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CHAIR

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Portland, OR 97239

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OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org

July 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:
S0307 Breast	Dec. 8, 2014 AE #2014179081 May 26, 2015 AE #2015262623

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Jennie Barrett
Larry Kaye
Iris Syquia
Keiko Nakajima, M.D. – Bayer Healthcare
Yingkai Cheng – Bayer Healthcare
NCI Coop Coverage – Genentech
Selin Hall – Genentech
Margaret Sykes – Genentech
Carole Wishneski – Genentech
Jenna Marsano – Novartis
Michelle Dubois – UVI, Inc.

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Distribution Date: February 1, 2015
CTEP Submission Date: December 19, 2014

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

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4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
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PO Box 19
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206-667-4623
206-667-4408 FAX

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Chairs: Drs. J. Gralow and R. Livingston.

REVISION #12

Study Chair: Julie Gralow, M.D.
Phone number: 206/288-7722
E-mail: pink@u.washington.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

REVISION #12

The protocol referenced above has been revised as follows:

1. Pages 1 and 3, Title Page: The version date has been updated. The participant list has been moved from Page 1 to Page 3 and revised to be consistent with the new NCTN/CTSU guidelines.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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July 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Report for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
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(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access this safety report via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

This safety report pertains to the following study:	Report:
S0307 Breast	June 21, 2014 AE #2014076996 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

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Charles D. Blanke, MD
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3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org

July 1, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:
S0307 Breast	June 17, 2014 AE #2013037506 FU June 17, 2014 AE #2014087122 June 18, 2014 AE #2014076996 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

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MC: L586
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503-494-5586
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OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

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Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

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June 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
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- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access this safety report via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

This safety report pertains to the following study:	Report:
S0307 Breast	May 27, 2014 AE #2014076996

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

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Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
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210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
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206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: May 1, 2014
CTEP Submission Date: March 28.2014

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Chairs: Drs. J. Gralow and R. Livingston.

REVISION #11

Study Chair: Julie Gralow, M.D.
Phone number: 206/288-7722
E-mail: pink@u.washington.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

REVISION #11

The protocol referenced above has been revised as follows:

1. Title Page: The version date has been updated. The version date has also been added to each page of the Model Consent Form (Pages 51-67).

2. Page 31a, Section 8.7: References to the Adverse Event Expedited Reporting System (AdEERS) have been changed to CTEP Adverse Event Reporting System (CTEP-AERS) in this section and throughout the protocol [Section 16.1 (Pages 42-45a) and Appendix 19.1 (Page 86)]. Associated url's have been updated on these pages as well.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

NOTE: This study remains permanently closed.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
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Jennie Barrett
Larry Kaye
Jenna Marsano– Novartis
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Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

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September 1, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Report for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
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- ( ) Increased risk to patient
- ( ) Complete study redesign
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- ( ) Study closure due to new risk information

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( ) No review required

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access this safety report via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

This safety report pertains to the following study:	Report:
S0307 Breast	Aug. 15, 2013 AE #2013098005

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

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3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

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503-346-8038 FAX

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San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

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206-342-1616 FAX

1100 Fairview Ave North
M3-C102
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Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org

August 15, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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- ( ) Complete study redesign
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- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	July 29, 2013	AE #2013091230
	July 29, 2013	AE #2013091248

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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210-614-0006 FAX

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206-342-1616 FAX

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M3-C102
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206-667-4408 FAX

swog.org

June 15, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	Feb. 4, 2013	AE #2012122211(3) FU
	Mar. 18, 2013	AE #2013031381
	Mar. 28, 2013	AE #2013037506
	Apr. 5, 2013	AE #2013031381(1) FU
	May 29, 2013	AE #2013066106

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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GROUP CHAIR'S OFFICE
Laurence H. Baker, DO
CHAIR

24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106

734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229

210-614-8808
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STATISTICAL CENTER
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January 15, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0307 Breast	Dec. 11, 2012 AE #2012130075 Dec. 14, 2012 AE #2012114410 FU Dec. 18, 2012 AE #2012122211 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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December 1, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0307 Breast	Nov. 16, 2012 AE #2012118376 Nov. 23, 2012 AE #2012122211 Nov. 23, 2012 AE #2012122249 Nov. 26, 2012 AE #2012123754

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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November 15, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:
S0307 Breast	Oct. 29, 2012 AE #2012022802 FU Nov. 2, 2012 AE #2012114410

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Jennie Barrett
Nicole Castillo
Larry Kaye
Iris Syquia
Keiko Nakajima, M.D. – Bayer Healthcare
Silke Thiele – Bayer Healthcare
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Jenna Marsano – Novartis
Michelle Dubois – UVI, Inc.

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Laurence H. Baker, DO
CHAIR

24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106

734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

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October 1, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0307 Breast	Aug. 30, 2012 AE #2012089597 Sep. 4, 2012 AE #2012091067 Sep. 4, 2012 AE #2012090774 Sep. 6, 2012 AE #2011057639 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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September 15, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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September 1, 2012

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FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0307 Breast	Aug. 7, 2012 AE #2012079512 Aug. 10, 2012 AE #2012080442

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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M3-C102
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Distribution Date: June 15, 2012
CTEP Submission Date: May 29, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Megan M. Hardin, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

REVISION #10

Study Coordinator: Julie Gralow, M.D.
Phone number: 206/288-7722
E-mail: pink@u.washington.edu

IRB Review Requirements

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REVISION #10

Institutions **do not need to** update their local consent forms to include the changes to the Model Consent Form unless required by the local Institutional Review Board (IRB).

Patients currently receiving and patients who have completed treatment with zoledronic acid (Zometa®) need not be informed of these changes unless required by the local Institutional Review Board (IRB).

The protocol referenced above has been amended as follows:

1. Title Page: The version date has been updated

2. Page 16a, Section 3.1g.3b: The contact information for Kristen White at Novartis Pharmaceuticals has been replaced with a reference to the **S0307** abstract page of the SWOG website, which is where the contact information is now located.

3. Page 58, Model Consent Form, What side effects or risks can I expect from being in the study?: Under the "Rare but Serious" section of risks for zoledronic acid, “atypical bone fractures” has been added.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

NOTE: This study remains permanently closed.

cc: PROTOCOL & INFORMATION OFFICE
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210-614-8808
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Seattle, WA 98101

206-652-2267
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M3-C102
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June 1, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Report for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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This safety report pertains to the following study:	Report:
S0307 Breast	May 7, 2012 AE #2012042926

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

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May 15, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

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RE: IND Safety Reports for Clodronate

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These safety reports pertain to the following study:	Reports:
S0307 Breast	Apr. 5, 2012 AE #2012032297 Apr. 24, 2012 AE #2012039215 Apr. 27, 2012 AE #2012032297 FU

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May 1, 2012

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FROM: Megan M. Hardin, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone number: 206/288-7722
E-mail: pink@u.washington.edu

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MEMORANDUM

The purpose of this memorandum is to remind sites that an incremental payment of $496.00 was awarded to help offset the cost of the end of study bone scan, Month 2, 3, 5 and 6 creatinine blood draws, specimen collection and specimen submission. The funds have been automatically distributed from SWOG-CTI based on accrual. This information can be found on the **S0307** funding memo which can be accessed from the **S0307** abstract page on the SWOG website (www.swog.org).

Please contact Kati Stoermer at Laszlo@med.umich.edu with any questions or concerns.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

NOTE: This study remains permanently closed.

cc: PROTOCOL & INFORMATION OFFICE
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May 1, 2012

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These safety reports pertain to the following study:	Reports:
S0307 Breast	Mar. 20, 2012 AE #2012022802 FU Mar. 28, 2012 AE #2012009073 FU Mar. 28, 2012 AE #2012029657 Mar. 29, 2012 AE #201030788NA FU Apr. 5, 2012 AE #2010001740 FU Apr. 5, 2012 AE #2012033102

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April 1, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0307 Breast	Feb. 28, 2012 AE #2012019312 Mar. 6, 2012 AE #2012021567 Mar. 9, 2012 AE #2012022802 FU

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March 15, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Report for Clodronate

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S0307 Breast	Feb. 16, 2012 AE #2012009073 FU

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206-342-1616 FAX

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M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

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February 15, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:
S0307 Breast	Jan. 23, 2012 AE #200935806NA FU Jan. 24, 2012 AE 201030788NA FU Jan. 24, 2012 AE #2011123505 FU Jan. 31, 2012 AE #2012009073

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Jennie Barrett
Jeri Jardine
Larry Kaye
Iris Syquia
Keiko Nakajima, M.D. – Bayer Healthcare
Silke Thiele – Bayer Healthcare
Jenna Marsano – Novartis
Michelle Dubois – UVI, Inc.

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Laurence H. Baker, DO
CHAIR

24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106

734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
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PO Box 19024
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206-667-4623
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January 15, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
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- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via study's abstract page or the safety report link on the SWOG website https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:
S0307 Breast	Dec. 28, 2011 AE #2011123505

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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206-652-2267
206-342-1616 FAX

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January 1, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0307 Breast	Nov. 29, 2011 AE #2011112939 FU Nov. 30, 2011 AE #2011105692 FU Dec. 1, 2011 AE #2011114944 Dec. 15, 2011 AE #2011034189 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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December 15, 2011

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Laurence H. Baker, DO
CHAIR

24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106

734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
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TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Megan M. Wardeski, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone number: 206/288-7722
E-mail: pink@u.washington.edu

IRB Review Requirements

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- ( ) Initial activation (should your institution choose to participate)
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- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites of the holiday shipment schedule for Uintavision, Inc. (UVI). UVI will not ship drug on the following days:

Monday, December 26, 2011
Monday, January 2, 2012

UVI will be open December 26 and January 2 to provide customer assistance but will not have shipment capabilities. Any submitted non-refrigerated orders will be processed Friday, December 23 and Friday, December 30, 2011. Please note that if a site needs refrigerated goods during this time, those orders should be placed by Thursday, December 22 and Thursday, December 29.

Please contact Michelle Dubois at 800/370-2508 me with any questions or concerns.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

NOTE: This study remains permanently closed.

cc: PROTOCOL & INFORMATION OFFICE
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Ann Arbor, MI 48106

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4201 Medical Dr
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December 15, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:
S0307 Breast	Nov. 21, 2011 AE #2011109917 FU Nov. 24, 2011 AE #2011112939

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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206-342-1616 FAX

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December 1, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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MEMORANDUM

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These safety reports pertain to the following study:

S0307 Breast

Reports:

Oct. 26, 2011 AE #201017651NA FU
Oct. 26, 2011 AE #2011029627 FU
Oct. 31, 2011 AE #2011104922
Oct. 31, 2011 AE #2011104959
Nov. 4, 2011 AE #2011105692
Nov. 16, 2011 AE #2011104922 FU
Nov. 16, 2011 AE #2011109917

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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November 15, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	Oct. 21, 2011	AE #2011081397 FU
	Oct. 21, 2011	AE #2011099069

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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GROUP CHAIR'S OFFICE
Laurence H. Baker, DO
CHAIR
24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106
734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
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November 1, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Report for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access this safety report via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

This safety report pertains to the following study:	Report:
S0307 Breast	Oct. 4, 2011 AE #2011061835 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

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206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
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206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: November 1, 2011
CTEP Submission Date: October 11, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Megan M. Wardeski, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

REVISION #9

Study Coordinator: Julie Gralow, M.D.
Phone number: 206/288-7722
E-mail: pink@u.washington.edu

IRB Review Requirements

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REVISION #9

Institutions **should** update their local consent forms to include the changes to the Model Consent Form.

SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk-benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes.

Patients currently receiving zoledronic acid (Zometa®) need not be informed of these changes unless required by the local Institutional Review Board (IRB).

The protocol referenced above has been amended as follows:

1. Title Page: The version date has been updated. “Southwest Oncology Group” has been updated to “SWOG” above the title and in the participant’s list.

2. Pages 14-16b, Section 3.1: The drug information for Zoledronic Acid has been updated. Therefore this section has been replaced with new standard language. Page 16b was added to prevent extensive repagination.

3. Page 32, Section 9.0: The “δ” footnote has been added to the “End of Treatment” column in the “Bone scan or roentgenological exam” row. The footnote reads, “Only a bone scan is acceptable at End of Treatment (see Section 7.10).”

4. Page 57, Model Consent Form, What side effects or risks can I expect from being in the study?: Under the "Likely" section of risks for zoledronic acid, “fatigue or tiredness” has been added. This risk was added to the “Less Likely” section in Revision #8. However, it should have been added to the “Likely” section. “Fever” was added to the “Less Likely” section in Revision #8. Because it was already correctly located in the “Likely” section, it has been removed from the “Less Likely” section.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

NOTE: This study remains permanently closed.

cc: PROTOCOL & INFORMATION OFFICE
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September 15, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0307 Breast	Aug. 18, 2011 AE #2011061835 FU Aug. 19, 2011 AE #2011028903 Aug. 23, 2011 AE #2010002638 FU Aug. 24, 2011 AE #2011029627 Aug. 24, 2011 AE #2011017224

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September 1, 2011

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FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

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S0307 Breast	July 26, 2011	AE #2011033511 FU
	July 27, 2011	AE #2011061835
	July 27, 2011	AE #2011062225
	July 29, 2011	AE #2011048943 FU
	Aug. 1, 2011	AE #2011063879
	Aug. 3, 2011	AE #200928049NA FU
	Aug. 3, 2011	AE #201030788NA FU
	Aug. 3, 2011	AE #2011067170
	Aug. 10, 2011	AE #2011033511 FU
	Aug. 12, 2011	AE #2011067170 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Jennie Barrett
Jeri Jardine
Larry Kaye
Iris Syquia
Keiko Nakajima, M.D. – Bayer Healthcare
Silke Thiele – Bayer Healthcare
Jenna Marsano – Novartis
Michelle Dubois – UVI, Inc.

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Laurence H. Baker, DO
CHAIR

24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106

734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: September 1, 2011
E-mailed Date: August 23, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Megan M. Wardeski, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone number: 206/288-7722
E-mail: pink@u.washington.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The August 15, 2011 safety report memo has been withdrawn. The reports were distributed in error and please disregard.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and SWOG Statistical Center.

NOTE: This study remains permanently closed.

cc: PROTOCOL & INFORMATION OFFICE
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August 1, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	July 12, 2011	AE #2011056748
	July 12, 2011	AE #2011057639
	July 13, 2011	AE #2011058737
	July 14, 2011	AE #2011044227 FU
	July 15, 2011	AE #2011060302
	July 18, 2011	AE #2011057605

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GROUP CHAIR'S OFFICE
Laurence H. Baker, DO
CHAIR
24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106
734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229
210-614-8808
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206-667-4623
206-667-4408 FAX

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July 15, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	July 4, 2011	AE #201020451NA FU
	July 4, 2011	AE #2011017730 FU
	July 4, 2011	AE #2011037975 FU
	July 6, 2011	AE #2011054922
	July 8, 2011	AE #2011017125 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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July 1, 2011

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FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0307 Breast	June 14, 2011 AE #2011048943 June 15, 2011 AE #2011048213 June 22, 2011 AE #2011048213 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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June 15, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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These safety reports pertain to the following study:	Reports:
S0307 Breast	May 27, 2011 AE #2011041929 May 30, 2011 AE #2011026058 FU June 7, 2011 AE #2011026058 FU June 9, 2011 AE #2011044227

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: June 1, 2011
CTEP Submission Date: April 21, 2011

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Megan M. Wardeski, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

REVISION #8

Study Coordinator: Julie Gralow, M.D.
Phone number: 206/288-7722
E-mail: pink@u.washington.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
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- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #8

Institutions **must** update their local consent forms to include the changes to the Model Consent Form.

SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk-benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes.

Patients currently receiving zoledronic acid (Zometa®) must be informed of these changes. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patients must be notified at the next visit and this notification process must be documented in the patient chart.

The protocol referenced above has been amended as follows:

1. Title Page: The version date has been updated.

2. Page 15, Section 3.1b, Toxicology Background: The zoledronic acid (Zometa®) drug information section has been updated to be consistent with the most recent zoledronic acid package insert. The labeling changes in the toxicology section include pyrexia, asthenia, fatigue and malaise persisting for greater than 30 days. These have been added to this section respectively.

3. Page 16, Section 3.1c: This section has been updated to include new standard language for drug returns and drug accountability. This change has also been made to Section 3.2c (Page 19) and Section 3.3c (Page 22). Handling/Disposal information referencing consideration of OSHA procedures has been removed from Sections 3.2c and 3.3c. Pages 16a and 22a were added to prevent extensive repagination. Information in Section 3.2c (Drug Accountability) has been reworded for clarity.

