failure of the FU + LV regimen. Actually this is the approach that was beaten by the Camptosar + FU + LV regimen in RCTs because many of the patients on the FU + LV control arm in those RCTs got secondary therapy with Camptosar after failure of FU + LV.

Non-inferiority Analysis

Non-inferiority analyses are sometimes used when a new agent is being compared to standard effective therapy. Ideally in oncology it is better to add the new agent to standard effective therapy to improve efficacy. But sometimes this is not feasible.

As used by the FDA non-inferiority has two important components. First, the new agent is not worse than the standard effective therapy. Second, the new agent is effective. Depending on the criteria applied, the first component can be present without the second and this has led to much confusion outside the FDA.

The confusion arises when time to event efficacy endpoints, such as survival, are used. For most advanced metastatic solid tumors most of the survival time would occur without any treatment. Only a modest proportion of the survival time is attributable to standard effective treatment.

To assess the second component of non-inferiority (that the new agent is effective) we need to know how much of the survival time is attributable to the standard effective treatment. We can then decide how much of the

survival time attributable to standard effective treatment must be retained by the new agent to justify declaring the new agent non-inferior and therefore effective. This latter decision is a clinical judgement and will vary depending on the type of efficacy of the standard effective regimen. For example, if the standard effective treatment is curative in a significant proportion of patients, we would require the new agent to retain a greater proportion of the treatment effect of the standard treatment than where there are no cures and most of the patients die relatively soon.

In this SNDA the review team and the Internal Working Group on Non-Inferiority Analyses in Clinical Trials in Advanced Incurable Cancer have used a standard requiring Xeloda to retain at least 50% of the survival effect of standard treatment (FU/LV) for approval. This is a low standard. A new treatment approved by the FDA using this low standard becomes the new legal standard. If each new treatment may be 50% worse than the present standard treatment, after two or three generations of such approvals most or all of the original efficacy may be lost. The new drug should have an important non-efficacy advantage to justify use of this low standard. (See OVERALL DISCUSSION below).

The amount of survival effect attributable to the standard effective therapy can not be ascertained from the clinical trials comparing the new agent to the standard effective therapy. A third treatment arm using a placebo or no-treatment would be needed and this may be unethical. Thus we must look to previous clinical trials for this information. We are unusually fortunate in this SNDA to have ten RCTs assessing the survival effect of the standard effective regimen (FU + LV). We do not have RCTs comparing the standard FU + LV regimen to placebo or to no treatment. So we must use RCTs comparing FU alone to FU + LV. FU alone is not shown to have any effect on survival. Thus a comparison of FU alone to FU + LV probably reflects the full effect of FU + LV on survival.

Pooling Results of Two Pivotal Trials for Efficacy Analysis

As always when one trial succeeds and another trial fails to succeed, the question arises whether to pool the patients in the two RCTs for efficacy analysis. It seems this is advocated where it will obscure the fact that one of the trials failed to succeed, but it is not advocated where it would obscure the fact that one of the trials succeeded. Pooling for efficacy analysis lowers the usual FDA standard. The two pivotal trials in this SNDA were designed as separate trials with separate hypotheses and separate statistical analyses with the Type I error rate controlled below a specified level for each trial. Pooling the two trials for further efficacy analysis violates the statistical integrity because the Type I error of the pooled trials can not be assessed. In

addition, if it is necessary to pool the two trials for efficacy analysis to achieve a successful result, there is no confirmatory trial.

Thus pooling of the two pivotal trials for efficacy analysis should require justification by an important non-efficacy advantage for Xeloda.

PIVOTAL CLINICAL TRIALS IN THIS SNDA

There are two essentially identical RCTs in this SNDA. There are 605 patients in one RCT and 602 patients in the other RCT. Patients were receiving initial treatment for advanced metastatic colorectal cancer. Xeloda 2500 mg/m2 daily in two divided doses for 14 days with 7 days off repeated every 3 weeks was compared with LV 20 mg/m2 IVB followed by FU 425 mg/m2 IVB daily for 5 days repeated every 4 weeks.

