

Overview of ClinicalTrials.gov Reporting Requirements

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National Library of Medicine

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Rationale for Registry and Results Database

What's All The Fuss About?

- Suppression of research results impedes the scientific process in all areas of science
- Suppression of clinical trial data is particularly problematic
 - Trials depend on human volunteers
 - Trial results inform our medical decisions

Three Key Problems

- Not all trials are published
- Publications do not always include all prespecified outcome measures
- Unacknowledged changes are made to the trial protocol that would affect the interpretation of the findings
 - e.g., changes to the prespecified outcome measures

Reasons to Register Clinical Trials and Report Results

- Human Subject Protections
 - Allows potential participants to find studies
 - Assists ethical review boards and others in determining appropriateness of studies being reviewed (e.g., harms, benefits, redundancy)
 - Promote fulfillment of ethical responsibility to human volunteers – research contributes to medical knowledge
- Research Integrity
 - Facilitates tracking of protocol changes
 - Increases transparency of research enterprise
- Evidence Based Medicine
 - Facilitates tracking of studies and outcome measures
 - Allows for more complete identification of relevant studies
- Allocation of Resources
 - Promotes more efficient allocation of resources

ClinicalTrials.gov Background

History of ClinicalTrials.gov

- FDAMA* 113 (1997) mandates registry
 - Investigational New Drug application (IND) trials for serious and life-threatening diseases or conditions
- ClinicalTrials.gov launched in February 2000
- Calls for increased transparency of clinical trials
 - Maine State Law; State Attorneys General
 - International Committee of Medical Journal Editors (ICMJE) statement (2004)
- ClinicalTrials.gov accommodates other policies
- FDAAA† Section 801 (2007): Expands registry & adds results reporting requirements

* Food and Drug Administration Modernization Act of 1997

† Food and Drug Administration Amendments Act of 2007

ClinicalTrials.gov Features

- **One record per trial**
- **Registration information**
 - Submitted at trial initiation
 - Summarizes information from trial protocol
 - Includes recruitment information (e.g., eligibility, locations)
- **Results information**
 - Submitted after trial completion
 - Summarizes trial results
- **Sophisticated search capabilities**
 - Allows for efficient identification of trials meeting the user's criteria

ClinicalTrials.gov Statistics

(as of 2/28/2011)

	<u>Registration</u>	<u>Results</u>
Total	103,643	3,086
Type of Trial		
Observational	18,086 (17%)	188 (6%)
Interventional*	85,227 (82%)	2,898 (94%)
– Drug & Biologic	60,437	2,542
– Behavioral, Other	16,001	223
– Surgical Procedure	10,111	86
– Device**	9,015	229
International Sites (>170 countries)		
US only	46,234 (45%)	1,180 (38%)
Non-US only	40,336 (39%)	885 (29%)
US & Non-US mixed	6,474 (6%)	410 (13%)
Missing	10,599 (10%)	611 (20%)

*A study record may include more than one type of intervention

**330 applicable device clinical trials submitted, but qualify for “delayed posting” under FDAAA

Protocol Information

- Description of Study
 - Study Type, Phase, Design, Outcome Measures,
- Recruitment Information
 - Eligibility criteria, locations, recruitment status
- Administrative and other information
 - Key dates, key contact information
- NLM inserted links to help readers
 - Publications via Medline
 - Consumer health information (drugs, condition, etc)
 - FDA information (from public site)

Results Information

- Participant Flow
- Baseline and Demographic Characteristics
- Primary and Secondary Outcomes
- Adverse Event Information
- Other Information
 - “Certain Agreements” related to *Restrictions on Results Disclosure*
 - Overall Limitations and Caveats
 - Results Point of Contact