4. Page 29, Section 7.3: The following definition of monthly has been added to this section: If treatment begins on the first of the month, then the subsequent doses are given on the first of each month thereafter.

5. Page 31, Section 7.12: The length of time for delay of protocol treatment has been changed from greater than 4 weeks to greater than 3 months to allow more flexibility. This change has also been made to Section 8.4 (Page 31a).

6. Page 31a, Section 8.7: This section has been updated to include new standard language for AE reporting. Unexpected or fatal toxicities has been replaced with toxicities that meet the expedited reporting criteria. The remainder of the section has been reworded for clarity but the content was not affected.

7. Page 32, Section 9.0: Study Calendar: A reference to Section 7.3 for the definition of monthly has been added to the "Ω" footnote.

8. Page 42, Section 16.0: This section has been updated to reflect new standard language for drug accountability. Specific accountability language has been removed and this section now refers sites to the Code of Federal Regulations 21 CFR 312 for procedures and requirements of drug accountability.

9. Page 45a, Section 16.1h: The guidelines for reporting secondary AML/ALL/MDS have been updated to the most current NCI guidelines which require second/secondary AML/ALL/MDS to be reported via AdEERS instead of the NCI/CTEP Secondary AML/ALL/MDS Report Form. Instructions for reporting in CTCAE Version 3.0 and Version 4.0 have been included separately.

10. Page 57, Model Consent Form, What side effects or risks can I expect from being in the study?: Under the "Less Likely" section of risks for zoledronic acid, the following new risks have been added as provided by the FDA MedWatch Safety program:

    - Fever
    - Fatigue or tiredness

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

NOTE: This study remains permanently closed.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
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206-342-1616 FAX

1100 Fairview Ave North
M3-C102
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206-667-4623
206-667-4408 FAX

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June 1, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0307 Breast	May 11, 2011 AE #2011038309 May 14, 2011 AE #2011038733 May 18, 2011 AE #2011041572 May 19, 2011 AE #2011040272 May 21, 2011 AE #2011038069 FU May 21, 2011 AE #2011038309 FU May 21, 2011 AE #2011039087

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May 15, 2011

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FROM: SWOG Operations Office

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S0307 Breast	Apr. 28, 2011 AE #2011033463 Apr. 29, 2011 AE #2011035555 May 2, 2011 AE #2011034683 May 2, 2011 AE #2011036333 May 4, 2011 AE #2011034494 May 4, 2011 AE #2011037975 May 5, 2011 AE #2011035321 May 9, 2011 AE #2011033511 FU May 9, 2011 AE #2011038069

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May 1, 2011

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FROM: SWOG Operations Office

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S0307 Breast	Apr. 11, 2011 AE #2011026058 Apr. 11, 2011 AE #2011026058 FU Apr. 21, 2011 AE #2011033462 Apr. 25, 2011 AE #2011034189 Apr. 28, 2011 AE #2011033511

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April 1, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

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( ) No review required

MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:
S0307 Breast	Mar. 14, 2011 AE #2011011929* Mar. 15, 2011 AE #2011020038 Mar. 15, 2011 AE #2011020044 Mar. 15, 2011 AE #2011020045 Mar. 17, 2011 AE #2011020656

* The initial report for this AE dated February 21, 2011 was circulated to sites in both the March 1, 2011 and March 15, 2011 SWOG distributions. Please disregard the second notification.

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Jennie Barrett
Jeri Jardine
Iris Syquia
Keiko Nakajima, M.D. – Bayer Healthcare
Silke Thiele – Bayer Healthcare
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Laurence H. Baker, DO
CHAIR

24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106

734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

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March 15, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

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The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:
S0307 Breast	Feb. 21, 2011 AE #2011011929 Feb. 24, 2011 AE #2011014149 Feb. 24, 2011 AE #2011017125 Mar. 1, 2011 AE #2011015886 Mar. 7, 2011 AE #2011017125 Mar. 8, 2011 AE #2011017730

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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swog.org

March 1, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0307 Breast	Feb. 7, 2011 AE #2011009105 Feb. 8, 2011 AE #2011011544 Feb. 11, 2011 AE #2011011544 Feb. 16, 2011 AE #2011011928 Feb. 21, 2011 AE #2011011929

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: February 15, 2011
CTEP Submission Date: February 1, 2011

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Megan M. Wardeski, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

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- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

Attached here is a Dear Doctor Letter which addresses the recent presentation of the AZURE clinical trial findings presented at the 33rd Annual San Antonio Breast Cancer Symposium and their implications on **S0307**. SWOG is not mandating that any information be conveyed to patients at this time. Investigators may choose to discuss these issues with their patients at their own discretion and subject to the guidance of their local IRB.

This protocol remains permanently closed to accrual.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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M3-C102
PO Box 19024
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206-667-4623
206-667-4408 FAX

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Date: February 2, 2011

To: Investigators participating in the SWOG clinical trial **S0307**

From: Julie Gralow, M.D. on behalf of SWOG

This letter addresses the recent presentation of the AZURE clinical trial findings presented at the San Antonio Breast Cancer Symposium in December (Coleman RE et al, abstract S4-5) and the implications regarding **S0307**. The co-PIs of the **S0307** trial met at San Antonio to review the safety data from S0307 and to discuss the implications of the AZURE presentation on **S0307**. As a result, we are encouraging continuation of the **S0307** trial as planned.

The AZURE trial randomized 3360 women with Stage II/III breast cancer receiving systemic therapy to zoledronic acid or not. The dosing of zoledronic acid used in this trial was 4 mg every 3-4 weeks for 6 doses, then every 3 months x 8, followed by every 6 months x 5, to complete 5 total years of treatment. Ninety-six percent received chemotherapy, only 152 patients received endocrine therapy alone. Serious adverse events were similar in both arms, and to date 14 cases of osteonecrosis of the jaw (ONJ) have occurred, all in the zoledronic acid arm. For the primary endpoint of disease-free survival (DFS) with a median follow-up of 59 months, the study shows no significant effect of zoledronic acid. In a preplanned subset analysis, a significant effect on both recurrence and overall survival was reported in women with well-established menopause (defined as more than 5 years after menopause, n=1101). This finding is unexpected and hypothesis-generating, requiring further investigation.

The AZURE presentation is in contrast to other previously reported adjuvant bisphosphonate trials suggesting clinical benefit. The ABCSG-12 study (Gnant M et al, NEJM 2009; ASCO 2010, abstract #533) demonstrated a 32% risk reduction in DFS events with zoledronic acid (4 mg every 6 months for 3 years) in a cohort of premenopausal women treated with endocrine therapy (including ovarian suppression) without chemotherapy at 62 months median follow-up. A randomized, placebo-controlled trial of daily oral clodronate for 2 years (Powles T et al, Breast Cancer Res 2006) in 1,069 patients with stage I-III breast cancer reported a reduction in bone relapse and improved survival. It is understood that this trial will be retrospectively evaluated with respect to menopausal status in the near future. The NSABP B-34 of clodronate versus placebo for 3 years in early stage breast cancer patients has not yet reported. The SWOG Breast Committee leadership feels strongly that the combined evidence of these trials, and not just a single trial, must be considered before making a definitive conclusion regarding the benefit of adjuvant bisphosphonates in specific breast cancer patient populations.

S0307 is a randomized clinical trial of 3 different bisphosphonates in Stage I-III breast cancer patients receiving adjuvant systemic therapy. The randomization is between a dosing schedule of zoledronic acid similar to AZURE (4 mg intravenously monthly for 6 months, then every 3 months) versus oral ibandronate (50 mg po daily) versus oral clodronate (1,600 mg po daily), all given for 3 years. **S0307** was activated November 15, 2005 and completed accrual February 1, 2010. All 6,097 patients have been followed for at least a year, and no patients remain in the monthly dosing portion of the zoledronic therapy.

No unexpected safety signals have emerged on study to date. Among 5,498 patients assessed for toxicity, 17 patients experienced Grade 4 toxicities, and an additional 7% have experienced Grade 3 events, primarily musculoskeletal pain. There have been 20 reported cases of ONJ, or about one case per 500 patients followed for a year.

Some important differences exist between the AZURE trial design and enrollment and **S0307**. **S0307** delivers zoledronic acid in a similar "intensive" regimen, although it additionally evaluates two other oral bisphosphonates in the protocol. The duration of therapy in **S0307** is 3 years, compared to 5 years in AZURE. The percentage of patients who did not receive chemotherapy is much higher in **S0307** (20% versus about 4% in AZURE), which may impact benefit of bisphosphonates. **S0307** mandates an end of study bone scan to provide a single time point at which bone metastases can be evaluated, with the thought that these high dose bisphosphonates might mask pain and other symptoms of bone involvement. **S0307** has additional substudies evaluating fracture rates on high dose bisphosphonates, the impact of statin therapy on recurrence, and important biological correlates (using baseline tissue, serum and DNA) including predictors of bone metastases and toxicities from these drugs. We are looking carefully at the incidence and risk factors for ONJ in this study. The first interim analysis of **S0307** is likely to occur in 2012 and then will occur annually thereafter. The analysis of **S0307** will include analyses in subsets defined by age, menopausal status, tumor stage, and other characteristics measured at baseline to determine if treatment effects are consistent over these factors.

In conclusion, the data so far are conflicting. The discrepant results of previously presented/published trials, including ABCSG-12 and AZURE, have generated hypotheses, but no compelling direction. We strongly believe that the role of adjuvant bisphosphonates in early stage breast cancer to reduce recurrences and deaths is unclear. There are no emerging safety issues in **S0307** that should impact patients' decisions to continue to participate in the trial. There is undoubtedly a bone density/osteoporosis benefit to these patients, who are at increased risk of bone loss due to their therapy. The correlative science components of **S0307** are important to understand the effect of the various bisphosphonates and perhaps identify biomarkers of benefit. We ask you to continue your support of **S0307** to help resolve the current controversy by encouraging your patients to stay on study to complete their intended treatment. Results from ongoing trials, including **S0307**, will help define this important issue.

Julie Gralow, M.D.

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Laurence H. Baker, DO
CHAIR

24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106

734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229

210-614-8808
210-614-0006 FAX

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Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

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M3-C102
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206-667-4623
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February 15, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Report for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

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This safety report pertains to the following study:	Report:
S0307 Breast	Feb. 7, 2011 AE #2011009105

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

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206-652-2267
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February 1, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Report for Clodronate

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This safety report pertains to the following study:	Report:
S0307 Breast	Jan. 6, 2010 AE #201101168

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

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January 15, 2011

TO: ALL SWOG, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:

S0307 Breast

Reports:	
Dec. 8, 2010	AE #2010001255
Dec. 9, 2010	AE #2010001008
Dec. 13, 2010	AE #2010001538
Dec. 13, 2010	AE #2010001740
Dec. 13, 2010	AE #2010002638
Dec. 13, 2010	AE #201044429GPV
Dec. 22, 2010	AE #2010004720

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January 1, 2011

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This safety report pertains to the following study:	Report:
S0307 Breast	Dec. 3, 2010 AE #201013586NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

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December 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

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S0307 Breast	Nov. 17, 2010	AE #201017693GPV
	Nov. 25, 2010	AE #201040920NA

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December 1, 2010

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( ) No review required

MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	Nov. 4, 2010	AE #201025921NA
	Nov. 4, 2010	AE #201036783NA
	Nov. 4, 2010	AE #20104405GPV
	Nov. 5, 2010	AE #201043226GPV
	Nov. 12, 2010	AE #200835032NA
	Nov. 12, 2010	AE #201013586NA
	Nov. 12, 2010	AE #201039369NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Jennie Barrett
Iris Buchanan
Jeri Jardine
Istvan Molnar – Bayer Schering Pharma Oy
Joyce Mull – NSABP
Ellen Antonio – CTSU

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Laurence H. Baker, DO
CHAIR

24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106

734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CEN ER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

swog.org

November 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Report for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following safety report has been posted regarding an adverse event that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access this safety report via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

This safety report pertains to the following study:	Report:
S0307 Breast	Oct. 28, 2010 AE #201043226GPV

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

November 1, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	Oct. 19, 2010	AE 201041755GPV
	Oct. 19, 2010	AE 201041769GPV

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

October 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0307 Breast	Sep. 28, 2010 AE 201033616NA Sep. 28, 2010 AE 201014956NA Sep. 29, 2010 AE 200919383NA Sep. 29, 2010 AE 201034050NA Sep. 30, 2010 AE 200938484NA Oct. 5, 2010 AE 201039272GPV

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

October 1, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0307 Breast	Sep. 15, 2010 AE 201032707NA Sep. 20, 2010 AE 200927870NA Sep. 20, 2010 AE 201030791NA Sep. 20, 2010 AE 201039272GPV

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: September 15, 2010
CTEP Submission Date: August 30, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Southwest Oncology Group Operations Office

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

REVISION #7

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
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REVISION #7

The protocol referenced above has been amended as follows:

1. Title Page: The version date has been updated.

2. Page 31-31a, Section 8.1: The criteria for reporting Adverse Events have been updated. Effective October 1, 2010 the CTCAE Version 4.0 will be utilized for SAE reporting. The CTCAE Version 3.0 will continue to be utilized for routine toxicity reporting.

3. Page 41, Section 15.4d: The e-mail address for Miguel Martinez (the contact at the SWOG Solid Tumor Tissue Bank) has been changed to miguel.martinez@ucdenver.edu.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

NOTE: This study remains permanently closed.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
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Istvan Molnar - Bayer Schering Pharma Oy
Diep Tran - Novartis
Benedicte Marion - Hoffman - Laroche, Ltd.

Southwest
Oncology Group
A National Clinical Research Group

September 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0307 Breast	Aug. 18, 2010 AE 201031813GPV Aug. 24, 2010 AE 201030788NA Aug. 25, 2010 AE 201028721NA Aug. 25, 2010 AE 201030791NA Aug. 26, 2010 AE 201024770NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

September 1, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0307 Breast	Aug. 13, 2010 AE 201029240NA Aug. 13, 2010 AE 201031813GPV Aug. 16, 2010 AE 201023699NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

August 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:			
S0307 Breast	July 15, 2010	AE 201031813GPV	July 20, 2010	AE 201020681NA
	July 15, 2010	AE 201026892NA	July 20, 2010	AE 201027733NA
	July 15, 2010	AE 201026764NA	July 20, 2010	AE 200836438NA

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Ellen Antonio – CTSU

Southwest
Oncology Group
A National Clinical Research Group

August 1, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:			
S0307 Breast	June 29, 2010	AE 200925055NA	June 30, 2010	AE 201025675NA
	June 29, 2010	AE 201024765NA	June 30, 2010	AE 201025786NA
	June 29, 2010	AE 201024770NA	June 30, 2010	AE 201025921NA
	June 29, 2010	AE 201025200NA	July 5, 2010	AE 201028474GPV
	June 29, 2010	AE 201025458NA	July 5, 2010	AE 201026135NA

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Southwest
Oncology Group
A National Clinical Research Group

July 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	June 9, 2010	AE 201012401NA
	June 16, 2010	AE 201023699NA
	June 16, 2010	AE 201024770NA
	June 16, 2010	AE 201027595GPV
	June 16, 2010	AE 201028474GPV

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

July 1, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

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These safety reports pertain to the following study:	Reports:			
S0307 Breast	May 12, 2010	AE 201021257NA	May 27, 2010	AE 200716245NA
	May 17, 2010	AE 201021912NA	May 27, 2010	AE 201014471NA
	May 18, 2010	AE 200929525NA	May 27, 2010	AE 201022634NA
	May 21, 2010	AE 201025523GPV	May 31, 2010	AE 201023391NA
	May 27, 2010	AE 201021912NA	May 31, 2010	AE 201023699NA

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Southwest
Oncology Group
A National Clinical Research Group

June 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Amanda Vidlak, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

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MEMORANDUM

UVI, Inc., the drug distributor for the **S0307** trial, will be closed for business on Monday, July 5, 2010 in observance of the July 4th holiday. As a result UVI will not be processing drug shipments on July 5, 2010. Please plan your drug orders accordingly. We apologize for any inconvenience this may cause.