EFFICACY RESULTS OF PIVOTAL CLINICAL TRIALS IN THIS SNDA

Tumor response rates are statistically significantly better for Xeloda than the FU + LV control in both RCTs (21% vs 11% , p=0.0014 and 21% vs 14%, p=0.027, respectively).

Time to tumor progression is similar for Xeloda and the FU + LV control in both RCTs (4.3 mo. vs 4.4 mo. and 4.7 mo. vs 4.4 mo., respectively).

The following Table shows the results of the survival analyses.

	Study #14695		Study #14 796	
	Xeloda N=302	FU/LV N=303	Xeloda N=301	FU/LV N=301
Median Survival Time	12.7 mo.	13.6 mo.	13.5 mo.	12.3 mo.
Number Deaths (%)	260 (86%)	273 (90%)	261 (87%)	272 (90%)
HR (Xeloda:FU/LV)	1.00		0.92	
HR 95% CI	(0.84, 1.18)		0.78, 1.09)	
≥ 50% FU/LV Survival Effect Retained	NO (9.6% retained)		YES (61% retained)	
Any FU/LV Survival Effect Retained	YES		YES	

DISCUSSION OF EFFICACY RESULTS OF PIVOTAL TRIALS

Some have argued that equivalent tumor response rates should be a sufficient basis for declaring non-inferiority and approving new agents where the active moiety of both the standard treatment and the new agent is FU. Of course Xeloda requires absorption and then conversion to FU.

I disagree with this approach because tumor response correlates so poorly with survival in this disease. The studies in this SNDA support my position. Although Xeloda had a much better tumor response rate than FU/LV, this was not reflected even slightly in the time to tumor progression or survival results.

The much better tumor response rates with Xeloda provide weak support, but would not be sufficient alone as the basis for FDA approval.

The FDA Xeloda review team and the internal FDA Working Group on Non-inferiority Analyses in Clinical Trials in Advanced Incurable Cancer have focused on retention by the new agent of at least 50% of the survival effect of the standard effective therapy as the minimum requirement for FDA approval. This is a low standard and it is hard to imagine a situation where a lesser standard would be appropriate. Certainly retention of ANY of the survival effect of the standard effective treatment is too low a standard for FDA approval.

The standard for approval requiring the new drug to retain at least 50% of the survival effect of the standard treatment is a low standard and should require justification by an important non-efficacy advantage of the new drug in each case where it is applied (See OVERALL DISCUSSION below).

In one RCT Xeloda retains at least 61% of the FU/LV survival effect. In the other RCT Xeloda retains at least 9.6% of the FU/LV survival effect.

As always when one trial succeeds and another trial fails to succeed, the question arises whether to pool the patients in the two RCTs for efficacy analysis. It seems this is advocated where it will obscure the fact that one of the trials failed to succeed, but it is not advocated where it would obscure the fact that one of the trials succeeded. Pooling for efficacy analysis lowers the usual FDA standard. The two pivotal trials were designed as separate trials with separate hypotheses and separate statistical analyses with the Type I error controlled below a specified level for each trial. Pooling the two trials for further efficacy analysis violates the statistical integrity because the Type I error for the pooled trials can not be assessed. In addition, if it is necessary

to pool the two trials for efficacy analysis to achieve a successful result, there is no confirmatory trial.

Thus there should be some important non-efficacy advantage to justify pooling of the two trials for efficacy analysis, e.g., there are non-efficacy factors such as less toxicity or patient convenience. Because the protocols for the two RCTs were essentially the same, from that standpoint there are fewer problems with pooling for efficacy analysis here than usual.

After pooling results of the two RCTs Xeloda retains at least 63% of the FU/LV survival effect.

SAFETY RESULTS OF PIVOTAL TRIALS IN THIS SNDA

The two pivotal RCTs were pooled for safety analysis. This is acceptable. Median drug exposure on Xeloda and the FU/LV control was 139 days and 140 days, respectively.

The following Table shows the FDA medical officer review of the incidence, severity and relationship of adverse events to study drug.