Clarifications about Results Reporting Requirements

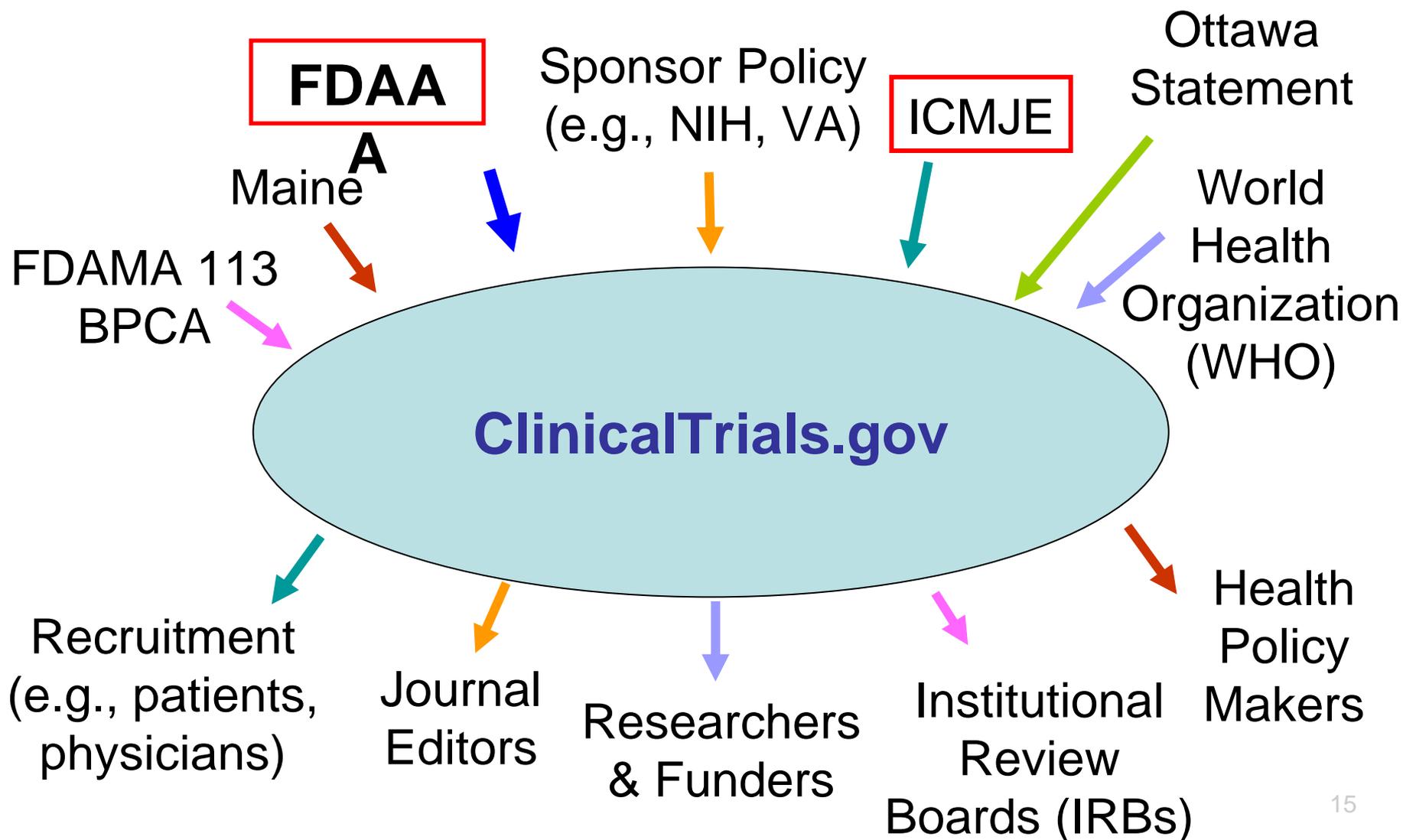
- Summary results at the end of the trial
 - No interim or “real time” reporting
 - No participant level reporting
- Information currently targeted at those who can understand the medical literature
 - “just the facts”
 - No conclusions or discussion
- Results reporting to ClinicalTrials.gov is independent of journal publication
 - Designed to complement, not replace, journal articles
 - Journals link to ClinicalTrials.gov via NCT #

Public Archive for Records

- Changes can and should be made to records
 - Estimated dates become “actual” dates
 - Estimated enrollment becomes “actual”
 - Other protocol changes
 - Overall recruitment status changes
 - Results may be added or changed
- All changes are publicly “tracked”

Key Policies and FDAAA

Policies and Users



FDAAA

Sec. 801. Expanded Clinical Trial Registry Data Bank

- Enacted on September 27, 2007
- Requires Trial Registration
- Requires Results Reporting
- Added enforcement provisions
 - Notices of non-compliance
 - Civil monetary penalties (up to \$10,000/day)
 - Withholding of NIH grant funds

Scope of Registration Policies

- ICMJE*
 - Interventional trials
 - All intervention types
 - All phases
- FDAAA**
 - Interventional trials
 - Drugs, biologics, devices
 - Not phase 1 drug or not small feasibility device
 - US FDA jurisdiction (e.g., IND/IDE or US site)

* Laine C, Horton R, DeAngelis C, et al. *Ann Intern Med.* 2007; http://www.icmje.org/faq_clinical.html

** <http://prsinfo.clinicaltrials.gov/fdaaa.html>

Results Reporting Policies— FDAAA

- Which Trials?
 - Interventional Trials
 - Drugs, biologics, devices
 - Once approved by FDA
 - Not phase 1 drug or not small feasibility device
 - US FDA jurisdiction (e.g., IND/IDE or US site)
- When?
 - Generally within 12 months of (primary) completion date
 - Delays possible

FDAAA Key Terms

- Applicable Clinical Trials (ACTs)
 - Interventional trials (with 1 or more arms)
 - Not phase 1; includes drug, biologic, or device
 - At least one site in U.S. (or IND/IDE)
- ACTs initiated on or after 9/27/07 or ongoing as of 12/26/07
- Responsible Party
 - Sponsor, grantee; OR
 - Principal Investigator (PI), if designated
- (Primary) Completion Date

Sample Posted Record*

*Adapted from NCT00312208

Search

Study 1 of 1 for search of: NCT00312208

[← Previous Study](#) [Return to Search Results](#) [Next Study →](#)

Full Text View

[Tabular View](#)

[Study Results](#)

[Related Studies](#)

Docetaxel in Breast Cancer

This study is ongoing, but not recruiting participants.