This protocol remains permanently closed to accrual.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Jeannie Barrett
Istvan Molnar– Bayer Schering Pharma Oy
Maddy Balois– CTSU
Michelle Dubois – UVI, Inc.
Lixian Jin - Novartis

Southwest
Oncology Group
A National Clinical Research Group

June 1, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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These safety reports pertain to the following study:	Reports:			
	May 4, 2010	AE 200929525NA	May 6, 2010	AE 201020341NA
S0307 Breast	May 4, 2010	AE 201019766NA	May 6, 2010	AE 201020678NA
	May 4, 2010	AE 201020451NA	May 6, 2010	AE 201020681NA
	May 5, 2010	AE 201020683NA		

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Southwest
Oncology Group
A National Clinical Research Group

May 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:			
S0307 Breast	Apr. 6, 2010	AE 201016159NA	Apr. 16, 2010	AE 201018522NA
	Apr. 6, 2010	AE 201017651NA	Apr. 26, 2010	AE 201017889NA
	Apr. 12, 2010	AE 201011319NA	Apr. 26, 2010	AE 201019766NA
	Apr. 12, 2010	AE 201017889NA	Apr. 27, 2010	AE 201019773NA
	Apr. 14, 2010	AE 201016369NA	Apr. 28, 2010	AE 201022066GPV

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Jennie Barrett
Iris Buchanan
Lisa Gavigan
Jeri Jardine
Istvan Molnar – Bayer Schering Pharma Oy
Joyce Mull – NSABP
Maddy Balois – CTSU
Ellen Antonio – CTSU

Southwest
Oncology Group
A National Clinical Research Group

April 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:

S0307 Breast

Reports:

Feb. 26, 2010	AE 201014472NA	Mar. 16, 2010	AE 201018181GPV
Feb. 26, 2010	AE 201016672GPV	Mar. 18, 2010	AE 201015688NA
Mar. 2, 2010	AE 201014471NA	Mar. 18, 2010	AE 201016159NA
Mar. 4, 2010	AE 201014475NA	Mar. 24, 2010	AE 200835032NA
Mar. 4, 2010	AE 201014672NA	Mar. 24, 2010	AE 201014471NA
Mar. 11, 2010	AE 201014472NA	Mar. 24, 2010	AE 201016369NA
Mar. 11, 2010	AE 201014956NA	Mar. 31, 2010	AE 201017173NA
Mar. 16, 2010	AE 200920427NA		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

March 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	Feb. 17, 2010	AE 201011714GPV
	Feb. 19, 2010	AE 201013586NA
	Feb. 24, 2010	AE 201011811NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

March 1, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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(√) Expedited review allowed

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MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	Feb. 8, 2010	AE 201012174NA
	Feb. 8, 2010	AE 201012401NA
	Feb. 8, 2010	AE 201012714NA
	Feb. 12, 2010	AE 201012616NA
	Feb. 12, 2010	AE 201013185NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Ellen Antonio – CTSU

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: February 15, 2010
CTEP Submission Date: January 21, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Amanda Vidlak, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

REVISION #6

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
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REVISION #6

1. Title Page – The version date has been updated.

2. Page 3: The contact information for Dr. Clemons has been updated.

3. Page 16, Section 3.1.c: For zolendronic acid drug returns, the incorrect contact information has been deleted. See the memorandum distributed 10/15/09 for current contact information.

4. Page 29, Sections 7.3 and 7.4: A note regarding dosing of zoledronic acid has been added to this section for clarification purposes. The table in Section 7.3 was modified; the interval for oral bisphosphonates was changed from 3 years to 35 months as the oral bisphosphonates are discontinued on Day 1 of Month 36. The SWOG Operations Office phone number has been updated.

5. Page 30, Section 7.10: Language has been inserted to clarify that all end of treatment evaluations are done on Day 1 of Month 36. The SWOG Operations office phone number has been updated.

6. Page 32, Section 9.0: The reference regarding bone scans related to the footnote "£" in the study calendar has been corrected from Section 5.9 to Section 5.10. The footnote "Ω" has been corrected to say that zolendronic acid can be given ± 2-day interval for the first six months. A note regarding dosing of zoledronic acid has been added to this section for clarification purposes. The footnote "€" has been added to clarify that all end of treatment evaluations are done on Day 1 of Month 36. In the column for Month 36, the X's have been deleted from the clodronate and ibandronate rows because these are to be discontinued on Day 1 of Month 36. The associated footnotes have been revised accordingly.

7. Page 33-34, Section 11.0: This section was modified, as requested by the NCI, to stratify the analysis by time period of randomization. In Section 11.2 the time a patient is followed was also corrected to 10 years from randomization.

8. Page 35, Section 13.3a: The SWOG Operations Office phone number has been updated.

9. Page 36, Section 14.3: The SWOG Operations Office phone number has been updated.

10. Page 37, Section 14.7: The **S0307** Serum Creatinine Reporting Form has been added to the list of forms submitted within 14 days of discontinuation of treatment.

11. Page 43, Section 16.1e: The SWOG Operations Office phone number has been updated.

12. Pages 45-45a, Section 16.1: A section on instructions and exceptions to AdEERS expedited reporting requirements has been added as section 16.1.f. The subsequent sections have been renumbered. In Section 16.1g and 16.1h the SWOG Operations Office phone and FAX number has been updated as well as the address. Page 45a has been inserted to prevent extensive repagination.

13. Page 56, Model Consent Form: The time a patient will be in this study has been clarified to 10 years from randomization.

14. Page 83, Section 19.0: Appendix 19.4, the **S0307** Statistical Analysis Plan, was added to the Appendix section of the protocol.

15. Pages 100-104, Appendix 19.4: This section has been inserted.

The Southwest Oncology Group considers that the Model Consent Form change does not represent an alteration in risk-benefit ratio. Patients currently on treatment need not be informed of this change unless required by the responsible Institutional Review Board (IRB).

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

NOTE: This study remains permanently closed.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
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Lisa Gavigan
Jeri Jardine
Jennie Barrett
Istvan Molnar - Bayer Schering Pharma Oy
Diep Tran - Novartis
Benedicte Marion - Hoffman - Laroche, Ltd.
Maddy Balois - CTSU

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: February 15, 2010
E-mailed Date: February 9, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Amanda Vidlak, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

( ) Full board review required. Reason:
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- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

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MEMORANDUM

UVI, Inc., drug distributor for the **S0307** trial, has confirmed that they are experiencing a temporary shortage of clodronate tablets. The clodronate tablets continue to be manufactured by Bayer Schering Pharma Oy; however, a new shipment is not expected in the UVI warehouse for up to three weeks.

We anticipate that this shortage will last no longer than three weeks and we hope that registered patients on the clodronate arm have necessary supplies on hand. There may be instances where an interruption in treatment may be experienced. If a treatment interruption occurs, please contact UVI, Inc., so that clodronate re-supply orders can be expedited once the shortage is resolved.

Note: Any treatment interruption due to the drug shortage will not be considered a protocol deviation; however, institutions should document in the research record the reason for the interruption.

The ibandronate shortage which was announced in a memorandum distributed 2/4/2010 has been resolved. All pending orders will be released from UVI, Inc., today, February 9, 2010.

This protocol remains permanently closed to accrual.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc:
PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Lisa Gavigan
Jeri Jardine
Jeannie Barrett
Istvan Molnar– Bayer Schering Pharma Oy
Maddy Balois– CTSU
Michelle Dubois – UVI, Inc.
Lixian Jin - Novartis

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: February 15, 2010
E-mailed Date: February 4, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Amanda Vidlak, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

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MEMORANDUM

UVI, Inc., drug distributor for the **S0307** trial, has confirmed that they are experiencing a temporary shortage of ibandronate tablets. The ibandronate tablets continue to be manufactured by Roche; however, a new shipment is not expected in the UVI warehouse until next week.

While we anticipate that this shortage will only last a week, we hope that registered patients on the ibandronate arm have necessary supplies on hand. There may be instances where an interruption in treatment may be experienced. If a treatment interruption occurs, please contact UVI, Inc., so that ibandronate re-supply orders can be expedited once the shortage is resolved.

Note: Any treatment interruption due to the drug shortage will not be considered a protocol deviation; however, institutions should document in the research record the reason for the interruption.

This protocol remains permanently closed to accrual.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

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Southwest
Oncology Group
A National Clinical Research Group

February 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	Jan. 5, 2010	AE 200943195NA
	Jan. 18, 2010	AE 201010540NA
	Jan. 22, 2010	AE 201011106GPV
	Jan. 22, 2010	AE 201011319NA
	Jan. 27, 2010	AE 201011811NA
	Jan. 28, 2010	AE 201011714GPV
	Jan. 28, 2010	AE 201013164GPV
	Jan. 29, 2010	AE 201011741NA
	Jan. 29, 2010	AE 201011940NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

January 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Amanda Vidlak, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston

STATUS NOTICE

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

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PERMANENT CLOSURE

The study referenced above has reached its accrual goal and will be permanently closed **effective February 1, 2010**. Registration will be open until 11:59 p.m. PST on Monday February 1, 2010.

Please attach this notice to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

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January 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	Dec. 15, 2009	AE 200942044NA
	Dec. 16, 2009	AE 200933062NA
	Dec. 18, 2009	AE 200942141NA
	Dec. 23, 2009	AE 200942675NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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A National Clinical Research Group

December 15, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	Nov. 16, 2009	AE 200937511GPV
	Nov. 16, 2009	AE 200938156NA
	Nov. 16, 2009	AE 200938484NA
	Nov. 19, 2009	AE 200924223LA
	Nov. 19, 2009	AE 200939069NA
	Nov. 20, 2009	AE 200938931NA
	Nov. 30, 2009	AE 200941024NA
	Nov. 30, 2009	AE 200938484NA
	Dec. 4, 2009	AE 200933062NA
	Dec. 7, 2009	AE 200939069NA

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December 1, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	Nov. 4, 2009	AE 200937014NA
	Nov. 5, 2009	AE 200937723NA
	Nov. 6, 2009	AE 200936680NA
	Nov. 9, 2009	AE 200937511GPV
	Nov. 9, 2009	AE 200937700GPV
	Nov. 9, 2009	AE 200938156NA
	Nov. 11, 2009	AE 200935806NA

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November 15, 2009

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	Oct. 19, 2009	AE 200935806NA
	Oct. 26, 2009	AE 200936074GPV
	Oct. 26, 2009	AE 200936680NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Istvan Molnar – Bayer Schering Pharma Oy
Joyce Mull – NSABP
Maddy Balois – CTSU
Ellen Antonio – CTSU

Southwest
Oncology Group
A National Clinical Research Group

November 1, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	Oct. 5, 2009	AE 200932010NA(1)
	Oct. 7, 2009	AE 200931478NA(1)
	Oct. 9, 2009	AE 200934396GPV
	Oct. 15, 2009	AE 200922983NA(1)

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Lisa Gavigan
Jeri Jardine
Jennie Barrett
Istvan Molnar – Bayer Schering Pharma Oy
Joyce Mull – NSABP
Maddy Balois – CTSU

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: October 15, 2009
E-mailed Date: October 8, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Amanda Vidlak, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

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MEMORANDUM

This memorandum serves to notify sites that the Novartis contact for drug returns for zoledronic acid has changed. The telephone and Fax numbers in the last paragraph of Section 3.1c are no longer correct. For drug returns and disposals, please request a zoledronic acid drug return form by contacting Kristen White (kristen.white@novartis.com) from Novartis at phone number: 862-778-2969 or Fax: 973-781-3322.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
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Lisa Gavigan
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Jeannie Barrett
Istvan Molnar– Bayer Schering Pharma Oy
Maddy Balois– CTSU
Michelle Dubois – UVI, Inc.
Diep Tran - Novartis

Southwest
Oncology Group
A National Clinical Research Group

October 15, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	Sep. 28, 2009	AE 200933062NA
	Sep. 30, 2009	AE 200931701NA(1)
	Oct. 2, 2009	AE 200933353NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

October 1, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Amanda Vidlak, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

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MEMORANDUM

This memorandum serves to clarify questions regarding Revision #5 and the Model Consent Form. The current consent form states that patients will be randomized to an arm of the study that has not met its accrual goal. The ibandronate arm (Arm 3) has reached its accrual maximum of 1,400 patients and is now closed. The clodronate and zoledronic acid arms have returned to their original accrual maximums of 2,000 patients and are still accruing. To make this abundantly clear in the Informed Consent Form, SWOG is allowing sites with the approval of their local IRB to add language to their local consent forms stating the ibandronate arm is closed and patients will not have a chance to be randomized to that arm of the study. The study design has not been changed, therefore SWOG will not be removing ibandronate from the Model Consent Form, protocol or Fast Facts Sheet. Sites must also keep this information in their local consent forms.

If you have any further questions, please contact the Southwest Oncology Group Operations Office at 210/450-8808.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc:
PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
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Jeannie Barrett
Istvan Molnar– Bayer Schering Pharma Oy
Maddy Balois– CTSU
Michelle Dubois – UVI, Inc.

Southwest
Oncology Group
A National Clinical Research Group

October 1, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Amanda Vidlak, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

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MEMORANDUM

The purpose of this memorandum is to clarify follow-up laboratory test requirements conducted for **S0307**. The Southwest Oncology Group Quality Assurance Department has expressed that there have been multiple deficiencies for failure to obtain magnesium and phosphate when conducting follow-up lab tests to assess for toxicity. Please be aware that these tests are required for patient safety as stated in the FDA label for zoledronic acid even though they may not be routinely included in institution's chemistry panel. Failure to obtain these tests will be noted as a Deficiency upon audit. If you have any questions, please contact the Southwest Oncology Group Operations Office at 210/450-8808.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
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Southwest
Oncology Group
A National Clinical Research Group

October 1, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	Aug. 25, 2009	AE 200924334NA(2)
	Aug. 25, 2009	AE 200929525NA
	Aug. 26, 2009	AE 200923557NA (1)
	Aug. 31, 2009	AE 200929599GPV
	Sep. 2, 2009	AE 200929996NA
	Sep. 3, 2009	AE 200929582GPV
	Sep. 7, 2009	AE 200929599GPV(1)
	Sep. 9, 2009	AE 200931859NA
	Sep. 9, 2009	AE 200929996NA(1)
	Sep. 10, 2009	AE 200931478NA
	Sep. 11, 2009	AE 200931701NA
	Sep. 15, 2009	AE 200932010NA
	Sep. 16, 2009	AE 200930721NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

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Maddy Balois – CTSU

Southwest
Oncology Group
A National Clinical Research Group

September 1, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Amanda Vidlak, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston

STATUS NOTICE

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

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RE-ACTIVATION

The above referenced protocol is now re-activated for accrual, effective immediately. Please disregard the statement at the end of the Revision #5 memorandum saying accrual does not need to be suspended pending implementation of these changes.

Sites must have IRB approval of Revision #5 within 90 days of release of this memorandum. Please submit proof of IRB approval of Revision #5 to:

Coalition for National Cancer Cooperative Groups
1818 Market Street
Suite 1100
Philadelphia, PA 19103
FAX: 215/569-0206
E-mail: CTSURegulatory@ctsu.coccg.org

IRB approval must be submitted prior to registering further patients.

Randomization has been changed to two arms. The ibandronate arm has met its accrual goal, and accrual will not be extended due to contractual limitations. The clodronate and zoledronic acid arms have been allowed to return to the original accrual size of 2000 patients. If you have any questions or concerns, please contact the Southwest Oncology Group Operations Office at 210/450-8808

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
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Maddy Balois– CTSU
Michelle Dubois – UVI, Inc.

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: September 1, 2009
CTEP Submission Date: July 13, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Southwest Oncology Group Operations Office

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

REVISION #5

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

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REVISION #5

The primary purpose of Revision #5 is to increase the study's sample size to take advantage of the increasing accrual rate to allow greater power for the statistical comparisons planned in the study. Another purpose is to add a pharmacogenomic translational medicine study to the protocol. Details related to these changes and additional protocol clarifications are outlined below:

Face page: The version date of the protocol has been updated.

Page 2: Dr. Catherine Van Poznak was added as a co-coordinator for pharmacogenomics.

Objectives, Page 6: Objective 1.7 was added to incorporate the primary study objective for the pharmacogenomic study:

> *"To investigate whether there is an association between inherited germ-line single nucleotide polymorphisms (SNP, rs2297480) in farnesyl diphosphate sythase (FDPS) and the adverse event of acute phase reactions in this cohort of patients (see Appendix 19.3)."*

Section 2.0, Page 13: Background on pharmacogenomics as well as a reference to the pharmacogenomic studies appendix (Appendix 19.3) were added. The paragraph on serum banking was updated to include WBC banking.

Section 2.0, Page 13a: The accrual table documenting the inclusion of race and ethnic subsets was updated to accommodate the new projected accrual numbers.

Section 3.2c and Section 3.3c, Pages 19 and 22: Handling and disposal/Drug returns – these sections have been updated to indicate that drug returns should be noted in the patient record (rather than the drug accountability ledger).