Incidence, Severity and Relationship of Adverse Event to Study Drug

	Capecitabine N = 596	5-FU/LV N = 593
[redacted]		
• All Grades No. of pts with at least one AE Total No. of AEs	574 (96.3%) 4919	559 (94.3%) 4890
• Grade 3 No. of pts with at least one AE Total No. of AEs	312 (52.3%) 612	268 (45.2%) 512
• Grade 4 No. of pts with at least one AE Total No. of AEs	54 (9.1%) 73	53 (8.9%) 83
[redacted]		
• All Grades No. of pts with at least one AE Total No. of AEs	532 (89.3%) 3009	528 (89.0%) 3310
• Grade 3 No. of pts with at least one AE Total No. of AEs	227 (38.1%) 342	202 (34.1%) 350
• Grade 4 No. of pts with at least one AE Total No. of Aes	18 (3.0%) 27	30 (5.1%) 46

Vol.33, p.82 and Appendix 15 in vol. 34

The following Table shows the FDA medical officer review of deaths on treatment or within 28 days of stopping drug.

Deaths on or within 28 Days of Treatment

	Capecitabine N = 596	5-FU/LV N = 593
Total	*50 (8.4%)*	*32 (5.4%)*
Death on Study	*19 (3.2%)*	*2 (0.3%)*
CVA	*1*	-
Cerebral Hemorrhage	*1*	-
GI Necrosis, GI Hemorrhage, Cerebral hemorrhage	*3*	-
PE	*2*	-
Sudden Death	*1*	-
MI, Cardiac Failure	*3*	-
Sepsis	*1*	-
Pneumonia/Sepsis	*1*	-
PD	*7*	*2*
Death within 28 Days	*31 (5.2%)*	*30 (5.0%)*
PD	*19*	*14*
Sepsis	*3*	*3*
Respiratory Failure, ARDS, URI	-	*3*
PE	*1*	*3*
MI, CAD, Cardiac Failure	*3*	*2*
CVA	*2*	-
Intestinal Obstruction	*0*	*2*
Enterocolitis, UGI Hemorrhage	*1*	*1*
Electrolyte: Hyperosmolar, Hypokalemia	*1*	*1*
Renal Tubular Necrosis	-	*1*

Appendix I: Listing of Deaths, vol. 36, p.1-3

The following Table shows the Applicant's results for the incidence of Grade 3-4 or Grade 4 Laboratory Events.

Incidence of Laboratory Events Representing a Grade 3-4 or Grade 4 Value

Lab Parameter	Capecitabine				5-FU/LV			
	Grade 3-4 N (%)		Grade 4 N (%)		Grade 3-4 N (%)		Grade 4 N (%)	
ALAT (SGPT)	3	0.50	0	-	4	0.67	0	-
ASAT (SGOT)	4	0.67	0	-	7	1.18	0	-
Alk Phos	20	3.36	1	0.17	24	4.05	0	-
Calcium (Hyper)	4	0.67	3	0.50	1	0.17	1	0.17
Calcium (Hypo)	4	0,67	1	0.17	1	0.17	0	-
Glucose (Hyper)	38	6.38	2	0.34	23	3.88	1	0.17
Glucose (Hypo)	2	0.34	2	0.34	1	0.17	0	-
Granulocytes	1	0.17	1	0.17	12	2.02	5	0.84
Hemoglobin	12	2.01	1	0.17	10	1.69	2	0.34
Lymphocytes	219	36.74	45	7.55	223	37.61	47	7.93
Neutrophils	13	2.18	9	1.51	125	21.08	76	12.82
Platelets	6	1.01	3	0.50	2	0.34	1	0.17
Potassium	6	1.01	1	0.17	2	0.34	0	-
S. Creatinine	5	0.84	2	0.34	0	-	0	-
Sodium	6	1.01	0	-	2	0.34	1	0.17
Total Bilirubin	136	22.82	27	4.53	35	5.90	15	2.53
WBC	8	1.34	2	0.34	69	11.64	20	3.37

Vol. 33, p. 136

The following Table shows the FDA medical officer results of adverse events occurring in ≥ 5% of patients regardless of relationship to the drug.