First Received: April 5, 2006 Last Updated: February 15, 2010 [History of Changes](#)

Sponsor:	Sanofi-Aventis
Collaborator:	Cancer International Research Group
Information provided by:	Sanofi-Aventis
ClinicalTrials.gov Identifier:	NCT00312208

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Collaborator:	Cancer International Research Group
Information provided by:	Sanofi-Aventis
ClinicalTrials.gov Identifier:	NCT00312208

Purpose

Primary objective :

- To compare disease-free survival after treatment with docetaxel in combination with doxorubicin and cyclophosphamide to doxorubicin and cyclophosphamide followed by docetaxel in operable adjuvant breast cancer HER2neu negative patients with positive axillary lymph nodes.

Secondary objectives :

- To compare toxicity and quality of life between the 2 above-mentioned arms.
- To evaluate pathologic and molecular markers for predicting efficacy.

<u>Condition</u>	<u>Intervention</u>	<u>Phase</u>
Breast Cancer	Drug: docetaxel, doxorubicin, cyclophosphamide Drug: Docetaxel,doxorubicin, cyclophosphamide	Phase III

Study Type: Interventional
Study Design: Allocation: Randomized
Control: Active Control

Health Topics

Drugs & Supplements

Videos & Cool Tools

ESPAÑOL

Other Topics: [A](#) [B](#) [C](#) [D](#) [E](#) [F](#) [G](#) [H](#) [I](#) [J](#) [K](#) [L](#) [M](#) [N](#) [O](#) [P](#) [Q](#) [R](#) [S](#) [T](#) [U](#) [V](#) [W](#) [XYZ](#) [All Topics](#)

Breast Cancer

Breast cancer affects one in eight women during their lives. Breast cancer kills more women in the United States than any cancer except lung cancer. No one knows why some women get breast cancer, but there are a number of risk factors. Risks that you cannot change include

- Age - the chance of getting breast cancer rises as a woman gets older
- Genes - there are two genes, BRCA1 and BRCA2, that greatly increase the risk. Women who have family members with breast or ovarian cancer may wish to be tested.
- Personal factors - beginning periods before age 12 or going through menopause after age 55

Other risks include being overweight, using hormone replacement therapy, taking birth control pills, drinking alcohol, not having children or having your first child after age 35 or having dense breasts.

Symptoms of breast cancer may include a lump in the breast, a change in size or shape of

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MEDICAL ENCYCLOPEDIA

[Breast biopsy](#)
[Breast biopsy -- stereotactic](#)

[Genetics Home Reference](#) related topics: [breast cancer](#)

[MedlinePlus](#) related topics: [Breast Cancer](#) [Cancer](#)

[Drug Information](#) available for: [Cyclophosphamide](#) [Doxorubicin](#) [Doxorubicin hydrochloride](#) [Docetaxel](#)

[U.S. FDA Resources](#)

Drugs@FDA

FDA Approved Drug Products

Start Over

Back to Search Results

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Drug and Device

[CDER](#) - Center for Drug Evaluation and Research
[CDRH](#) - Center for Drug Research and Evaluation
[CBER](#) - Center for Biologics Evaluation and Research

Drug Action Page

[Drugs@FDA](#) - drug
[New Drug Application](#)
[Licensed Product Approval](#)

Device Approval

[PMA CDRH](#) - device premarket approval applications
[PMA CBER](#) - biological device premarket approval applications
[510\(k\) CDRH](#) - device premarket notifications
[510\(k\) CBER](#) - biological device premarket notifications

Overview

Drug Name **CYCLOPHOSPHAMIDE**

Active Ingredient(s) • **CYCLOPHOSPHAMIDE**

Form(s) and Strength(s) Available • **INJECTABLE; INJECTION: 100MG/VIAL ; 1GM/VIAL ; 200MG/VIAL ; 2GM/VIAL ; 500MG/VIAL**
• **TABLET; ORAL: 25MG ; 50MG**

Details about drugs are organized by FDA Application Number (NDA or ANDA or BLA).