Section 5.3, Page 26: This section has been clarified by adding "…for the cancer." to the end of the second sentence regarding surgery timing. In the third sentence, "completion" was clarified as "the last administration".

Section 5.4, Page 26: The collection of whole blood was added to the specimens referenced in this section.

Section 7.3, Page 29: An editorial error was corrected. During the first six months of dosing, it is suggested that infusions of zoledronic acid be given within ± 2 days (rather than ± 7 days).

Section 7.7, Page 30 : This section was revised to ensure consistency with the drug information instructions. Oral bisphosphonates should be taken at least one hour (rather than 30 minutes) before the first food or drink of the day other than water.

Section 7.10, Page 30 and Section 9.0, "£" footnote, Page 32: A sentence was added to clarify that "Patients who have had a bone scan within 6 months prior to ending treatment will not be required to have the scan repeated."

Section 7.12a, Page 31: The first criterion for removal from protocol treatment was clarified to exclude the diagnosis of a second non-breast primary as a reason for removal from protocol treatment and to clarify that diagnosis of DCIS without an invasive component is not considered to be a recurrence or second primary.

Section 8.3, Page 31: The first sentence of this section was revised to clarify the levels of creatinine increase requiring action.

Section 8.4, Page 31: This section has been updated to clarify timing of treatment, and treatment delays and rescheduling on zoledronic acid arm of the study. Page 31a was added to prevent extensive repagination.

Section 9.0 (Study Calendar), Page 32: The Study Calendar was revised to delete the "End of Treatment" column as for most patients the end of treatment will occur at Month 36. The requirements for the end of treatment dental exam and bone scan were moved to Month 36. The "Ψ" and "α" footnotes were edited to delete the phase "for 36 months" because the oral drug treatment actually ends on the first day of Month 36. The "ƒ" footnote was edited to change the section reference from 7.8 to 7.11. The whole blood specimen collection and an associated "β" footnote was added.

Sections 10.1 and 10.2, Page 33: These sections were updated to clarify that DCIS without an invasive component is not considered to be a recurrence.

Sections 11.1, 11.2 and 11.4-11.6, Pages 33-34b: The Statistical Considerations were updated to accommodate the increased sample size for the study. The overall planned accrual of eligible patients will be 5,400 (2,000 to receive zoledronic acid, 2,000 to receive clodronate and 1,400 to receive ibandronate). Page 34b was added to prevent extensive repagination.

Sections 15.1 and 15.4 (Pages 38 and 40): These sections were revised to incorporate the submission of a single whole blood specimen per patient

Tables 16.1 and 16.2 (Pages 44 and 45): The title of Table 16.1 was edited. Footnote "3" in Table 16.1 and footnote "c" in Table 16.2 were both updated to indicate that osteonocrosis of the jaw (regardless of grade, attribution or expectedness) is to be reported in an expedited fashion.

Section 17.0, Page 46: Bibliography entry #16 was corrected.

Model Informed Consent Form: Under "How Many People will take part in the study?" Page 53, the number of participants was updated from 4,500 to 5,400. A bullet item was added to page 54 to describe the optional collection of whole blood. Also on page 54 the description of the randomization process was updated to match the current accrual plan. Page 54a was added to prevent extensive repagination.

A new question related to optional participation in the submission of a whole blood specimen for DNA analysis was added to the optional studies questions on Page 62. A reference to "whole blood" was added into the list of the types of specimens applicable to the "Consent Form for Use of Specimens for Research on Page 63.

The **S0307** Registration Form has been updated to collect the answer to the consent question related to the submission of whole blood. The form number has been changed from #63147 to #46563. This change is also reflected in Section 18.2a, Page 50. The **S0307** Adverse Event Summary Form has been updated to add details regarding the reporting of osteonocrosis of the jaw. The form number has been changed from #11983 to #22831. This change is also reflected in Sections 14.5, 14.7 and 14.9 (Page 37), as well as Section 18.2d (Page 50).

Appendix 19.3 has been inserted (Pages 89-95) and has been added to the appendix list on Page 83.

Institutions must update their local consent forms to reflect these changes for future registrations and are expected to have received IRB approval of these consent form changes within 90 days after distribution of this revision. **It is strongly recommended that patients already registered to the protocol (including those who have been removed from protocol treatment) as well as newly registered patients be given the opportunity to consent to submission of a whole blood specimen prior to the time of their next blood draw for routine laboratory testing so that the specimen may be collected at the same time**. The whole blood specimen may be drawn at any time during the patient's clinical care or planned phlebotomy and at any time during study participation or follow-up. Patients need not be on protocol treatment at the time of this draw. Patients currently registered to the protocol need not be informed of the accrual requirement changes unless required by the local Institutional Review Board (IRB).

The Southwest Oncology Group considers that the Model Consent Form changes do not represent an alteration in risk-benefit ratio. Therefore, local accrual does not need to be suspended pending implementation of these changes.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Diep Tran - Novartis
Benedicte Marion - Hoffman - Laroche, Ltd.
Maddy Balois - CTSU

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: September 1, 2009
Emailed Date: August 20, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Amanda Vidlak, Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

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MEMORANDUM

UVI, Inc., drug distributor for the **S0307** trial, has confirmed that they are experiencing a temporary shortage of clodronate tablets. The clodronate tablets continue to be manufactured by Bayer Schering Pharma Oy; however, a new shipment is not expected in the UVI warehouse until early next week.

While we anticipate that this shortage will only last a week, please contact UVI, Inc. at 800/370-2508 before registering a patient to check on available clodronate supplies and to adjust registration plans and/or treatment start dates accordingly. While it is our hope that registered patients on the clodronate arm have necessary supplies on hand, there may be instances where an interruption in treatment may be experienced. If a treatment interruption occurs, please contact UVI, Inc. so that clodronate re-supply orders can be expedited once the shortage is resolved.

Note: Any delay in the treatment start date or treatment interruption due to the drug shortage will not be considered a protocol deviation; however institutions should document in the research chart the reason for the delay/interruption.

Please attach this memorandum to the front of your copy of the protocol.

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Southwest
Oncology Group
A National Clinical Research Group

September 1, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	Aug. 6, 2009	AE 200928049NA
	Aug. 7, 2009	AE 200928622NA
	Aug. 10, 2009	AE 200925618NA(1)
	Aug. 11, 2009	AE 200927439GPV
	Aug. 17, 2009	AE 200927923NA(1)

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Southwest
Oncology Group
A National Clinical Research Group

August 15, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	July 29, 2009	AE 200926222GPV
	July 31, 2009	AE 200927870NA
	Aug. 5, 2009	AE 200927923NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Lisa Gavigan
Jeri Jardine
Jennie Barrett
Istvan Molnar – Bayer Schering Pharma Oy
Joyce Mull – NSABP
Maddy Balois – CTSU

Southwest
Oncology Group
A National Clinical Research Group

Mailed: August 1, 2009
Emailed: July 24, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Southwest Oncology Group Operations Office

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

STATUS NOTICE

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

TEMPORARY CLOSURE

The study referenced above will be temporarily closed, **effective August 24, 2009**, due to significant protocol changes currently under development.

Please attach this memorandum to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to inform the Southwest Oncology Group Statistical Center and the NCI.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Lisa Gavigan
Jeri Jardine
Jennie Barrett
Istvan Molnar – Bayer Schering Pharma Oy
Diep Tran – Novartis
Benedicte Marion – Hoffman-LaRoche, Ltd.
Maddy Balois – CTSU
Michelle Dubois - UVI

Southwest
Oncology Group
A National Clinical Research Group

July 1, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	May 27, 2009	AE #200920113GPV(1)
	May 28, 2009	AE #200920420GPV(1)
	June 1, 2009	AE #200921670NA
	June 3, 2009	AE #200911902BNE
	June 3, 2009	AE #200913597NA(1)
	June 3, 2009	AE #200921359NA*
	June 8, 2009	AE #200920427NA(1)
	June 10, 2009	AE #200913597NA(2)
	June 12, 2009	AE #200922309NA
	June 15, 2009	AE #200922677GPV
	June 16, 2009	AE #200923025NA
	June 17, 2009	AE #200921359NA(1)*
	June 18, 2009	AE #200922882GPV
	June 19, 2009	AE #200915232NA(1)
	June 19, 2009	AE #200911902BNE(1)
	June 22, 2009	AE #200922983NA
	June 22, 2009	AE #200923344GPV
	June 22, 2009	AE #200923338GPV
	June 22, 2009	AE #200923273GPV
	June 22, 2009	AE #200923327GPV
	June 22, 2009	AE #200923211GPV*

* Note: The numbering system differs from the numbering noted on the manufacturer's report.

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

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Joyce Mull – NSABP
Maddy Balois – CTSU

Southwest
Oncology Group
A National Clinical Research Group

June 15, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following study:

S0307 Breast

Reports:

April 29, 2009	AE #200918353NA
May 7, 2009	AE #2006032513(6)
May 11, 2009	AE #200919383NA
May 11, 2009	AE #200919936GPV
May 11, 2009	AE #200920113GPB
May 13, 2009	AE #200920420GPV
May 21, 2009	AE #200917399NA(1)
May 25, 2009	AE #200920427NA

* Note: The numbering system differs from the numbering noted on the manufacturer's report.

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Joyce Mull – NSABP
Maddy Balois – CTSU

Southwest
Oncology Group
A National Clinical Research Group

June 1, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

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- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

UVI, Inc., drug distributor for the **S0307** trial, has confirmed that they are experiencing another temporary shortage of clodronate tablets. The clodronate tablets continue to be manufactured by Bayer Schering Pharma Oy; however, a new shipment is not expected to be released for shipment until next week.

While we anticipate that this shortage will only last approximately 1-2 weeks, please contact UVI, Inc. at 800/370-2508 before registering a patient to check on available clodronate supplies and to adjust registration plans and/or treatment start dates accordingly. While it is our hope that registered patients on the clodronate arm have necessary supplies on hand, there may be instances where an interruption in treatment may be experienced. If a treatment interruption occurs, please contact UVI, Inc. so that clodronate re-supply requests will be expedited once the shortage is resolved.

Note: Any delay in the treatment start date or treatment interruption due to the drug shortage will not be considered a protocol deviation; however institutions should document in the research chart the reason for the delay/interruption.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
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Lisa Gavigan
Jeri Jardine
Jeannie Barrett
Istvan Molnar– Bayer Schering Pharma Oy
Maddy Balois– CTSU

Southwest
Oncology Group
A National Clinical Research Group

May 15, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
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(√) Expedited review allowed

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MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	April 14, 2009	AE #200916443NA(1)
	April 15, 2009	AE #200916901NA
	April 17, 2009	AE #200917399NA
	April 20, 2009	AE #2006032513(5)*

* Note: The numbering system differs from the numbering noted on the manufacturer's report.

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

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Maddy Balois – CTSU

Southwest
Oncology Group
A National Clinical Research Group

April 15, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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- ( ) Addition of tissue banking requirements
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MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	March 18, 2009	AE #200914480NA
	March 19, 2009	AE #200916296GPV
	March 24, 2009	AE #200915232NA
	March 27, 2009	AE #200815097NA(3)
	April 1, 2009	AE #200916443NA
	April 1, 2009	AE #200916112NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Joyce Mull – NSABP
Maddy Balois – CTSU

Southwest
Oncology Group
A National Clinical Research Group

April 1, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	March 2, 2009	AE #200913597NA
	March 2, 2009	AE #2007006800(2)*
	March 3, 2009	AE #200913939GPV*
	March 6, 2009	AE #200912953NA(1)

* Note: The numbering system differs from the numbering noted on the manufacturer's report.

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Joyce Mull – NSABP
Maddy Balois – CTSU

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: March 15, 2009
E-mailed Date: March 10, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

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- ( ) Complete study redesign
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MEMORANDUM

UVI, Inc., drug distributor for the **S0307** trial, has confirmed that they are experiencing another temporary shortage of clodronate tablets. The clodronate tablets continue to be manufactured by Bayer Schering Pharma Oy; however, a new shipment is not expected to be released for shipment until next week.

While we anticipate that this shortage will only last a few days, please contact UVI, Inc. at 800/370-2508 before registering a patient to check on available clodronate supplies and to adjust registration plans and/or treatment start dates accordingly. While it is our hope that registered patients on the clodronate arm have necessary supplies on hand, there may be instances where an interruption in treatment may be experienced. If a treatment interruption occurs, please contact UVI, Inc. so that clodronate re-supply requests will be expedited once the shortage is resolved.

Note: Any delay in the treatment start date or treatment interruption due to the drug shortage will not be considered a protocol deviation; however institutions should document in the research chart the reason for the delay/interruption.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
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Lisa Gavigan
Jeri Jardine
Jeannie Barrett
Istvan Molnar– Bayer Schering Pharma Oy
Maddy Balois– CTSU

Southwest
Oncology Group
A National Clinical Research Group

March 15, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	February 12, 2009	AE #200812671NA(3)
	February 16, 2009	AE #200815097NA(2)
	February 20, 2009	AE #200913537GPV
	February 23, 2009	AE #200913715GPV
	February 23, 2009	AE #200912953NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Jennie Barrett
Istvan Molnar – Bayer Schering Pharma Oy
Joyce Mull – NSABP
Maddy Balois – CTSU

Southwest
Oncology Group
A National Clinical Research Group

February 15, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	January 6, 2009	AE #200833071NA(1)
	January 6, 2009	AE #200836438NA(1)
	January 8, 2009	AE #200839971NA(2)*
	January 19, 2009	AE #200910081NA*

* Note: This is a follow-up report which differs from the numbering noted on the manufacturer's report.

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

January 15, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	December 24, 2008	AE #200831463NA
	December 31, 2008	AE #200839971NA*

* Note: This is a follow-up report which differs from the numbering noted on the manufacturer's report.

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Megan Rossmann – CTSU

Southwest
Oncology Group
A National Clinical Research Group

January 1, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	December 3, 2008	AE #200812671NA(2)
	December 3, 2008	AE #200837950NA(1)
	December 3, 2008	AE #200831128GPV
	December 5, 2008	AE #200831457GPV
	December 11, 2008	AE #200839971NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

December 15, 2008

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following study:

S0307 Breast

Reports:

November 3, 2008	AE #200828012GPV(2)
November 3, 2008	AE #200836245NA
November 6, 2008	AE #200835467NA(1)
November 6, 2008	AE #200836438NA
November 6, 2008	AE #200829635GPV
November 19, 2008	AE #200823590GPV(1)
November 21, 2008	AE #200829635GPV(1)
November 21, 2008	AE #200837950NA
November 21, 2008	AE #200838304NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

November 15, 2008

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	October 9, 2008	AE #200834239NA
	October 9, 2008	AE #200835032NA
	October 17, 2008	AE #200828012GPV
	October 21, 2008	AE #200835467NA
	October 22, 2008	AE #200824407NA(2)
	October 22, 2008	AE #200834239NA(1)
	October 22, 2008	AE #200828565GPV
	October 27, 2008	AE #2007006800(1)*
	October 27, 2008	AE #200828012GPV(1)

* Note: This is a follow-up report which differs from the numbering noted on the manufacturer's report.

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This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Lisa Gavigan
Jeri Jardine
Jennie Barrett
Jens Kuhlmann – Bayer Schering Pharma Oy
Joyce Mull – NSABP
Megan Rossmann – CTSU

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Oncology Group
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These safety reports pertain to the following study:	Reports:	
S0307 Breast	September 5, 2008	AE #2007041732(1)
	September 5, 2008	AE #200829546NA(1)
	September 23, 2008	AE #200833071NA
	October 1, 2008	AE #200824407NA(1)
	October 1, 2008	AE #200833892NA
	October 3, 2008	AE #200826944GPV

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October 1, 2008

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	August 8, 2008	AE #200823590GPV
	August 14, 2008	AE #200829546NA
	August 20, 2008	AE #200816114GPV(1)
	August 28, 2008	AE #200824957GPV
	August 29, 2008	AE #200831463NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: September 15, 2008
CTEP Submission Date: July 25, 2008

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

REVISION #4

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

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REVISION #4

The protocol referenced above has been amended as follows:

1. (Title page): The version date has been updated (version 07/25/08).

2. (Page 9a, Section 2.0, Background): Recent information regarding the use of adjuvant bisphosphonate therapy has been added.

3. (Page 26, Section 5.6, Eligibility Criteria): The first sentence has been revised.

   "Patients must not be co-enrolled on protocols that have bone density as an endpoint, such as NCIC-CTG study MA.27."

   Has been changed to:

   "Patients must not be co-enrolled on protocols that have bone density as an endpoint."