Percent Incidence of AE Irrespective of Cause in ≥ 5% of Patients

Body System/ Adverse Event	Capecitabine N = 596			5-FU/LV N = 593		
	Total	Gr 3	Gr 4	Total	Gr 3	Gr 4
GI						
Diarrhea	52.9	12.2	1.5	59.5	10.5	1.9
Nausea	42.8	4.0	-	50.6	2.7	0.2
Vomiting	27.2	3.7	0.2	30.4	3.5	0.2
Stomatitis	24.8	2.0	0.2	61.7	14.2	0.5
Abdominal Pain NOS	25.0	6.5	-	21.4	3.4	-
Abdominal Pain Upper	12.1	1.7	-	9.4	1.7	-
Constipation	13.9	1.0	0.2	17.2	0.8	-
Dyspepsia	7.2	0.2	-	7.9	0.5	-
Flatulence	6.2	-	-	4.2	-	-
Dry Mouth	4.7	-	-	4.2	-	-
Skin & Subcutaneous						
Hand-Foot Syndrome	53.7	17.1	-	6.2	0.5	-
Dermatitis NOS	10.9	0.2	-	12.1	-	-
Dry Skin	7.7	0.2	-	5.9	0.3	-
Alopecia	6.0	-	-	21.1	0.2	-
Rash Erythematous	5.5	0.2	-	5.1	0.2	-
General						
Fatigue	26.0	2.0	-	28.7	1.9	-
Weakness	9.7	1.2	-	9.9	1.5	-
Lethargy	4.0	0.3	-	6.4	0.7	-
Asthenia	5.4	0.8	-	5.7	0.5	-
Pyrexia	17.4	1.0	-	20.7	1.7	-
Pain in Limb	8.2	0.3	-	5.2	0.5	-
Neurological						
Headache NOS	9.6	1.0	-	7.4	-	-
Dizziness (exc.vertigo)	8.4	0.3	-	7.6	0.2	-
Insomnia	7.2	-	-	6.9	-	-
Taste Disturbance	4.9	0.3	-	10.1	0.3	-
Metabolism						
A	12.8	1.0	-	16.4	0.8	-
anorexia	10.4	1.2	-	11.0	0.8	-
Appetite Decreased	7.0	2.0	0.2	7.9	2.7	0.5
Dehydration	6.0	0.2	-	9.3	0.3	-
Weight Decrease						
Eye						
Lacrimation Increased	7.4	-	-	5.6	-	-
Respiratory						
Dyspnea	10.6	1.0	-	7.9	0.3	0.3
Cough	7.2	0.2	-	7.6	-	-
Nasopharyngitis	4.7	-	-	3.7	-	-
Epistaxis	3.0	0.2	-	6.2	-	-
Sore Throat NOS	2.2	-	-	5.6	-	-
Infection						
UTI NOS	5.7	0.3	-	5.4	-	-
URINOS				5.1	0.2	-
Cardiac						
Edema Lower Limb	10.6	0.8	-	6.6	0.7	-
Vascular						
DVT, limb	5.0	2.0	0.3	2.9	1.7	-
Musculoskeletal						
Back Pain	10.1	1.5	-	9.1	0.3	-
Arthralgia	7.2			5.6	0.7	-

DISCUSSION OF SAFETY RESULTS OF PIVOTAL TRIALS

As indicated in the above Tables the most notable aspects of safety are that Xeloda has less stomatitis and neutropenia than the FU/LV control, but more hand foot syndrome and hyperbilirubinemia.

OVERALL DISCUSSION

Xeloda retains at least 62% of the survival effect of the standard treatment (FU/LV) in one RCT and 9.6% in the other RCT. If the two RCTs are pooled, Xeloda retains 63% of the survival effect of the standard treatment. The much better tumor response rate on Xeloda may provide some weak support for approval.

Xeloda has acceptable safety in this patient population. Xeloda has no overall clear safety advantage over the standard treatment (FU/LV).