Click on a drug name or application number to view drug details:

Click on a column header to re-sort the table:

Drug Name and FDA Application Number	Dosage Form/Route	Strength	Marketing Status	Company
CYCLOPHOSPHAMIDE (ANDA # 040032)	TABLET; ORAL	Multiple Strengths	Prescription	ROXANE
CYCLOPHOSPHAMIDE (ANDA # 040745)	INJECTABLE; INJECTION	Multiple Strengths	Prescription	BAXTER HLTHCARE

[Genetics](#)

[MedlinePlus](#) related topics: [Breast Cancer](#) [Cancer](#)

Drug Information available for: [Cyclophosphamide](#) [Doxorubicin](#) [Doxorubicin hydrochloride](#) [Docetaxel](#)

[U.S. FDA Resources](#)

Full Text View

More Information

Additional Information

[Click here to find](#)

[More information](#)

Publications:

[Schneider LS, Tariot PN, Lyketsos GS, Dagerman RS, Davis CE, Hsiao JK, Jeste DV, Kane RL, Simpson J, Sneed SB, Rabins PV, Rosenheck RA, Small GW, Lebowitz B, Lieberman JA. National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness \(CATIE\): Alzheimer disease trial methodology. Am J Geriatr Psychiatry. 2001 Fall;9\(4\):346-60.](#)

[Schneider LS, Tariot PN, Lyketsos GS, Dagerman RS, Davis CE, Hsiao JK, Jeste DV, Kane RL, Simpson J, Sneed SB, Rabins PV, Rosenheck RA, Small GW, Lebowitz B, Lieberman JA. National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness \(CATIE\): Alzheimer disease trial methodology. Am J Geriatr Psychiatry. 2001 Fall;9\(4\):346-60.](#)

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 12, 2006 VOL. 355 NO. 15

Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease

Lon S. Schneider, M.D., Pierre N. Tariot, M.D., Karen S. Dagerman, M.S., Sonia M. Davis, Dr.P.H., John K. Hsiao, M.D., M. Saleem Ismail, M.D., Barry D. Lebowitz, Ph.D., Constantine G. Lyketsos, M.D., M.H.S., J. Michael Ryan, M.D., T. Scott Stroup, M.D., David L. Sultzer, M.D., Daniel Weintraub, M.D., and Jeffrey A. Lieberman, M.D., for the CATIE-AD Study Group*

ABSTRACT

CONCLUSIONS

Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease. (ClinicalTrials.gov number, NCT00015548.)

N ENGL J MED 355;15 WWW.NEJM.ORG OCTOBER 12, 2006

CONCLUSIONS: Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease. (ClinicalTrials.gov number, NCT00015548 [ClinicalTrials.gov]).

Copyright 2006 Massachusetts Medical Society.

Secondary Source ID:

ClinicalTrials.gov/NCT00015548

Docetaxel in Breast Cancer

This study is ongoing, but not recruiting participants.

Study NCT00312208 Information provided by Sanofi-Aventis

First Received: April 5, 2006 Last Updated: February 15, 2010 [History of Changes](#)

Tracking Information

First Received Date

April 5, 2006

[ICMJE](#)

Last Updated Date

February 15, 2010

Start Date

[ICMJE](#)

August 2000

Primary Completion Date

October 2008 (final data collection date for primary outcome measure)

Current Primary Outcome Measures

Local, Regional or Metastatic Relapse, or Second Primary Cancer, or Death From Any Cause
[Time Frame: Median follow-up 65 months]

[Designated as safety issue: No]

[ICMJE](#)

(submitted: February 15, 2010)

Original Primary Outcome Measures

Disease-Free Survival (DFS) [Time Frame: interval from the date of randomization to the date of local, regional or metastatic relapse or the date of second primary cancer (or death from any cause whichever occurs first)

[ICMJE](#)

(submitted: January 25, 2008)

Change History

[Complete list of historical versions of study NCT00312208 on ClinicalTrials.gov Archive Site](#)

Docetaxel in Breast Cancer

This study is ongoing, but not recruiting participants.

Study NCT00312208 Information provided by Sanofi-Aventis
Study First Received: April 5, 2006 Last Updated: February 15, 2010 [History of Changes](#)
Results First Received: October 29, 2009

Study Type:	Interventional
Study Design:	Allocation: Randomized; Control: Active Control; Endpoint Classification: Safety/Efficacy Study; Intervention Model: Parallel Assignment; Masking: Open Label; Primary Purpose: Treatment
Condition:	Breast Cancer
Interventions:	Drug: docetaxel, doxorubicin, cyclophosphamide Drug: Docetaxel,doxorubicin, cyclophosphamide

Participant Flow: Overall Study

	Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -> T)	Docetaxel + Doxorubicin and Cyclophosphamide (TAC)
STARTED	1649 ^[1]	1649 ^[2]
COMPLETED	1477	1526
NOT COMPLETED	172	123
Adverse Event	97	61
Protocol Violation	5	3
Death	2	1
Lack of Efficacy	7	4
Lost to Follow-up	3	5
Withdrawal by Subject	53	42
Not specified	5	7

Reasons Not Completed

[1] 1649 patients randomized, 1634 patients treated

[2] 1649 patients randomized 1635 patients treated

Baseline Measures

	Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -> T)	Docetaxel + Doxorubicin and Cyclophosphamide (TAC)	Total
Number of Participants [units: participants]	1649	1649	3298
Age, Customized [units: Participants]			
> =65 years	85	83	168
Between 65 and 50 years	784	783	1567
Between 49 and 35 years	689	710	1399
< =35 years	91	73	164
Age [units: years] Median (Full Range)	50 (22 to 74)	50 (24 to 72)	50 (22 to 74)
Gender [units: participants]			
Female	1649	1649	3298
Male	0	0	0
Region of Enrollment [units: participants]			