   (Rationale: With the recent closure of the bone density substudy, MA.27B, S0307 patients are allowed to co-enroll in MA.27.)

4. (Page 30, Section 7.10, Treatment Plan): Following the 2nd sentence, the following additional sentence regarding the end of treatment dental exam has been added for clarification:

"*The end of treatment dental examination must be performed regardless of how long the patient was on treatment (including one month or less)."*

5. (Page 32, Section 9.0, Study Calendar): The first sentence of the "λ" footnote has been revised for clarification purposes.

"Dental exam should be performed at the beginning and end of the treatment."

Has been changed to:

"Dental exam should be performed at the beginning and end of the treatment (regardless of how long the patient was on protocol treatment, see Section 7.10)."

6. (Pages 36-37, Section 14.0, Data Submission Schedule): The following changes have been made to this section:

- Section 14.3b: The following information regarding the submission of faxed data has been added at the end of this section:

  "Please make sure that each page of all faxed data includes the SWOG patient number, study ID, and patient initials."

- Section 14.6: The data submission instructions have been revised to be consistent with the end of treatment evaluation schedule as outlined in Section 7.10:

  *"*WITHIN 90 DAYS OF DISCONTINUATION OF TREATMENT"

  Has been changed to:

  "WITHIN *6 MONTHS* OF DISCONTINUATION OF *PROTOCOL* TREATMENT"

7. (Pages 44-45, Section 16.1, Adverse Event Reporting Guidelines): The following changes have been made to this section:
   - Table 16.1: This table has been updated to reflect additional reporting instructions for possible cases of osteonecrosis of the jaw associated with the commercial agent zoledronic acid (Arm 1). More specifically, an additional footnote ("3") has been added to Table 16.1 stating the following:

     "Protocol-specific reporting requirements: *The adverse events listed below also require expedited monitoring for this trial: Osteonecrosis of the jaw, occurring in Arm 1 patients who have received zoledronic acid. All other adverse events on Arm 1 patients should be reported per guidelines in Table 16.2."*

   - Table 16.2: This table has been updated to reflect additional reporting instructions for possible cases of osteonecrosis of the jaw. More specifically, an additional footnotes ("c & d") have been added to Table 16.2 stating the following, respectively:

     "***Protocol-specific expedited reporting requirements:*** *The adverse events listed below also require expedited monitoring for this trial: Osteonecrosis of the jaw (see Table 16.1)*"

     "***Any Group-specific instructions.*** *The SWOG Operations Office will notify Novartis as required*."

8. (Page 49, Section 17.0, Bibliography): The bibliography section has been updated. References #66-67 have been added.

9. (Page 50, Section 18.2, Master Forms Set): The following changes have been made to this section:
   - Section 18.2a: The **S0307** Registration Form has been updated from Form #50085 to Form #*63147*.
   - Sections 18.2f & 18.2l: The 6/1/08 version date has been included next to each form number.

10. (Page 54, Model Consent Form, During the study...): Under the paragraph that begins "You will need these tests and procedures...", the first bullet regarding PTHrP testing has been revised for editorial purposes.

    "Tumor block for PTHrP testing and banking: a sample of tumor from the original biopsy will be removed and analyzed for parathyroid hormone related protein (PTHrP) to see if the breast cancer has spread to the bones. If you consent, any remaining sample will be stored frozen for future scientific studies."

    Has been changed to:

    "Tumor block for PTHrP testing and banking: a sample of *your* tumor from the original biopsy will be removed and analyzed for parathyroid hormone related protein (PTHrP) to see if *this predicts the risk of your* breast cancer *spreading* to the bones. If you consent, any remaining sample will be stored frozen for future scientific studies."

11. (Page 54, Model Consent Form, During the study...): The paragraph that begins, "If you are in Group 1 (often called "Arm 1")...", has been revised to be consistent with the current treatment plan for zoledronic acid.

    "...every 4 weeks for the first six months..."

    Has been changed to:

    "...every *month* for the first six months..."

12. (Page 59a, Model Consent Form, Are there benefits to taking part in the study?): An additional paragraph relating to the recent information regarding the use of adjuvant bisphosphonate therapy has been added:

    "*Some small trials of clodronate have suggested some possible benefit for that drug, although with conflicting results, and now a study with zoledronic acid showed benefit for dosing twice a year in pre-menopausal women, with estrogen-receptor positive breast cancer receiving ovarian suppression and not chemotherapy. However, at present, it is not standard of care to give these drugs in the majority of breast cancer patients*."

13. Page 62, Model Consent Form, Additional research studies): The following editorial changes have been made to each of the yes/no questions relating to tissue/blood testing:

    - Tissue

      "I agree to submit a tissue specimen...to see if this predicts the risk of your breast cancer spreading to the bones."

      Has been changed to:

      "I agree to submit a tissue specimen...to see if this predicts the risk of *my* breast cancer spreading to the bones."

- Blood

  "I agree to submit a blood sample...to see if high levels will predict the risk of your breast cancer spreading to the bones."

  Has been changed to:

  "I agree to submit a blood sample...to see if high levels will predict the risk of *my* breast cancer spreading to the bones."

- Formatting changes were made throughout the section which did not affect content.

Institutions should update their Model Consent Forms to include the above information for future registrations. Patients currently being treated on this study should be informed of these changes in the manner determined by the local institutional review board (IRB).

The Southwest Oncology Group considers that the changes in the Model Consent Form that are associated with this revision are solely administrative and editorial in nature and do not significantly impact the risk/benefit ratio for participants on this study. Local accrual to the study does not need to be suspended pending implementation of these changes.

Please attach this memorandum to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to inform the Southwest Oncology Group Statistical Center and the NCI.

cc: PROTOCOL & INFORMATION OFFICE
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September 1, 2008

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	July. 31, 2008	AE 200816556GPB(1)
	August. 4, 2008	AE 200822387NA(1)
	August. 4, 2008	AE 200828478NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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August 1, 2008

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	June 27, 2008	AE #200825602NA
	June 27, 2008	AE #200715313NA(2)
	July 14, 2008	AE #200825602NA(1)

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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July 1, 2008

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	June 10, 2008	AE #200815097NA(1)
	June 11, 2008	AE #200824407NA
	June 12, 2008	AE #200811207LA(1)

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June 15, 2008

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S0307 Breast	May 14, 2008	AE #200821861NA
	May 14, 2008	AE #200821886NA
	May 16, 2008	AE #200822387NA
	May 20, 2008	AE #200820008NA(2)
	May 29, 2008	AE #200818891GPV
	May 30, 2008	AE #200818690GPV
	May 30, 2008	AE #200812671NA(1)
	June 3, 2008	AE #200819168GPV
	June 4, 2008	AE #200715313NA(1)
	June 5, 2008	AE #200811207LA

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	April 22, 2008	AE #200816643GPV
	April 23, 2008	AE #200816556GPV
	April 23, 2008	AE #200820008NA
	May 1, 2008	AE #200820008NA(1)

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Distribution Date: June 1, 2008
CTEP Submission Date: March 11, 2008

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FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

AMENDMENT #2

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

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AMENDMENT #2

The protocol referenced above has been amended as follows:

1. (Amendment #1, distributed 10/15/07, item #7, page 2): A typo in the change was incorrectly described as Section 3.2a. The correct section should be *Section 3.2c*.

2. (Fast Fact Sheet): The following changes have been made to this page:
   - Treatment (Arm 1 – Zoledronic acid): "q 4 weeks for 6 months…" has been changed to "q *monthly* for 6 months".
   - Prestudy requirements: The timeframe for the prestudy pregnancy test has corrected. "≤ 24-72 hours" has been changed to ""≤ 72 hours".

   (Reason: The prestudy requirement and treatment sections have been changed to match the modifications to the eligibility criteria and treatment plan, Sections 5.0 and 7.0, respectively. See also items #6 and #9 below.)

3. (Title page): The following changes have been made to this page:
   - The version date has been updated (version 03/11/08).
   - Under the participant list, the bolded statement "Patient enrollments…should be sent to the SWOG Data Operations unless otherwise specified…" has been changed to: "Patient enrollments…should be sent to the SWOG Data Operations *Center as* specified…"

4. (Page 4, CTSU Contact Information): In the patient enrollment column, the following updated CTSU information has been added:
   - The CTSU office hours have changed from 8:00 am – 8:00 pm EST to *9:00 am – 5:30 pm* EST.
   - The statement in brackets that begins "For CTSU patient enrollments that must be completed within approximately one hour…" has been replaced with the following:

   "*Registrations received after 5:00 pm EST will be handled the next business day. For CTSU enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301/704-2376 between 9:00 am – 5:30 pm EST.*"

5. (Page 15, Section 3.1b, Background): The zoledronic acid (Zometa®) drug information section has been modified to include new adverse event information. **Particularly important are the new labeling changes in the toxicology section regarding musculoskeletal pain, ocular adverse events, and hypersensitivity reactions.** (*Reason: This section was updated to be consistent with the most recent zoledronic acid package insert.*) Page 15a has been added to prevent extensive repagination.

6. (Page 27, Section 5.12, Eligibility Criteria): The last sentence has been amended. "Women of child-bearing potential must have a pregnancy test within 24-72 hours prior to initiation of treatment" has been changed to "Women of child-bearing potential must have a pregnancy test within *72 hours* prior to initiation of treatment". *(Reason: This change was made in order to allow pregnancy tests to be performed on Friday preceding treatment the following Monday.)*

7. (Page 28, Section 7.1, Good Medical Practice): The following changes have been made to this section:
   - Section 7.1d: Magnesium testing has been added. *(Reason: This change was made to provide consistency as magnesium testing is listed in the study calendar, Section 9.0.)*
   - Section 7.1e: The electrolyte chemical names for "Na^+, K^+, Cl^-, HCO_3^-" have been changed to "*sodium, potassium, chloride, and bicarbonate*", respectively. *(Reason: This change was made for editorial purposes.)*

8. (Page 28, Section 7.2, Treatment Plan): This section has been titled "*Pre-Treatment Guidelines*." In the second bolded paragraph, "Women of child-bearing potential must have a pregnancy test performed within 24-72 hours prior to initiation of treatment" has been changed to "Women of child-bearing potential must have a pregnancy test performed within *72 hours* prior to initiation of treatment". *(Reason: See item #6 above.)*

9. (Page 29, Section 7.3, Treatment Plan): The following changes have been made to this page:
   - This title of this section, "Treatment Plan" has been changed to "*Treatment Schedule*". (*Reason: This change was made for editorial purposes*.)
   - The following dosing instructions have been amended:

   "For patients receiving zoledronic acid, peripheral or central intravenous access may be used. Every effort should be made to administer zoledronic acid to patients in Arm 1 every 4 weeks during the first 6 months of dosing, however minor deviances from these dosing intervals are acceptable. It is suggested that the infusions be given within ± 2 days (2 days earlier or later). During the remaining period of dosing, zoledronic acid may be given within ± 7 days (7 days earlier or later). The last dose of zoledronic acid in Arm 1 should be administered at Month 33. Oral bisphosphonates given in Arms 2 and 3 are to continue daily until the first day of Month 36 and are then discontinued."

Has been changed to:

"For patients receiving zoledronic acid, peripheral or central intravenous access may be used. *During the first 6 months of dosing, zoledronic acid should be administered to patients in Arm 1 monthly, however, minor deviances from this dosing interval are acceptable. It is suggested that the infusions be given within ± 1 week (7 days earlier or later).* During the remaining period of dosing, zoledronic acid may be given within ± *1 week* (7 days earlier or later). The last dose of zoledronic acid in Arm 1 should be administered at Month 33. Oral bisphosphonates given in Arms 2 and 3 are to continue daily until the first day of Month 36 and are then discontinued." (*Reason: This change from q 4 weeks to q monthly was made to provide consistency with the schema of the trial*.)

- Treatment table: The interval of zoledronic acid dosing has been changed from "q 4 weeks x 6 months…" to "q *monthly* x 6 months…" (*Reason: This change from q 4 weeks to q monthly was made to provide consistency with the schema of the trial*.)

10. (Page 29, Section 7.4, Treatment Plan): The section has been titled "*Dental Examination*". (*Reason: This change was made for editorial purposes*.)

11. (Page 30, Section 7.9, Treatment Evaluations): A new Section 7.9 titled "Treatment Evaluations" has been included that clarifies the timing of physical exams and lab testing while on protocol treatment as follows (subsequent sections have been re-organized):

"*Physical exams and labs (including CBC, electrolytes, calcium, phosphate, magnesium, albumin, and LFTs) should be performed prior to dosing (ideally Day 1) of Month 2, 4, 6, then q 3 months until Month 36.*

For Arm 1, serum creatinine testing must be performed within 7 days prior to administering subsequent zoledronic acid dosing q monthly for Months 2-6, then q 3 months until Month 36.

For Arms 2 & 3, serum creatinine testing should be performed ± 7 days (7 days earlier or later) q monthly for Months 2-6, then q 3 months until Month 36."

Page 30a has been added to prevent extensive repagination.

12. (Page 30, Section 7.10, End of Treatment Evaluation): The first sentence has been amended. "A bone scan will be obtained in all patients…" has been changed to "*An end of treatment physical examination and a* bone scan will be obtained in all patients…" (*Reason: This change was made to highlight the end of treatment physical examination that is required upon study completion in addition to the bone scan and final dental examination*.)

13. (Page 31, Section 8.2, Toxicities to be Monitored): Patient removal instructions have been amended as follows:

"Any Grade 3 or greater toxicity (that is attributed to the bisphosphonate by the treating physician) will require removal of the patient from protocol treatment."

Has been changed to:

"*Bisphosphonate therapy must be held for any Grade 3 or greater toxicity (that is attributed to the bisphosphonate by the treating physician). If toxicity has not resolved within 4 weeks, then the patient must be removed from protocol treatment. If toxicity resolves (Grade 0-1) within 4 weeks, the protocol treatment should be restarted. If Grade 3 or greater toxicity reoccurs, then the patient must be removed from protocol treatment.*"

(*Reason: This change was made to allow patients to remain on bisphosphonate treatment after resolution of Grade 3 or greater toxicity*.)

14. (Page 32, Section 9.0, Study Calendar): The following changes have been made to this page:

- Ω footnote: The instructions for the zoledronic acid treatment footnote have been amended.

  "Zoledronic acid will be administered by IV on Day 1 q 4 weeks for the first 6 months, however minor deviations are acceptable. It is suggested that the infusions be given within ± 2 days (2 days earlier or later). During the remaining period of dosing, zoledronic acid may be given within ± 7 days (7 days earlier or later)."

  Has been changed to:

  "Zoledronic acid will be administered by IV on Day 1 q *monthly* for the first 6 months, however minor deviations are acceptable. It is suggested that the infusions be given within *± 1 week (7 days earlier or later).* During the remaining period of dosing, zoledronic acid may be given within *± 1 week* (7 days earlier or later)."

- *ƒ* footnote: The instructions for the patient follow-up footnote have been amended.

  "Patients off treatment prior to recurrence should return for disease assessments at least every 6 months for 5 years…"

  Has been changed to:

  "*All patients including* patients off treatment prior to recurrence should return for disease assessments at least every 6 months for 5 years…"

- ◊ footnote: The instructions for the serum creatinine footnote have been amended.

"To be performed within 7 days prior to registration, and within 7 days prior to administering all subsequent doses."…"

Has been changed to:

"*Arm 1:* To be performed within 7 days prior to registration, and within 7 days prior to administering all subsequent doses. *Arm 2/Arm 3: To be performed within 7 days prior to registration, and within ± 7 days (7 days earlier or later) of q monthly for Months 2-6 and q 3 month patient visits."*

(Reason: Study calendar changes were made provide consistency with the protocol changes as noted above.)

15. (Page 37, Section 14.0, Data Submission Schedule): The following changes have been made to this section:

- Section 14.5: A new **S0307** Serum Creatinine Reporting Form (Form #60188) has been added. This form should be submitted during treatment at 6 months, and Year 1, 2 and 3.

- Section 14.7: The data submission instructions have been amended as follows:

  WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

  Submit the Off Treatment Notice Form (Form #8756) and **S0307** Supplementary Off-Treatment Form (Form #24801).

  Has been changed to:

  "WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

  Submit copies of the following:

  a. Off Treatment Notice (Form #8756)
  *b. **S0307** Supplementary Off Treatment Form (Form #24801)*
  *c. Final **S0307** Treatment Form (Form #31453) for current reporting period*
  *d. Final **S0307** Adverse Event Summary Form (Form #11093)"*

- Section 14.8: The **S0307** Supplementary Follow-Up Form (Form #9679) has been replaced with Form #36846.