Xeloda is an oral regimen, which many patients prefer. Of course this is contingent on their belief that Xeloda is as effective as the standard treatment.

The matter is further complicated because Camptosar + FU/LV has now been shown to produce better survival than the previous standard (FU/LV). Thus at best, Xeloda is non-inferior to an inferior regimen. We do not know whether Xeloda could be substituted for the FU/LV in the Camptosar + FU/LV regimen with acceptable safety and efficacy. The patient convenience of an oral regimen would be lost if this were done. Patients would have the combined inconvenience of the Camptosar infusions and the daily oral Xeloda.

Apparently some oncologists have not adopted the new Camptosar +FU/LV regimen, preferring to use FU/LV alone because of the Camptosar toxicity and perhaps using Camptosar alone after failure on the FU/LV regimen.

The FDA requirement that a new treatment for an advanced metastatic cancer with essentially no long term cure rate, but improved survival with standard treatment, retain at least 50% of the standard treatment survival effect for approval is a new standard that has not been previously used. It is a low standard for approval. The newly approved drug becomes the new legal standard for comparison with future new treatments. If each new drug may be 50% worse than the previous one, it is apparent that most or all of the efficacy could be lost after two or three generations of such approvals. Thus

there should be some important compensatory non-efficacy advantage when this standard is used for drug approval.

Pooling of the two pivotal clinical trials for efficacy analysis should also require justification by an important non-efficacy advantage for Xeloda. The two pivotal trials were designed as separate trials with separate hypotheses and separate statistical analyses with the Type I error for each trial controlled below a specified level. Pooling the two studies for efficacy analysis violates the statistical integrity because the Type I error for the pooled trials can not be assessed. In addition, if the two trials must be pooled to achieve successful results, there is no confirmatory trial.

The important non-efficacy advantage for Xeloda that justifies using the low standard of retaining at least 50% of the survival effect of the standard treatment and pooling of the two pivotal clinical trials for efficacy analysis is that many patients consider Xeloda more convenient than the standard treatment because it is an oral regimen.

RECOMMENDATION

This SNDA is approvable with labeling revisions (See labeling revised by the FDA review team).

The following Phase 4 commitments by the Applicant are required.

- Update of the survival analyses after a total of 1180 deaths has occurred in the two randomized controlled trials (SO 14695 and SO 14796).
- Submit results of clinical trials in advanced metastatic colorectal cancer studying Xeloda in combination with irinotecan (_____) when completed.

/S/ MD

John R. Johnson, M.D.
September 19, 2000

CSO NDA LABELING REVIEW OF PACKAGE INSERT

NDA: 20-896 / SE1-006

DATE OF RESUBMISSION: October 31, 2000

DATE OF REVIEW: January 9, 2001

DRUG: Xeloda (capecitabine) Tablets

SPONSOR: Hoffman-La Roche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

This submission duplicates the clinical pharmacology data for renal insufficiency with proposed draft labeling for a contraindication in patients with severe renal impairment (creatinine clearance below 30 mL/min and warning for dose reduction in patients with moderate renal impairment (creatinine clearance below 30-50 mL/min) previously submitted as SLR-009 and reviewed by me on 11/13/00. It also provides for revised draft labeling for the colorectal cancer indication.

I have reviewed the labeling, compared it with the labeling that accompanied the Dear Doctor Letter (FA from supplement 009 reviewed by me on 12/11/00) and our labeling from the approvable letter. I found no changes other than those proposed in this resubmission.

The OCBP reviewer and the Medical Officer should determine whether these proposals are acceptable, or if not, what additional changes are required.

/S/ 1-9-01
Maureen A. Pelosi
Regulatory Project Manager

/S/ 1-9-01
Dotti Pease
Supervisor, Project Manager Staff

CC: Original NDA 20-896 /se1-006
HFD-150/Div File
/Martin, Rahman, Ibrahims, Pelosi

Electronic Mail Message

Date: 9/15/00 4:39:23 PM
From: Safaa Ibrahim (IBRAHIMS)
To: Maureen Pelosi (PELOSIM)
Cc: Alison Martin (MARTINA)
Cc: Atiqur Rahman (RAHMANA)
Subject: Re: Current label with spec pop changes

Maureen,

The following statement should be deleted from the "Renal Insufficiency" under the clinical pharmacology/special populations section.
>

DRAFT

The above statement could stay in the PRECAUTION section if Alison want it.