“Default” Required Measures

User-Specified Baseline Measures

Hormonal Receptor Status [units: Participants]			
Positive	1348	1346	2694
Negative	301	303	604
Karnofsky Performance Status at Baseline [units: Participants]			
80 - Activity with effort; some signs of disease	36	33	69
90 - Normal activity; minor signs of disease	315	323	638
100 - Normal no complaints; no evidence of disease	1298	1293	2591
Menopausal status [units: Participants]			
Pre-Menopausal or Other age < 50 Years	866	863	1729
Post-Menopausal or Other age > 50 Years	783	786	1569
Number of Positive Lymph Nodes [units: Participants]			
[0]	0	1	1
[1 to 3]	1010	1005	2015
[4 to 10]	462	456	918
> 10	177	187	364
Patients with at least one surgery [units: Participants]			
Mastectomy	955	973	1928
Lumpectomy	283	276	559
Quadrantectomy/Segmental	411	400	811
Primary Tumor [units: Participants]			
pT1: Tumor <= 2cm	692	668	1360
pT2: Tumor in [2 - 5]	824	844	1668
pT3: Tumor > 5cm	131	135	266
pT4: Tumor with extension to chest	4	0	0

Primary Outcome Measure

Local, Regional or Metastatic Relapse, or Second Primary Cancer, or Death From Any Cause

[Time Frame: Median follow-up 65 months]

Measured Values

	Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -> T)	Docetaxel + Doxorubicin and Cyclophosphamide (TAC)
Number of Participants Analyzed [units: participants]	1649	1649
Local, Regional or Metastatic Relapse, or Second Primary Cancer, or Death From Any Cause [units: Participants]	356	352

Statistical Analysis 1 for Local, Regional or Metastatic Relapse, or Second Primary Cancer, or Death From Any Cause

Groups ^[1]	All groups
Method ^[2]	Log Rank
P Value ^[3]	0.978
Hazard Ratio (HR) ^[4]	1.00
95% Confidence Interval	(0.86 to 1.16)

Secondary Outcome Measure

Death From Any Cause
[Time Frame: Median follow-up of 65 months]

Measured Values

	Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -> T)	Docetaxel + Doxorubicin and Cyclophosphamide (TAC)
Number of Participants Analyzed [units: participants]	1649	1649
Death From Any Cause [units: Participants]	187	202

Statistical Analysis 1 for Death From Any Cause

Groups ^[1]	All groups
Method ^[2]	Log Rank
P Value ^[3]	0.371
Hazard Ratio (HR) ^[4]	0.91
95% Confidence Interval	(0.75 to 1.11)

Serious Adverse Events

	Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -> T)	Docetaxel + Doxorubicin and Cyclophosphamide (TAC)
Total, serious adverse events		
# participants affected / at risk	331/1634 (20.26%)	520/1635 (31.80%)
Blood and lymphatic system disorders		
Anemia † ¹		
# participants affected / at risk	3/1634 (0.18%)	5/1635 (0.31%)
Coagulation disorders † ¹		
# participants affected / at risk	1/1634 (0.06%)	0/1635 (0.00%)
Hemorrhage Vaginal † ¹		
# participants affected / at risk	1/1634 (0.06%)	0/1635 (0.00%)
Leukopenia † ¹		
# participants affected / at risk	18/1634 (1.10%)	56/1635 (3.43%)
Lymphadenopathy † ¹		
# participants affected / at risk	0/1634 (0.00%)	1/1635 (0.06%)
Lymphedema † ¹		
# participants affected / at risk	0/1634 (0.00%)	2/1635 (0.12%)
Pancytopenia † ¹		
# participants affected / at risk	0/1634 (0.00%)	1/1635 (0.06%)
Thrombocytopenia † ¹		
# participants affected / at risk	0/1634 (0.00%)	1/1635 (0.06%)
Cardiac disorders		
Arrhythmia † ¹		
# participants affected / at risk	3/1634 (0.18%)	3/1635 (0.18%)
Arrhythmia Ventricular † ¹		

† Events were collected by systematic assessment

¹ Term from vocabulary, COSTART

Other Adverse Events

	Doxorubicin + Cyclophosphamide Followed by Docetaxel (AC -> T)	Docetaxel + Doxorubicin and Cyclophosphamide (TAC)
Total, other (not including serious) adverse events # participants affected / at risk	1634/1634	1629/1635
Blood and lymphatic system disorders		
Anemia † ² # participants affected / at risk	461/1634 (28.21%)	658/1635 (40.24%)
Epistaxis † ¹ # participants affected / at risk	123/1634 (7.53%)	72/1635 (4.40%)
Leucopenia † ¹ # participants affected / at risk	59/1634 (3.61%)	88/1635 (5.38%)
Lymphedema † ¹ # participants affected / at risk	101/1634 (6.18%)	109/1635 (6.67%)
Neutropenia † ² # participants affected / at risk	1133/1634 (69.34%)	1049/1635 (64.16%)