- Section 14.9: The data submission instructions have been amended as follows:

  WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

  Submit the Follow-Up Form (Form #64587) and **S0307** Supplementary Follow-Up Form (Form #9679).

  Has been changed to:

  "WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

  Submit copies of the following:

  a. Follow-up Form (Form #64587) documenting date, site and method for determining malignancy
  *b. **S0307** Supplementary Follow-Up Form (Form #36846)*
  *c. If patient was still on treatment, final **S0307** Treatment Form (Form #31453) for current reporting period*
  *d. If patient was still on treatment, final **S0307** Adverse Event Summary Form (Form #11093)"*

  Page 37a was added to prevent extensive repagination.

16. (Page 38, Section 15.2c, Special Instructions): In the paragraph that begins, "To report technical problems with Specimen Tracking…", the website link for the Specimen Tracking system has been changed from "http://dnet.crab.org/SpecTrack/Documents/SpecTPrimer-Insts.pdf" to "*https://gill.crab.org/SpecTrack/Documents/Instructions.pdf*".

17. (Pages 39 & 41, Sections 15.3e & 15.4d, respectively, Special Instructions): The room number for shipping specimens to the SWOG Solid Tumor Bank has changed from "L18-5104" to "L18-*5400A*". Also, the zip code has been updated from "80010" to "*80045".*

18. (Page 42, Section 16.1, Adverse Event Reporting Requirements): The following changes have been made to this section:
    - Section 16.1b: CTEP no longer accepts phone or fax notification of SAEs which require 24-hour reporting. All such reports must now be submitted via AdEERS. In addition, use of AdEERS paper templates as a substitute for on-line AdEERS reporting is no longer allowed. Thus, the ADEERS reporting instructions have been updated as follows:

      "This study requires that expedited adverse event reporting use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at http://ctep.cancer.gov. An AdEERS report must be submitted to the Southwest Oncology Group Operations Office *electronically via the AdEERS Web-based application located at http://ctep.cancer.gov*."

    - Section 16.1c: The following instructions have been amended. "When the adverse event requires expedited reporting, submit the report within 7 working days of learning of the event" has been changed to "When the adverse event requires expedited reporting, submit the report within *the number of calendar days of learning of the event as specified in Table 16.1 or 16.2, as applicable*." (*Reason: This change was made to provide consistency with the ADEERS reporting instructions as specified in Tables 16.1 and 16.2.*)

19. (Page 45, Section 16.0, Adverse Event Reporting Requirements): The following changes have been made to this section:
    - Table 16.1: Table 16.1 has been updated to reflect changes in Southwest Oncology Group Policy No. 23. More specifically, an additional footnote ("b") has been added to Table 16.1 stating that following an AdEERS report, supporting data need not be submitted unless specifically requested by SWOG.
    - Section 16.1f: The instructions for reporting secondary AML/MDS to the Investigational Drug Branch have been updated.

      "All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following chemotherapy for cancer must be reported using the NCI/CTEP Secondary AML/MDS Report Form in lieu of AdEERS. The following supporting documentation must also be submitted within 30 days."

      Has been changed to:

      "All cases of acute myeloid leukemia (AML), *acute lymphocytic leukemia (ALL)*, and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following chemotherapy for cancer must be reported using the NCI/CTEP Secondary AML/MDS Report Form in lieu of AdEERS. *The form can be downloaded at http://ctep.cancer.gov/forms/33-AML_20Form_20v1.pdf.* The following supporting documentation must also be submitted within 30 days."

20. (Page 50, Section 18.0, Master Forms Set): The following changes have been made to this section:

    - Section 18.2f: The **S0307** Supplementary Follow-Up Form (Form #9679) has been replaced with Form #36846.
    - Section 18.2l: The **S0307** Serum Creatinine Reporting Form (Form #60188) has been added.

21. (Page 53, Model Consent Form, Before you being the study…): The last bullet has been amended. "Women …must have a pregnancy test performed within 24-72 hours…" has been changed to "Women…must have a pregnancy test performed within *72* hours…" *(Reason*: *See item #6 above.)*

22. (Page 55, Model Consent Form, Study Chart): The timing of pregnancy testing in the first column, fourth row, has been updated. "Within 24-72 hours prior to starting study" has been changed to "Within *72 hours* prior to starting study". (*Reason: See item #6 above*.)

23. (Page 56, Model Consent Form, When you are finished taking study drugs…): "You will need to see your study doctor for a physical examination and bone scan. Additionally, you will need to have a dental examination within 90 days of completing treatment" has been changed to "You will need to see your study doctor for a physical examination and bone scan. Additionally, you will need to have a dental examination within *6 months of completing treatment or being removed from study*." (*Reason: This change was made for editorial purposes.*)

24. (Page 58, Model Consent Form, What side effects or risks can I expect from being in the study?): The following changes have been made to this section:
    - Zoledronic Acid: Under the rare, but serious category of risks for zoledronic acid the following new risks related to inflammation of the eyes and allergic reaction have been added as provided by the FDA MedWatch Safety Program:
        - *Inflammation of the eyes can occur with zoledronic acid use. Symptoms can include red eye, eye pain, and/or decreased/blurry vision. In some cases, these events did not improve until the zoledronic acid was discontinued.*
        - *Allergic reaction: There have been rare reports of allergic reaction with intravenous zoledronic acid including swelling in the mouth or throat making it difficult to breath. Very rare cases of anaphylactic reaction/shock have also been reported.*

25. (Page 59, Model Consent Form, What side effects or risks can I expect from being in the study?): A new paragraph regarding severe bone pain has been included to address recent toxicity information regarding the incidence of severe bone pain while on bisphosphonate treatment:

    <u>Severe bone pain</u>: Rare reports of severe and occasionally disabling bone, joint, and/or muscle pain has been reported with bisphosphonate use. The severe bone, joint, and/or muscle pain may occur within days, months, or years after starting a bisphosphonate. Some patients have reported complete relief of symptoms after discontinuing the bisphosphonate, whereas others have reported slow or incomplete recovery. The risk factors that contribute to severe bone, joint, and/or muscle pain associated with bisphosphonates are unknown.

    Page 59a was added to prevent extensive repagination.

26. (Page 63, Model Consent Form, Consent Form for Use of Specimens for Research): The room number for the SWOG Solid Tumor Bank has changed from "L18-5104" to "L18-*5400A*" and the zip code has been changed from "80010" to "*80045*".

27. (Page 85, Section 19.1, CTSU Participation Procedures): Under the "CTSU Procedures for Patient Enrollment" section, item #3, the CTSU office hours have changed from 8:00 a.m. and 8:00 p.m. to *9:00 a.m. and 5:30 p.m*.

Institutions must update their local consent form to include the above information. Patients currently being treated on this study must be informed of these changes at their next scheduled visit and the notification process documented.

Please attach this memorandum to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to inform the Southwest Oncology Group Statistical Center and the NCI.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Lisa Gavigan
Jeri Jardine
Christine McLeod
Lars H. Breimer – Bayer Schering Pharma Oy
Diep Tran – Novartis
Edward McKenna – Roche
Megan Rossmann – CTSU

Southwest
Oncology Group
A National Clinical Research Group

May 1, 2008

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	April 9, 2008	AE #200810824GPV(1) *
	April 10, 2008	AE #200816114GPV

***** Bayer's F/U #1 and F/U #2 were issued within days of each other. Instead of issuing both reports, F/U #2 was issued since it was the most current report (and inclusive of all information known to date). Therefore, this report is considered F/U #1 since this was the first time we were issuing a follow-up report for Bayer #200810824GPV.

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Southwest
Oncology Group
A National Clinical Research Group

April 15, 2008

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	March 3, 2008	AE #200711360BNE(3)
	March 3, 2008	AE #200813940GPV
	March 6, 2008	AE #200715690NA(1)
	March 11, 2008	AE #200814162GPV
	March 11, 2008	AE #200815097NA
	March 14, 2008	AE #200816063NA
	March 14, 2008	AE #200816075NA
	March 21, 2008	AE #200813940GPV(1)

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

March 15, 2008

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	February 20, 2008	AE #200813728NA
	February 21, 2008	AE #200813730NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

March 1, 2008

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate, IND# 71,481). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	January 21, 2008	AE #200810824GPV
	January 30, 2008	AE #200811720GPV
	February 8, 2008	AE #200812652NA
	February 8, 2008	AE #200812671NA
	February 13, 2008	AE #200813174NA

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

January 15, 2008

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate, IND# 71,481). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	December 19, 2007	AE #200718095GPV
	December 20, 2007	AE #200715690NA
	December 24, 2007	AE #200716245NA
	January 3, 2008	AE #200711360BNE(1)

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

January 1, 2008

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
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(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate, IND# 71,481). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	November 21, 2007	AE #2007042893
	December 4, 2007	AE #200714883NA
	December 11, 2007	AE #200715679NA
	December 12, 2007	AE #200715313NA(1)

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

December 15, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	November 9, 2007	AE #2007040750
	November 9, 2007	AE #2007041732

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

December 15, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations unless otherwise specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone number: 206/288-7722
E-mail: pink@u.washington.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

In order to familiarize advocacy groups with current Southwest Oncology Group (SWOG) clinical trials and to help with accrual to these trials, the SWOG Lay Advocate Committee will be disseminating trial and study information to advocacy groups. We encourage you to print the attached patient information sheet regarding the **S0307** trial (approved by the NCI Central IRB, August 29, 2007) in newsletters and/or to distribute in any other manner to your constituencies.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Lisa Gavigan
Jeri Jardine
Christine McLeod
Lars H. Breimer – Bayer Schering Pharma Oy
Simone Lake – Novartis
Marie-Paule Schoerlin – Roche
Megan Rossmann – CTSU

S0307

Research Study of Bisphosphonate Therapy for Breast Cancer

This study is investigational and is being done to find out if adding a drug (called a bisphosphonate) to hormonal therapy and/or chemotherapy will help prevent cancer from spreading to the bones or other parts of the body.

If you choose to participate in this study, a computer will assign you by chance to 1 of the 3 groups below. This research study is being done to see if there is any difference between the 3 different bisphosphonate drugs.

Group 1 (or Arm 1): You will be given a 4 mg infusion of zoledronic acid through a needle in your vein. This drug will be given for 15 minutes once every 4 weeks for the first 6 months and then once every 3 months after that for 30 more months (36 months total).

Group 2 (or Arm 2): You will take 1600 mg of clodronate by mouth once every day for 36 months

Group 3 (or Arm 3): You will take 50 mg of ibandronate by mouth once every day for 36 months

Bisphosphonates are drugs that prevent bone from breaking down. Low doses of bisphosphonate drugs are used to treat osteoporosis; higher doses of bisphosphonate drugs are used to treat cancer that has spread to the bone. Higher doses of bisphosphonate drugs will be used in this study in the amounts listed above for Group 1, Group 2, or Group 3.

All 3 groups will be asked to take bisphosphonates for 3 years. Throughout the 3-year period, you will visit your study doctor on a regular basis (see schedule on next page). After you are finished taking bisphosphonates, your study doctor will ask you to visit the office for follow-up exams every year for a length of 10 years. You can stop your participation at any time by contacting your study doctor to discuss how to stop safely.

Side Effects:

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects; however, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Common side effects associated with bisphosphonates include nausea, vomiting, reflux, and diarrhea. Uncommon, but serious, side effects include the possibility of a specific type of damage to the jawbone (a condition called osteonecrosis of the jaw) and damage to an unborn baby or a baby who is breastfeeding.

Your study doctor will discuss the specific risks of each treatment.

This document does not take the place of the informed consent or information provided by your study doctor.

S0307

Research Study of Bisphosphonate Therapy for Breast Cancer

If you choose to participate in this study, a computer will assign you by chance to 1 of the 3 groups listed below. There is no "placebo" in this study.

- zoledronic acid (4 mg, given by infusion once a month for 6 months, then once every 3 months for a total of 3 years)
- clodronate (1600 mg, given as 2 pills taken daily for 3 years)
- ibandronate (50 mg, given as 1 pill taken daily for 3 years)

The drugs used in this study have been tested in research studies around the world.

Brief Study Schedule

Prior to study	• Routine exams (including dental exam), tests, and procedures to find out if you can be in the study
Day 1: Month 1	• If using **zoledronic acid**, you will receive an infusion in your vein at your study doctor's office • If using **clodronate**, you will begin taking the medication • If using **ibandronate**, you will begin taking the medication
Months 2, 4, 6	• Routine blood tests • Physical examination (x-ray and scans as needed for disease assessment) • Serum creatinine blood tests (to be sure your kidneys are working properly)
Months 3, 5	• Serum creatinine blood tests (to be sure your kidneys are working properly)
Months 9, 12, 15, 18, 21, 24, 27, 30, 33, 36	• Routine blood tests • Physical examination (x-ray and scans as needed for disease assessment) • Serum creatinine blood tests (to be sure your kidneys are working properly)
End of study drug treatment	• Physical examination • Dental exam • Bone scan
After completing the study	• Physical exams with your study doctor every 6 months for 5 years then yearly until Year 10

This document does not take the place of the informed consent or information provided by your study doctor.

S0307

Osteonecrosis of the Jaw in a Research Study of Bisphosphonate Therapy for Breast Cancer

What is osteonecrosis of the jaw?

Osteonecrosis of the jaw is another name for a specific type of damage to the jawbone. It is a very uncommon but serious possible side effect of taking drugs called bisphosphonates.

Why do I need to understand osteonecrosis of the jaw?

Although this possible side effect is very uncommon, recent reports suggest a possible link between the use of bisphosphonates that are given intravenously (through a vein in your arm), such as zoledronic acid, and osteonecrosis of the jaw. Bisphosphonate drugs that are given by mouth, such as clodronate and ibandronate, may also increase the risk of osteonecrosis of the jaw. It is possible that you are more likely to experience osteonecrosis of the jaw if you are taking other cancer treatment drugs at the same time you are taking a bisphosphonate drug.

How will I know if I have osteonecrosis of the jaw?

Your study doctor will help you determine if you could have osteonecrosis of the jaw. Some of the signs may be pain in your jaw, toothaches, loose teeth, or sores on your gums that do not heal. This condition may happen after you have a tooth pulled or after other dental procedures.

What can I do to prevent osteonecrosis of the jaw?

We do not know exactly what causes osteonecrosis of the jaw so it is important to diagnose it early. You should continue to have regular dental exams throughout your participation in this trial. If you have any major dental work planned, please talk to both your dentist and your study doctor. In addition, you should tell your study doctor immediately if you have infections or sores in your mouth that do not go away.

Keeping your teeth and gums healthy is important to your overall health. Good oral health begins with a well-balanced diet, the use of mouth rinses (as directed by your health care providers), follow-up dental care, and avoidance of tobacco and alcohol.

Your study doctor can provide additional information and answer any questions you may have.

Southwest
Oncology Group
A National Clinical Research Group

November 15, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate, IND# 71,481). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	October 18, 2007	AE #2007038758
	October 23, 2007	AE #2007038539
	November 7, 2007	AE #2007040962

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc:
PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
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Simone Lake - Novartis
Ulf Wiegand – Roche
Joyce Mull – NSABP
Megan Rossmann – CTSU

Southwest
Oncology Group
A National Clinical Research Group

November 1, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	September 20, 2007	AE #2007034510
	September 20, 2007	AE #2007028574
	September 26, 2007	AE #2007034745

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

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Joyce Mull – NSABP
Megan Rossmann – CTSU

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: October 15, 2007
CTEP Submission Date: June 18, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations unless otherwise specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston

AMENDMENT #1

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

(√) Full board review required. Reason:
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AMENDMENT #1

The protocol referenced above has been amended as follows:

1. (Revision #3, distributed 4/1/07, item #2): A typo in the version date incorrectly described the version date as 01/15/07. The version date has been corrected to "01/*25*/07".

2. (Fast Fact Sheet): The following changes have been made to this page:
   - Drugs provided: Berlex/Schering (producer of clodronate) has merged with Bayer and has changed its name to "*Bayer Schering Pharma Oy*".
   - Eligibility: In the second row, the first sentence has been revised. "Must receive standard adjuvant therapy for breast cancer" has been changed to "Must receive standard *(systemic)* adjuvant therapy for breast cancer". Also, the following new statements have been added: "*Additional therapies are allowed including radiation therapy and biologic agents (e.g. Herceptin®, Avastin®, hematopoietic growth factors). Neoadjuvant therapy is permitted, but enrollment must occur after completion of surgery.*"
   - Eligibility: In the third row, the following new statement has been added to the end of the paragraph: "*Additional biological therapy or radiation therapy is allowed at any time before or after registration.*"
   - Eligibility: In the eighth (last) row, the criterion that begins with "Must not be co-enrolled on protocols that have bone density as an endpoint..." has been moved to the ineligibility criteria column.