Alison, Safaa and Atik,
>
>The label entitled "clean" is clean except for Roche's changes to what Safaa sent on Wed for the speical population section. Safaa, see if their changes to your language is acceptable and let me know.
>
>The label revmode shows all their clinical section changes (proposals) to the approved labeling.
>
>Maureen

1 pages redacted from this section of the approval package consisted of draft labeling

TELECON MINUTES

TELECON DATE: 22 DEC 99 **TIME: 11 AM** **LOCATION:** Conference Rm B (2064)

NDA 20-896 / SE1-006 New Correspondence /SNC 10-26-99 (Request)
/SNC 11-2-99 (Briefing Doc)
/SNC 12-3-99 (New Question)

DRUG: Xeloda (capecitabine) Tablets

SPONSOR/APPLICANT: Roche

TYPE of TELECON: Bayesian Survival Analysis

FDA PARTICIPANTS:

Robert Justice, MD, Deputy Division Director
Julie Beitz, MD, Team Leader
Alison Martin, Medical Reviewer
Gang Chen, PhD, Biometrics Team Leader
David Smith, PHD, Biometrics Reviewer
Maureen Pelosi, RPh, Project Manager

INDUSTRY PARTICIPANTS:

Bruno Osterwalder, MD, Oncologist
Dvorit Samid, MD,Clinical Science, Oncology
Hans Ulrich Burger, PhD, Biometircs
Olga Rutman, PhD, Biometrics
Candice Shepherd, PharmD, Regulatory Affairs
Dr. Peter Teuber, Project Leader
Stefan Frings, MD, International Medical Director

TELECON OBJECTIVES:

1. To Discuss FDA questions on the package and Bayesian Survival Analysis
2. To address Roche questions in the package
3. To reach final agreement and discuss next steps

DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Does FDA agree with the use of M.A. Poon et al. (1989) as the basis for the selection of a prior information for β ?

FDA Response:

- The Poon article is relevant as one source of information in constructing a prior designation of β. As presented at ODAC, there are other relevant articles in the literature. Prior distribution should be based on a random-effects meta-analysis of the complete set of studies from the literature.

- FDA to fax the table to Roche.

2. Does the FDA agree with using the prior information for β as well as for γ ?

FDA Response:

- In a case such as this, where no prior information is available for γ, it seems more appropriate to choose a non-informative prior on γ. There is insufficient evidence that the sponsor's statement "capecitabine and 5-FU [do not] have identical activity for survival" is true based on either a superiority trial or a non-inferiority trial. A non-informative prior reflects the lack of information that we have for γ. The Bayesian analysis under the sponsor's proposed prior for γ may be useful to quantify the sensitivity of the model to the choice of prior.

- Dr. Burger believes that he has identified an error in Dr. Simon's paper. He will fax a description of the error found and FDA will discuss with Dr. Simon.

- If Dr. Burger is correct, question #2 will become a non-issue.

3. Should the resulting estimate for γ be standardized as proposed above?

FDA Response:

- This standardization may aid in interpretation of the posteriors. FDA suggests that both versions of the posterior (i.e., untransformed and standardized) be reported.

4. Should the proposed bayesian analysis also be performed for SO14796 (even though at least equivalence has been established for this study)?

FDA Response:

- Performing the proposed Bayesian analysis on SO14796 would be useful in terms of robustness and sensitivity of the model.