† Events were collected by systematic assessment

1 Term from vocabulary, COSTART

2 Term from vocabulary, NCI-CTCAE

Certain Agreements

“Whether there exists an agreement (other than an agreement solely to comply with applicable provisions of law protecting the privacy of participants) between the sponsor or its agent and the principal investigator (unless the sponsor is an employer of the principal investigator) that restricts in any manner the ability of the principal investigator, after the completion date of the trial, to discuss the results of the trial at a scientific meeting or any other public or private forum, or to publish in a scientific or academic journal information concerning the results of the trial.”

[Sec. 282(j)(3)(C)(iv)]

Certain Agreements:

Principal Investigators are **NOT** employed by the organization sponsoring the study.

There **IS** an agreement between Principal Investigators and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The agreement is:

- The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **less than or equal to 60 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.
- The only disclosure restriction on the PI is that the sponsor can review results communications prior to public release and can embargo communications regarding trial results for a period that is **more than 60 days but less than or equal to 180 days**. The sponsor cannot require changes to the communication and cannot extend the embargo.

Other disclosure agreement that restricts the right of the PI to discuss or publish trial results after the trial is completed.

- Restriction Description:** If no publication has occurred within 12 months of the completion of the study, the Investigator shall have the right to publish/present independently the results of the study. The Investigator shall provide the Sponsor with a copy of any such presentation/publication for comment at least 30 days before any presentation/submission for publication. If requested by the Sponsor, any presentation/submission shall be delayed up to 90 days, to allow the Sponsor to preserve its proprietary rights.

Protocol/Results Review Criteria

- Protocol and results must be clear and informative
- Review focuses on:
 - Logic and internal consistency
 - Apparent validity
 - Meaningful entries
 - Formatting

Basic Uses of ClinicalTrials.gov

- Identify trials of potential interest for specific individual
- Track progress of a specific trial, including access to summary results
- Identify all trials that are completed or ongoing for a given set of conditions/interventions
- Identify investigators and/or research centers of relevance to given set of conditions/interventions

Uses of ClinicalTrials.gov Aggregate Data

- Examination of the “Clinical Research Enterprise”
 - Clinical Trials Transformation Initiative (CTTI)
 - Creating and maintaining a research data set to facilitate use of data
- Providing information to specific user communities, e.g.,
 - breastcancertrials.org
- Examination of quality and completeness of reporting, e.g.,
 - Fidelity of reports to research protocol
 - Publication bias

Enhancements and Adaptability for Various Uses

Current and Planned ClinicalTrials.gov Features

- Accommodates Different Policies
 - ICMJE/WHO
 - State of Maine
 - Harmonization with EMA EudraCT results database
- Allows for Disclosure Broader than FDAAA
 - All intervention types (e.g., behavioral interventions)
 - Various study types (e.g., phase I, outside the US, observational studies)
 - Optional data elements
- Allows for linkages to improve utility for different audiences
 - E.g., systematic reviews with critical appraisals

Atorvastatin Versus Simvastatin In The Prevention Of Coronary Heart Disease (CHD) In Patients With Known CHD (IDEAL)

This study has been completed.

First Received: September 8, 2005 Last Updated: May 1, 2007 [History of Changes](#)

Sponsored by:	Pfizer
Information provided by:	Pfizer
ClinicalTrials.gov Identifier:	NCT00159835

► Purpose

[Drug Class Review on HMG-CoA Reductase Inhibitors \(Statins\)](#)

To investigate whether a long-term strategy to lower LDL cholesterol with atorvastatin as much as possible will improve prognosis in CHD patients compared with a strategy reflecting current best clinical practice with simvastatin.

Condition	Intervention	Phase
Cardiovascular Diseases	Drug: atorvastatin Drug: simvastatin	Phase IV

[MedlinePlus](#) related topics: [Heart Diseases](#)

[Drug Information](#) available for: [Simvastatin](#) [Atorvastatin](#) [Atorvastatin calcium](#)

[U.S. FDA Resources](#)

Study Type: **Interventional**

Study Design: Treatment, Randomized, Open Label, Active Control, Parallel Assignment, Efficacy Study

Official Title: **Atorvastatin** Compared With **Simvastatin** In The Prevention of CHD Morbidity And Mortality In Patients With CHD

Full Text View

[Tabular View](#)

No Studies

Atorvastatin Versus Simvastatin In The Prevention of CHD Morbidity And Mortality In Patients With CHD

This study

First Received: September 8, 2006

Informa
ClinicalTri

► Purpose

[Drug Class Review on HMG-CoA Reductase Inhibitors \(Statins\)](#)

To investigate whether a long-term strategy to lower LDL cholesterol in patients with CHD compared with a strategy reflecting current practice.