- Ineligibility: In the second row, the following ineligibility criteria have been added: "*Use of biologic agents only or local radiation therapy only (without chemotherapy and/or hormone therapy)" and "Patients who are at such a low risk of recurrence that adjuvant therapy will not be prescribed.*
- Prestudy requirements: Regarding the timing of the dental examination, "≤ 6 months before registration" has been changed to "≤ 6 months before *initiation of treatment*". Also, the following has been added under the prestudy requirements: "*≤ 24 – 72 hours before initiation of treatment: Pregnancy test (for women of childbearing potential)*".

(Reason: The eligibility, ineligibility, and prestudy requirement sections have been changed to match the modifications to the eligibility criteria, Section 5.0 [see item #8 below].)

3. (Title page): The following changes have been made to this page:
   - The version date has been updated (version 06/18/07).
   - The table of contents has been updated.
   - Under the participant list, the bolded statement "Non-Southwest Oncology Group participants must register through the CTSU" has been changed to "*Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations unless otherwise specified in the CTSU logistical appendix (See Section 19.1).*
   - Under the agent list, "Berlex/Schering" has been changed to "*Bayer Schering Pharma Oy".*

4. (Page 11, Section 2.0, Background): Under the discussion of osteonecrosis of the jaw (ONJ), third paragraph, recent toxicity information regarding the incidence of ONJ with zoledronic acid use is presented. Page 11a was added to prevent extensive repagination.

5. (Page 13a, Section 2.0, Background): The ethnic/racial table has been updated to reflect the revised accrual goal of the study. (*Reason: See item #13 below)*

6. (Page 16, Section 3.2a, Drug Information): "Schering Oy", the manufacturer of clodronate, has merged with Bayer and changed its name to "*Bayer Schering Pharma Oy*".

7. (Page 18, Section 3.2c, Drug Information): In the clodronate supplier information, the third sentence has been revised. "However, for this study it is being supplied free-of-charge by Berlex/Schering" has been changed to "However, for this study it is being supplied free-of-charge by *Bayer Schering Pharma Oy*".

8. (Pages 26-27, Section 5.0, Eligibility Criteria): The following changes have been made to this section:
   - Section 5.2: "Patients must receive standard adjuvant therapy for their breast cancer. Chemotherapy, hormone therapy, or combined chemo/hormone therapy is permitted. Hematopoietic growth factors are allowed. Neoadjuvant therapy is permitted for inclusion, but enrollment must occur post-operatively. Patients who are at such a low risk of recurrence that adjuvant therapy will not be prescribed are excluded."

     The above eligibility criteria have been replaced with the following revised section:

     "Patients must receive standard *(systemic)* adjuvant therapy for their breast cancer. Chemotherapy, hormone therapy, or combined chemo/hormone therapy is permitted. *Additional therapies are allowed including radiation therapy and biologic agents (e.g. Herceptin®, Avastin®, hematopoietic growth factors). Patients who*

receive biologic agents only or local radiation therapy only (without chemotherapy and/or hormone therapy) are not eligible. Patients who are at such a low risk of recurrence that adjuvant therapy will not be prescribed are *ineligible. Neoadjuvant therapy is permitted, but enrollment must occur after completion of surgery.*

(Reason: These changes were made in order to provide clarification on the types of therapies that are allowed while on study.)

- Section 5.3: The following new statement has been added at the end of this eligibility criterion: "*Additional biological therapy or radiation therapy is allowed at any time before or after registration.*" *(Reason: This change was made in order to provide clarification on the timing of therapies that are allowed while on study.)*
- Section 5.6: The first sentence has been revised. "Patients may not be co-enrolled..." has been changed to "Patients *must* not be co-enrolled..." *(Reason: This change was made for editorial purposes.)*
- Section 5.9: "Patients must undergo a dental examination within 6 months prior to registration per Section 7.3" has been changed to "Patients must undergo a dental examination within 6 months prior to *initiation of treatment* per Section *7.4*". *(Reason: This change was made in order to provide clarification on the timing of the dental examination prior to the initiation of treatment not prior to study enrollment.)*
- Section 5.12: The third sentence has been revised. "Women of child-bearing potential must have a pregnancy test within 24-48 hours..." has been changed to "Women of child-bearing potential must have a pregnancy test within 24-*72* hours..." *(Reason: This change was made in order to allow pregnancy tests to be performed on Friday so that initiation of treatment can begin the following Monday.)*

9. (Page 28, Section 7.2, Treatment Plan): The second bolded paragraph has been revised. "Women of child-bearing potential must have a pregnancy test within 24-48 hours prior to initiation of treatment" has been changed to "Women of child-bearing potential must have a pregnancy test within 24-*72* hours prior to initiation of treatment." *(Reason: See item #8, fifth bullet, above)*

10. (Page 29, Section 7.4, Treatment Plan): In the first paragraph, the first sentence has been revised. "Patients will undergo a dental exam within 6 months prior to registration" has been changed to "Patients will undergo a dental exam within 6 months prior to *initiation of treatment*". The parenthetical statement regarding the Dental Examination Form in the second sentence has been revised. "...(may be retrospectively completed if the exam was prior to registration)" has been changed to "...(may be retrospectively completed if the exam was prior to *initiation of treatment*)". *(Reason: See item #8, fourth bullet, above)*

11. (Page 30, Section 7.9, Treatment Plan): The second sentence has been revised. "Additionally, a dental examination will also be required at the end of protocol treatment (within 3 months prior to or after study completion)" has been changed to "Additionally, a dental examination will also be required at the end of protocol treatment (within *6* months after study completion *or removal from protocol treatment, see Section 7.11*)". *(Reason: This change was made in order to allow dental exams within 6 months for patients that complete treatment or are removed from protocol treatment early.)*

12. (Page 32, Section 9.0, Study Calendar): The following changes have been made to this page:
    - The third sentence of the dental exam footnote (λ) has been updated. "To keep in line with patient's normal dental exam schedule, exams 6 months pre-enrollment and 3 months pre- or post-completion of study are required" has been changed to "To keep in line with patient's normal dental exam schedule, exams 6 months pre-enrollment and *6* months post-completion of study *(or removal from protocol treatment, see Section 7.11)* are required". *(Reason: See item #10 above)*

- The pregnancy test footnote (∆) has been updated. "To be performed within 24-48 hours prior to initiation of treatment" has been changed to "To be performed within 24-*72* hours prior to initiation of treatment." *(Reason: See item #8, fifth bullet, above)*

13. (Pages 33-34a, Sections 11.0, Statistical Considerations): The statistical considerations (Sections 11.1-11.6) have been replaced with updated sections (new Sections 11.1-11.8). *(Reason: Due to a lower than anticipated accrual rate, the statistical design assumptions were adjusted to be more in line with the currently observed accrual rate. The adjusted accrual goal will be lowered from 6,000 to 4,500 women. The accrual period would be extended from 4 years to 6 years, but the follow-up period would be shortened by one year. The Bonferroni corrected pairwise comparisons will be replaced by using the Fisher's Least Significant Difference for adjusting for multiple comparisons. The adjusted statistical design has been approved by the SWOG DSMC.)* Page 34a was added to prevent extensive repagination.

14. (Page 49, Section 17.0, Bibliography): The bibliography has been updated. References #63 - #65 have been added.

15. (Page 50, Section 18.2, Master Forms Set): The Southwest Oncology Group Registration Form Code Sheet (version 12/8/04) has been updated and replaced with version 10/24/06.

16. (Page 51, Model Consent Form, Readability Statistics): The readability statistics have been updated. Flesch reading ease has been updated from 63.9 to 57.6. Flesch-Kincaid grade level has been changed from 8.1 to 9.3.

17. (Page 53, Model Consent Form, How many people will take part in the study?): "About 6,000 people will take part in this study" has been changed to "About *4,500 women* will take part in this study." *(Reason: See item #13 above)*

18. (Page 53, Model Consent Form, Before you begin the study...): The seventh (last) bullet has been revised. "Women of child-bearing potential must have a pregnancy test performed within 24-48 hours prior to initiation of treatment" has been changed to "Women of child-bearing potential must have a pregnancy test performed within 24-*72* hours prior to initiation of treatment." *(Reason: See item #8, fifth bullet, above)*

19. (Page 55, Model Consent Form, Study Chart): In the first column, fourth row, "Within 24-48 hours prior to starting study" has been changed to "Within 24-*72* hours prior to starting study". *(Reason: See item #8, fifth bullet, above)*

20. (Page 55a, Model Consent Form, Study Chart): In the second row, first column, the timing of the dental examination has been revised. "Within 3 months before or after completing study" has been changed to "Within *6* months after completing study *or ending the study early*". *(Reason: See item #11 above)*

21. (Page 58, Model Consent Form, What side effects or risks can I expect from being in the study?): Under the rare, but serious category of risks for zoledronic acid the following new risk related to irregular heartbeats (atrial fibrillation) has been added as provided by Novartis:
"*<u>Irregular heartbeat</u>: In a recent study in post-menopausal women with osteoporosis, a small number of patients treated with zoledronic acid experienced an irregular heartbeat called atrial fibrillation. More patients who received zoledronic acid experienced this kind of irregular heartbeat than patients who did not receive zoledronic acid. So far, this symptom has not been seen in cancer patients taking zoledronic acid. Atrial fibrillation is a common condition which can be treated; however, more research is needed before the importance of this finding becomes clear.*"

22. (Page 59, Model Consent Form, What side effects or risks can I expect from being in the study?): The paragraph regarding osteonecrosis of the jaw (ONJ) has been modified to include recent toxicity information regarding the incidence of ONJ with zoledronic acid use.

"Osteonecrosis of the jaw: Recent reports suggest a possible association between the use of intravenous bisphosphonates, such as zoledronic acid, and osteonecrosis of the jaw (permanent damage to the jawbone), a rare, but serious potential side effect. This condition may be painful and may happen after tooth extraction or other dental procedures such as tooth cleaning or when a patient is also getting chemotherapy while taking bisphosphonates. Oral clodronate and ibandronate may also increase the risk of osteonecrosis of the jaw, although this link is not as well established.

The above paragraph has been changed to:

"Osteonecrosis of the jaw: Recent reports suggest a possible association between the use of intravenous bisphosphonates, such as zoledronic acid, and osteonecrosis of the jaw (permanent damage to the jawbone), a rare, but serious potential side effect. This condition may be painful and may happen after tooth extraction or other dental procedures such as tooth cleaning or when a patient is also getting chemotherapy while taking bisphosphonates. *A recent study of 3,360 patients receiving standard treatment with or without zoledronic acid reported seven cases of osteonecrosis of the jaw, all in the zoledronic acid arm, with an average of eight doses received at the time of the event. This represented 0.4% of patients on the zoledronic acid arm.* Oral clodronate and ibandronate may also increase the risk of osteonecrosis of the jaw, although this link is not as well established.

23. (Page 60, Model Consent Form, What are the costs of taking part in this study?): In the third paragraph, the first sentence has been revised. "The drug manufacturers, Berlex/Schering and Roche, will provide you..." has been changed to "The drug manufacturers, *Bayer Schering Pharma Oy* and Roche, will provide you..."

24. (Page 62, Model Consent Form, Additional Research Studies): Before the future contact question, "I agree to allow my study doctor...to contact me regarding future research involving my participation in this study", the following language has been added to provide rationale for the "future contact" question:

"Occasionally, researchers working with the Southwest Oncology Group (SWOG) may have another research idea that relates to people who were on a SWOG study. In some cases, to carry out the new research, we would need to contact participants in a particular study. You can agree or not agree to future contact."

25. (Page 86, Appendix 19.1, CTSU Participation Procedures): In the drug procurement section, "Berlex/Schering" has been changed to "*Bayer Schering Pharma Oy*".

Institutions must update their local consent forms to include the above information for future registrations. Patients currently being treated on this study should be informed of these changes as directed by the local Institutional Review Board (IRB).

Please attach this memorandum to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to inform the Southwest Oncology Group Statistical Center and the NCI.

cc:

PROTOCOL & INFORMATION OFFICE	Christine McLeod
William E. Barlow, Ph.D.	Lars H. Breimer – Bayer Schering Pharma Oy
Danika Lew, M.A.	Simone Lake – Novartis
Jean Barce	Edward McKenna – Roche
Lisa Gavigan	Megan Rossmann – CTSU
Jeri Jardine	

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: March 15, 2009
E-mailed Date: March 10, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND PATHOLOGISTS; CTSU. **Patient enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations as specified in the CTSU logistical appendix (See Section 19.1).**

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

MEMORANDUM

Study Coordinator: Julie Gralow, M.D.
Phone: 206/288-7722
Email: pink@u.washington.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
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- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

Please note that the intellectual property terms applicable to participation in this trial, as partially funded by an industry collaborator, are different from the terms set forth in the Purchase Service Agreement (PSA) signed by registering members. Specifically, participation in this trial requires agreement and compliance with allowing the industry collaborator a non-exclusive license to any intellectual property resulting from this trial, including use for commercial purposes. This is in contrast to the standard intellectual property terms in the PSA which restricts the industry collaborator to a non-exclusive license for research purposes only. This exception to the standard intellectual property terms has been approved by the NCI. You are required to inform your site's appropriate grants and contracts office about this modification to the PSA. Please direct any questions related to this modification to the legal department at Group Headquarters Office at 734- 998-7173.

Please attach this memorandum to the front of your copy of the protocol.

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Southwest
Oncology Group
A National Clinical Research Group

September 1, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	August 1, 2007	AE #2007027436
	August 2, 2007	AE #2007027975
	August 8, 2007	AE #2007028574

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

August 1, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate, IND# 71,481). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	June 15, 2007	AE #2006032513(4)
	June 29, 2007	AE #2007023743
	July 9, 2007	AE #2007024457

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc:
PROTOCOL & INFORMATION OFFICE
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Southwest
Oncology Group
A National Clinical Research Group

June 15, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	May 21, 2007	AE #2006032513(3)
	May 31, 2007	AE #2007019013

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
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June 1, 2007

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RE: IND Safety Reports for Clodronate (IND-71,481)

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This safety report pertains to the following study:	Report:
S0307 Breast	May 2, 2007 AE #2007014121(1)

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

May 1, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate, IND# 71,481). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	April 4, 2007	AE #2007010897(1)
	April 12, 2007	AE #2007012082

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Edward McKenna – Roche
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Southwest
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A National Clinical Research Group

April 15, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	March 5, 2007	AE #2007006800
	March 12, 2007	AE #2006032513(1)
	March 15, 2007	AE #2006040116(2)
	March 21, 2007	AE #2006032513(2)
	March 29, 2007	AE #2006031029(1)
	April 2, 2007	AE #2007010897

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
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Revised June 18, 2007
Distribution Date: April 1, 2007
CTEP Submission Date: January 25, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU.

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

REVISION #3

Study Coordinator: Julie Gralow, M.D.
Phone number: 206/288-7722
E-mail: 206/288-2054

IRB Review Requirements

( ) Full board review required. Reason:
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- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

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( ) No review required

REVISION #3

The protocol referenced above has been revised as follows:

1. (Fast Fact Sheet): Under "prestudy requirements", serum creatinine testing has been changed from "≤ 14 days before registration" to "≤ *7 days* before registration". *(This change was made to be consistent with the eligibility requirement in Section 5.7.)*

2. (Title page): The version date has been updated (version 01/25/07). The contact information for Dr. Robert Livingston has been updated.

3. (Page 19, Section 3.2c, Drug Information): In the first sentence of the clodronate handling and disposal section, "ibandronate" has been changed to "*clodronate*".

4. (Page 28, Section 7.0, Treatment Plan; Page 31, Section 8.6, Dosage Modifications): The phone number for Dr. Robert Livingston has been updated.

5. (Pages 29 & 30, Sections 7.4 & 7.9, respectively; Treatment Plan): In each section the phone number for the Southwest Oncology Group Operations Office has been changed from 210/677-8808 to 210/*450*-8808.

6. (Page 32, Section 9.0, Study Calendar): The following changes have been made to this page:

   - X-rays and scans: Chest x-rays and CT scans are NOT required every 6 months for the assessment of disease. The checkmarks (for Months 6, 12, 18, 24, 30, and 36) and corresponding "**" footnote have been removed. (*We DO, however, want patients on protocol treatment assessed for side effects and disease recurrence at 3 month intervals (starting with Month 6) as noted in the study calendar.)*
   - "◊" footnote: The serum creatinine footnote has been revised. "To be performed within 14 days prior to registration..." has been changed to "To be performed within *7 days* prior to registration..."