APPEARS THIS WAY
ON ORIGINAL

5. As recognized in our attached analysis plan, the bayesian survival analysis assumes that 1.0 is outside the limits of the confidence interval for the hazard ratio (HR). This would confirm statistically superior activity of the active control 5-FU/LV over 5-FU alone. However, in the paper of M.A. Poon et al (1989) 1.0 is within the limits of the 95% CI (lower limit 95% CI HR of 0.94, upper limit of 1.93). Given that the HR of the proposed prior information does not meet the assumed criteria of significant superiority (in contrast to the p value of the logrank test), how will this impact the Division's interpretation of the analysis results?

FDA Response:

- It is difficult to make a judgement on this at this time, as it will probably have to be addressed in the formal review, as well as subsequent conversations with experts.

6. Roche's proposal/question on safety update formatting is acceptable.

APPEARS THIS WAY
ON ORIGINAL

ACTION ITEMS: (Include description, identify person responsible and due date.)

1. **FDA faxed the following table to Roche on12-22-99:**

AUTHOR & CIT>	# OF PTS
Erlichman, 1988 JCO	130
Poon, 1989 JCO	140
Meta-Analysis, 1992 JCO	1381
Pallavincini, 1993 J Chemo	150
Borner, 1998 Ann Onc	309
Doroshow, 1990 JCO	79
Labianca, 1991 Ann Onc	182
DiCostanzo, 1992 Ann Onc	181
Leichman, 1995 JCO	174

2. **Dr. Simon's possible error from Dr. Burger:**

Electronic Mail Message

Date: 12/27/99 2:20:42 PM
From: David Smith
To: See Below
Subject: Clarification on your Bayesian Design and Analysis of Active Control Trials Paper
Hi Rich,

I had a discussion with Uli Burger, a Hoffman-La Roche statistician last week; during the course of our conversation, he brought up the point that there is a possible typo in your June 99 Biometrics article: "Bayesian Design and Analysis of Active Control Trials." I missed it when I first read your paper, but upon closer inspection and reading his reasoning, I believe that Uli may be right.

Could you take a look at this and please get back to me with respect to your findings? If prior information on g (in Uli's notation) is the only prior information necessary, it would greatly simplify a problem on which we're currently working.

Thanks, and I hope you enjoyed your holidays.

/S/
- David Smith
U.S. Food and Drug Admin.

PS Uli's write-up follows:

Notation and Problem:

g= log(HR) of exp treatment versus placebo (or other previous treatment)
b = log(HR) of active control versus placebo
y is an estimate of log(HR) of exp treatment verses active control, i.e. of g-b

Then formula (5) in the paper of Dr Simon states that the posteriori distribution for g is normal with mean y+g' in case g' is a prior information for g. Mean and variance of this normal distribution are further standardized by dividing each term by the corresponding variance.

We currently believe that the posteriori distribution is not y+g' but rather y+b' where b' denotes the prior information on b, i.e. that there is a typo in formula (5) such that b and g simply have to be exchanged.

In case this is true then only the result of the active control treatment and the prior information on b are needed to derive a posteriori estimate for g. Prior information on g would only be needed to update further the information on b which would be in our case irrelevant.

Justification:

1) y is an estimate for g-b and b can be dervied e.g. from a previous independent study with active control versus treatment. An easy estimate for g would then be achieved by y+b which is again normally distributed with expectation g-b+b = g. The correction factor here is b and clearly not g and the more generalized thinking behind bayesian analysis should be consistent with this.

2) Formula (2) in Dr Simon's paper has for the posteriori estimate of the mean of g in the term made up b and g also the addition of b and not g as a correction factor for the outcome of the active control experiment.

3) Consistent with this thinking Dr Simon used in his recent presentation at the Dec ODAC as well b as a correction factor and not g as in the paper in formula (5). (Actually he used them without standardizing y+b.)

Therefore, we currently believe that there is a typo in formula (5) and that b and g should be exchanged in that formula.

3. **Roche to propose a date for submission of the 4 month safety update.**

4. **Roche to confirm the expected lenth of time needed to do the literature search.**

The telecon was concluded at 12 noon. There were no unresolved issues or discussion points.

/S/

Maureen A. Pelosi
Project Manager
Minutes preparer

Concurrence: /S/

Alison Martin, MD, Medical Officer
Medical Officer