Condition

Cardiovascular Diseases

[MedlinePlus](#) related topics: [Heart Diseases](#)

[Drug Information](#) available for: [Simvastatin](#) [Atorvastatin](#)

[U.S. FDA Resources](#)

Study Type: **Interventional**

Study Design: Treatment, Randomized, Open Label, A

Official Title: **Atorvastatin** Compared With **Simvastatin** In The Prevention of CHD Morbidity And Mortality In Patients With CHD

Drug Class Review on HMG-CoA Reductase Inhibitors (Statins)

Final Report

August 2006



The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Mark Helfand, MD, MPH
Susan Carson, MPH
Cathy Kelley, PharmD

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director

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Key Question 3. How do statins compare in their ability to reduce the risk of nonfatal myocardial infarction, angina, CHD mortality, all-cause mortality, stroke or need for revascularization (coronary artery bypass graft, angioplasty or stenting)?

[Link back to
NCT00159835](#)

Summary of the Evidence

- Information from head-to-head trials is limited.
 - There is no information from head-to-head trials in patients who have never had coronary disease or coronary disease equivalents.
 - *In patients with known coronary heart disease:*

In patients who had a recent myocardial infarction, high dose **atorvastatin 80mg** daily reduced all-cause mortality and CV events compared with **pravastatin 40 mg** daily (PROVE-IT). For every 25 patients treated with **atorvastatin 80mg** instead of **pravastatin 40mg**, one coronary event was prevented.

In patients who had a history of myocardial infarction (**IDEAL**), high-dose **atorvastatin (80 mg)** and **simvastatin (20 mg)** did not differ in the primary endpoint (coronary death, hospitalization for nonfatal acute MI, or cardiac arrest with resuscitation). More high-dose atorvastatin patients discontinued due to adverse events (9.6% vs. 4.2%, $p < 0.001$), and there were more cases of elevated liver enzymes and myalgia with high-dose atorvastatin.
- The amount of information on cardiovascular outcomes available from placebo-controlled trials for each statin differs substantially.
 - In patients with known coronary heart disease:*
 - **Simvastatin** reduced all-cause mortality and CV events.
 - **Pravastatin** reduced all-cause mortality and CV events.
 - **Fluvastatin** reduced coronary events when started after percutaneous coronary intervention.
 - Studies of angiographic progression of atherosclerotic plaques provide fair-quality but indirect evidence that **lovastatin** is effective in preventing CV events in patients with CHD. This finding is weakened because of possible reporting bias (see below.)
 - There are no completed studies of **rosuvastatin** with CHD endpoints in patients with coronary disease.

Table Evidence Table 2. Trials with primary coronary heart disease endpoints

Author Year Study Name	Study Characteristics	Study Population	Intervention	Mean Study Duration	Mean Baseline LDL-c	Percent LDL-c Reduction from Baseline	Myocardial Infarction (active vs. control)	Coronary Heart Disease (new angina, unstable angina)	Cardiovascular or CHD Death
Pederson TR et al. 2005 Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL)	Randomized, open-label with blinded end-point classification, multicenter	8888 men and women aged 80 or younger with a history of a definite MI who qualified for statin therapy according to national guidelines at the time of recruitment.	Simvastatin 20 mg or atorvastatin 80 mg. Dose of simvastatin could be increased I to 40 mg if, at 24 weeks, TC was higher than 190 mg/dL. The dose of atorvastatin could be decreased to 40 mg for adverse events.	Median 4.8 years	122±0.5 mg/dL	33% simvastatin, 49% atorvastatin at 12 weeks	Nonfatal MI: 7.2% simva vs 6.0% atorva (p=0.02) Hazard ratio=0.83 (0.71, 0.98)	Hospitalization for unstable angina: 5.3% simva vs 4.4% atorva (p=0.06) Hazard ratio=0.83 (0.69, 1.01)	CHD death: 4.0% simva vs 3.9% atorva (p=0.90) Hazard ratio=0.99 (0.80, 1.22) Cardiovascular death: 4.9% simva vs 5.0% atorva (p=0.78) Hazard ratio=1.03 (0.85, 1.24)

[Link back to NCT00159835](https://www.clinicaltrials.gov/ct2/show/study/NCT00159835)

Expanding FDAAA requirements Through Rulemaking: Some Key Issues for Consideration

- **UNAPPROVED PRODUCTS** – Whether to require reporting of results of trials of drugs and devices that have not been approved by FDA
- **NARRATIVE SUMMARIES** – Whether technical or lay summaries can be included without being misleading or promotional
- **PROTOCOLS** – Whether to require submission of the full protocol or such information on the protocol for the trial as may be necessary to help to evaluate the results of the trial

“Gaps” in FDAAA-mandated Disclosure Requirements

- Trials that do not include a drug or device
- Trials of unapproved drugs/devices
- Phase 1 trials
- Trials that do not have a site in the U.S. and/or that are not conducted under an IND/IDE
- Trials that completed prior to 9/27/07
- Observational studies

Other Issues with FDAAA Results Reporting Requirements

- Results are technical and require expertise to interpret
- Timeline for results reporting may extend up to three years after trial completion in some cases
- Compliance is not universal
- IRBs may not be aware and/or may choose to not use the information

Non-FDAAA based rules regarding use of ClinicalTrials.gov

- ICMJE
- State of Maine
- Israel, Canada
- State Attorney General Settlements
 - May require compliance with FDAAA
 - May extend FDAAA requirements
- HHS OIG Agreements
 - Impose specific sanctions for non-compliance with FDAAA

States Attorneys General Settlements

AG MYERS FILES JUDGMENT AGAINST PFIZER FOR \$60 MILLION CONCERNING IT'S MARKETING OF DRUGS CELEBREX & BEXTRA

October 22, 2008

Attorney General Hardy Myers Files Judgment Against Pfizer, Inc. Resolving A Five-Year Investigation Into The Company's Marketing Of Bextra And Celebrex

Oregon, 32 other states and District of Columbia to share in \$60 million settlement; Injunctive terms of settlement apply to all Pfizer prescription drugs and biological products

Attorney General Hardy Myers today filed a stipulated judgment with Pfizer, Inc. of New York resolving a five-year multi-state investigation organized and led by the Oregon Attorney General concerning the company's deceptive promotion of the "Cox-2" drugs Celebrex and Bextra. In addition to a \$60 million payment to the participating states with Oregon's share being more than \$4 million, the judgment filed in Marion County Circuit Court will largely restrict Pfizer's ability to deceptively promote any Pfizer products.

Disclosure Obligations

- 2(e) “...Pfizer shall submit, as soon as practicable, clinical trial results to the clinical trial registry and results data bank created by the FDA Amendments Act for all ‘applicable clinical trials’ (as defined by the Act) of FDA-approved Pfizer Products that were initiated **after July 1, 2005.**”
- 3 “Pfizer shall register clinical trials and submit results to the registry and results data bank as required by the FDA Amendments Act and any accompanying regulations that may be promulgated pursuant to that Act”

HHS Office of the Inspector General Corporate Integrity Agreement

- Part of the settlement of federal civil false claims investigations
- Ensures the integrity of the Federal health care program claims submitted by the provider
- Negotiated by HHS OIG with health care providers and entities involved in the settlement
- Typical term of agreements: 5 years

Sample C

"Allergan has also executed a Corporate Integrity Agreement (CIA) with the Department of Health and Human Services, Office of Inspector General (HHS-OIG). ... Allergan is subject to exclusion from federal health care programs, including Medicare and Medicaid, for a material breach of the CIA and subject to monetary penalties for less significant breaches."

JUSTICE NEWS

Office of Public Affairs

FOR IMMEDIATE RELEASE

Wednesday, September 1, 2010

Allergan Agrees to Plead Guilty and Pay \$600 Million to Resolve Allegations of Off-Label Promotion of Botox®

WASHINGTON – American pharmaceutical manufacturer Allergan Inc. has agreed to plead guilty and pay \$600 million to resolve its criminal and civil liability arising from the company's unlawful promotion of its biological product, Botox® Therapeutic, for uses not approved as safe and effective by the Food and Drug Administration (FDA), the Justice Department announced today. The resolution includes a criminal fine and forfeiture totaling \$375 million and a civil settlement with the federal government and the states of \$225 million.

Under the Food, Drug and Cosmetic Act (FDCA), a company in its application to the FDA must specify each intended use of a biological product. After the FDA approves the product as safe and effective for a specified use, any promotion by the manufacturer for other uses – known as “off-label” uses – renders the product misbranded.

Transparency/Disclosure Obligation

“Allergan represents that for all applicable clinical trials (as defined by 42 U.S.C. §282(j)) where Allergan is a sponsor, it [or another responsible party] **registers and reports the results on the National Institutes of Health (NIH) sponsored website (www.clinicaltrials.gov)**... Allergan shall continue to comply with ... applicable requirements relating to the reporting of clinical study information throughout the term of this CIA. In addition, if there is a change..., Allergan shall fully comply with such requirements.”

Select Publications

Tse T, Williams RJ, Zarin DA. Update on registration of clinical trials in ClinicalTrials.gov. *Chest* 2009;136:304-5.

Tse T, Williams RJ, Zarin DA. Reporting basic results in ClinicalTrials.gov. *Chest* 2009;136:295-303.

Zarin DA, Tse T. Moving toward transparency of clinical trials. *Science* 2008;319:1340-2.

Wood AJ. Progress and deficiencies in the registration of clinical trials. *N Engl J Med* 2009;360:824-30.

Additional Information

General ClinicalTrials.gov information:

<http://prsinfo.clinicaltrials.gov>

FDAAA related information:

<http://prsinfo.clinicaltrials.gov/fdaaa.html>

Office of Extramural Research (OER)

http://grants.nih.gov/Clinicaltrials_fdaaa/

Questions?

register@clinicaltrials.gov