7. (Page 55, Model Consent Form, Study Chart): The following changes have been made to this page:

   - Third row: In the first column, "Within 14 days prior to starting study" has been changed to "Within *7 days* prior to starting study". In the second column, "Get serum creatinine and calculated creatinine clearance blood tests" has been changed to "Get *kidney function test*." *(This 'patient friendly' description was made at the request of several IRBs.)*
   - Sixth row: In the second column, "Get serum creatinine blood test" has been changed to "Get *kidney function test*."
   - Seventh row: In the second column, first bullet, "Get routine blood tests (including serum creatinine)" has been changed to "Get routine blood tests (including *kidney function test*)."
   - Seventh row: In the second column, second bullet, the sentence "X-rays and scans as needed for disease assessment only for Months 6, 12, 18, 24, 30, and 36" has been removed.

8. (Page 62, Model Consent Form, Additional Research Studies): The following changes have been made to this page;

   - First banking sentence (tissue): "I agree to submit a tissue specimen...to see if the breast cancer has spread to the bones" has been changed to "I agree to submit a tissue specimen...to see if *this predicts the risk of your breast cancer spreading to the bones. This is an experimental test that may indicate a higher chance that breast cancer has spread to the bones. Since the significance of this test is not proven, neither you nor your doctor will be given the results of this test*."
   - Second banking sentence (blood): "I agree to submit a blood sample...to see if high levels will predict if breast cancer will spread to the bones" has been changed to "I agree to submit a blood sample...to see if high levels will predict *the risk of your breast cancer spreading to the bones. This is an experimental test that may indicate a higher chance that breast cancer has spread to the bones. Since the significance of this test is not proven, neither you nor your doctor will be given the results of this test*."

9. (Page 63, Model Consent Form, Consent Form for Use of Specimens in Research): Under "Where will my specimens be kept", a typo has been corrected in the address. "RT-1 South" has been changed to "*RC-1* South".

CTSU related changes

10. (Page 4, CTSU Address and Contact Information; Pages 84-86a, Section 19.1, CTSU Participation Procedures): These sections have been revised to incorporate the Cancer Trials Support Unit (CTSU) form tracking change to *basic service* for this protocol. Page 86a was added to prevent extensive repagination.

Institutions should update their local consent forms to include the above-noted changes for future registrations. Patients currently being treated on this study should be informed of the changes in the manner determined by the local Institutional Review Board (IRB).

Please attach this memorandum to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
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Southwest
Oncology Group
A National Clinical Research Group

March 15, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
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MEMORANDUM

The following safety reports have been posted regarding adverse events that occurred in association with the drug Bonefos® (clodronate disodium tetrahydrate, IND# 71,481). Please access these safety reports via the safety report link in the member section of the Southwest Oncology Group website (https://swog.org/SafetyReports/SafetyReports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	February 19, 2007	AE #2006027512(2)
	February 19, 2007	AE #2006040116(1)
	February 19, 2007	AE #2006005298

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Southwest
Oncology Group
A National Clinical Research Group

February 15, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

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The safety report pertains to the following study:	Report:	
S0307 Breast	January 25, 2007	AE #2006032523(1)

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

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Oncology Group
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February 1, 2007

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	January 10, 2007	AE #2006040021(1)
	January 11, 2007	AE #2006032513
	January 15, 2007	AE #2007000323

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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Oncology Group
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January 15, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	November 29, 2006	AE #2006036528
	December 13, 2006	AE #2006036528(1)
	December 15, 2006	AE #2006027512(1)
	January 2, 2007	AE #2006040116
	January 2, 2007	AE #2006040021

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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November 15, 2006

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

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RE: IND Safety Reports for Clodronate (IND-71,481)

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	October 13, 2006	AE #2006030074
	October 20, 2006	AE #2006031029
	November 1, 2006	AE #2006032523

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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These safety reports pertain to the following study:	Reports:	
S0307 Breast	April 6, 2006	AE #2006003411(1)
	July 17, 2006	AE #2006018731
	July 28, 2006	AE #2006015298(1)
	August 24, 2006	AE #2006015297(1)
	August 30, 2006	AE #2006024776
	August 31, 2006	AE #2006018731(1)
	September 18, 2006	AE #2006026124
	September 25, 2006	AE #2006003780(1)
	September 29, 2006	AE #2006027512

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Distribution Date: November 1, 2006
CTEP Submission Date: September 25, 2006

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU.

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

REVISION #2

Study Coordinator: Julie Gralow, M.D.
Phone number: 206/288-7722
E-mail: 206/288-2054

IRB Review Requirements

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( ) No review required

REVISION #2

The protocol referenced above has been revised as follows:

1. (Revision #1 change memo, distributed 8/15/06): Item #28, fourth bullet incorrectly reported the change made to the model consent form. "Day 1 of Months 1-6 and..." has been changed to "Day 1 of Months *2*-6 and..."

2. (Title page): The version date has been updated (version 09/25/06).

3. (Page 16, Section 3.1c): A new section entitled "Handling and disposal/Drug returns" has been added that discusses procedures for zoledronic acid drug returns and disposal.

4. (Page 19, Section 3.2c): A new section entitled "Handling and disposal/Drug returns" has been added that discusses procedures for clodronate drug returns and disposal. Page 19a has been added to prevent repagination. Page 19a was added to prevent extensive repagination.

5. (Page 22, Section 3.3c): A new section entitled "Handling and disposal/Drug returns" has been added that discusses procedures for ibandronate drug returns and disposal. Page 22a has been added to prevent repagination.

6. (Page 28, Section 7.1): Formatting changes have been made to this section, but the content remains unchanged.

7. (Pages 32, Section 9.0): The following changes have been made to this page:

   - Title: The study calendar title has been corrected to match the title page.
   - X-rays/Scans: Chest x-rays and CT scans have been checked at Months 6, 12, 18, 24, 30, and 36 as these months were previously unchecked. *(This corresponds with the disease assessment interval outlined in the study.)*
   - λ footnote: The sentence "Flexibility will be allowed" has been removed, as it is a requirement that dental exams be performed at the beginning and end of treatment.
   - ** footnote: A new "**" footnote corresponding to the disease assessment schedule has been added as follows: "*Disease will be assessed clinically at Months 6, 12, 18, 24, 30, and 36. X-rays and scans as needed for tumor measurement will use the same methods used at baseline*."

8. (Page 35, Section 13.3a): In the paragraph that begins, "For assistance...", the phone number for the Southwest Oncology Group Operations Office has been changed from 210/677-8808 to 210/*450*-8808.

9. (Pages 36-37, Section 14.2-14.3): The SWOG data submission procedures have been replaced with updated sections. Page 37 (Sections 14.4-14.12) has been reformatted.

10. (Page 38, Section 15.2c): The following changes have been made to this section:

    - In the second paragraph, the last two sentences have replaced with an updated section.

    "ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS. For any questions or problems regarding the Specimen Tracking program, please send an email to technicalquestion@crab.org"
    The sentences above have been replaced with the following text:

    "**ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.**

    To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (http://dnet.crab.org/SpecTrack/Documents/SpecTPrimer-Insts.pdf); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance."

    - The paragraph that begins with "A copy of the Shipment Packing list produced by the Specimen Tracking system..." has been removed.

11. (Pages 39 & 41, Sections 15.3e & 15.4d, respectively): The SWOG Solid Tumor Tissue Bank has moved from the University of Cincinnati to the University of Colorado HSC at Fitzsimons, and the contact information has been updated.

12. (Pages 43 & 45, Sections 16.1e & 16.1f, respectively): In the last sentence, the Southwest Oncology Group Operations Office has been changed from 210/677-8808 to 210/*450*-8808.

13. (Page 55, Model Consent Form, Study Chart): The following changes have been made to this page:

    - Sixth row, first column: Month 24 was inadvertently left out as mentioned in the Revision #1 change memo. This has been corrected.
    - Seventh row, second column: "Return to your doctor's office...for your next physical examination (only for Months 6, 12, 18, 24, 30, and 36)" has been changed to "Return to your doctor's office...for your next physical examination (*X-rays and scans as needed for disease assessment* only for Months 6, 12, 18, 24, 30, and 36)."

14. (Page 63, Model Consent Form, Where will my specimens be kept?): The contact information for the Southwest Oncology Group Solid Tumor Tissue Bank at the University of Colorado HSC at Fitzsimons has been added.

Institutions should update their local consent forms to include the above-noted changes for future registrations. Patients currently being treated on this study should be informed of the changes in the manner determined by the local Institutional Review Board (IRB).

Please attach this memorandum and the attachments to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Christine McLeod
Lisa Gavigan
Jean Barce
Jeri Jardine
Kendra Godfrey Barrow - CTSU
Edward McKenna - Roche
Susan Lanz - Berlex
Gail A. Larkins - Novartis

Southwest
Oncology Group
A National Clinical Research Group

Protocol Distribution Date: August 15, 2006
Re-revised: June 12, 2006
Revised: April 14, 2006
CTEP Submission Date: February 7, 2006

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU.

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: Drs. J. Gralow and R. Livingston.

REVISION #1

Study Coordinator: Julie Gralow, M.D.
Phone number: 206/288-7722
E-mail: 206/288-2054

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #1

The protocol referenced above has been revised as follows:

1. The **S0307** Fast Fact Sheet has been inserted before the title page.

2. (Title page): The version date has been updated (version 06/12/06). The table of contents has been updated.

3. (Page 2, PI information): Added "Special Consultant" next to Mark Schubert, D.D.S, M.D.S.

4. (Page 3, PI information): Updated the email address for Dr. Mark J. Clemons (NCIC-CTG Study Coordinator). Updated the phone number for Kim Dammann, Research RN for **S0307**.

5. (Page 5, Schema): The dose information for each bisphosphonate has been removed.

6. (Page 7, Section 2.0): Added additional background information at the beginning of the paragraph that begins, "The intriguing but contradictory results of these three adjuvant bisphosphonate studies...". Three new citations were introduced and included in the bibliography section as #18-20. Subsequent background information in Section 2.0 has been reformatted.

7. (Pages 9-13a, Section 2.0): In the first paragraph on Page 9, the author references have been replaced with citation numbers (see bibliography Section 17.0). On pages 9-13, the citation numbers have been updated. Page 13a was added to prevent extensive repagination.

8. (Page 16, Section 3.1c): Under zoledronic acid supplier information, the drug supplier name has been changed from UintaVision to "UVI, Inc.". Also, the address has been removed as this information is no longer current. Institutions should continue to use the phone and/or fax number to order study drug.

9. (Page 18, Section 3.2c): In the first sentence, "Clodronate is not commercially available in the United States" has been changed to "Clodronate is *investigational for this study*." Under clodronate supplier information, the drug supplier name has been changed from UintaVision to "UVI, Inc.". Also, the address has been removed as this information is no longer current. Institutions should continue to use the phone and/or fax number to order study drug.

10. (Page 22, Section 3.3c): Under ibandronate supplier information, the drug supplier name has been changed from UintaVision to "UVI, Inc.". Also, the address has been removed as this information is no longer current. Institutions should continue to use the phone and/or fax number to order study drug.

11. (Page 26-27, Section 5.0): The following changes have been made to these pages:

- New instructions have been inserted at the top of the eligibility criteria page. The third sentence "For each patient, this section must be photocopied, completed, and submitted to the Date Operations Center in Seattle (see Section 14.0)" has been replaced with "*For each criterion requiring test results and dates, please complete the Prestudy Form and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Office in Seattle at 206/652-2267 prior to registration*."
- Section 5.3: This eligibility criterion has been replaced with the following: "Patients may be enrolled prior to, simultaneously with, or after beginning adjuvant systemic therapy. Patients receiving hormonal therapy alone (no chemotherapy) or pre-operative chemotherapy should be enrolled within 84 days (12 weeks) after the date of final surgical procedure. Patients receiving adjuvant post-operative chemotherapy may be enrolled up to 8 weeks after completion of chemotherapy." The final surgery blank has been removed.
- Section 5.4: "Patients must be offered the opportunity to consent for tissue and serum specimen submission and banking as per Section 15.0" has been replaced with the following: "*Institutions are encouraged to seek patient consent to submit tissue and serum for banking.* Patients *who wish to participate in the tissue and serum sample submissions for banking as outlined in Sections 15.3 and 15.4 must consent to the procedures. Written informed consent must be obtained prior to submitting samples*."
- Section 5.5: The performance status blank has been removed.
- Section 5.7: "Patients must have a serum creatinine that is ≤ 2 times the institutional upper limit of normal within 7 days prior to enrollment" has been changed to "Patients must have a serum creatinine that is ≤ 2 times the institutional upper limit of normal *(IULN) and a calculated creatinine clearance of ≥ 30 mL/min within* 7 days prior to enrollment." The serum creatinine, IULN, and date blanks have been removed.
- Section 5.8: The date of previous IV or oral bisphosphonate blank has been removed.
- Section 5.9: The blank for date of dental examination has been removed.

- Section 5.10: Blanks for bone pain and for ruling out metastatic disease have been removed.
- Section 5.12: Added the following sentence to the end of this section: "Women of child-bearing potential must have a pregnancy test performed within 24 - 48 hours prior to initiation of treatment (see Section 7.2)."
- Section 5.14: "If Day 28 or 84..." has been changed to "If Day *14*, 28, or 84..." In the bolded paragraph, the second sentence "...the Monday four weeks later would be considered Day 28" has been changed to "...the Monday *two* weeks later would be considered Day *14*."

12. (Page 28, Section 7.0): The following changes have been made to this page:

- First paragraph: Updated the phone number for Kim Dammann.
- Section 7.2: In the second paragraph, the bolded information has been replaced with the following updated section: "Investigators are encouraged to begin bisphosphonate therapy as soon as possible after surgery. Patients may be registered and begin bisphosphonate therapy prior to, simultaneously, or after systemic therapy. Patients receiving hormonal therapy alone (no chemotherapy) or pre-operative chemotherapy should be enrolled within 84 days (12 weeks) after the date of final surgical procedure. Patients receiving adjuvant post-operative chemotherapy may be enrolled up to 8 weeks after completion of chemotherapy (see Section 5.3)."

13. (Pages 29-31, Section 7.0): The following changes have been made to these pages:

- The treatment plan table has been renumbered as Section 7.3. Subsequent sections have been reformatted.
- Section 7.3 has been titled "treatment plan". The following text has been added to the first paragraph: "Every effort should be made to administer zoledronic acid to patients in Arm 1 every 4 weeks during the first 6 months of dosing, however minor deviances from these dosing intervals are acceptable. It is suggested that the infusions be given within ± 2 days (2 days earlier or later). During the remaining period of dosing, zoledronic acid may be given within ± 7 days (7 days earlier or later). The last dose of zoledronic acid in Arm 1 should be administered at Month 33. Oral bisphosphonates given in Arms 2 and 3 are to continue daily until the first day of Month 36 and are then discontinued."
- Section 7.4: In the first sentence, the **S0307** Dental Exam Form has been changed to "Dental Examination Form". The final form number has been inserted.
- Section 7.7: A new section discussing pill compliance has been added. Subsequent sections have been reorganized.
- Section 7.11: A new criteria for removal from protocol treatment has been added as "(c) Greater than 4 weeks in delay of protocol treatment." Subsequent sections have been reorganized.

14. (Page 31, Section 8.0): The following changes have been made to this page:

- Section 8.4: A new Section 8.4 has been added: "Bisphosphonates from any of the three arms may be held or delayed for up to four weeks for any reason without requiring removal from the study. The total duration of treatment will be 36 months. Missed treatments will not be made up." Subsequent sections have been renumbered.
- Section 8.5: "Osteonecrosis of the jaw: Completion of the **S0307** Osteonecrosis Jaw Lesion Form..." has been changed to "Osteonecrosis of the jaw: Completion of the Osteonecrosis Jaw Lesion Form..." The Osteonecrosis Jaw Lesion Form is no longer a study specific form. The final form number has been inserted. Also, the phone number for Dr. Mark Schubert has been corrected.
- Section 8.6: The phone number for Kim Dammann has been updated.

15. (Page 32, Section 9.0): The following changes have been made to this page:

- The study calendar has been restructured to include months instead of weeks. Treatment: Zoledronic acid treatment has been revised to clarify that treatment is to be given on Day 1 every 4 weeks for 6 months and then on Day 1 every 3 months until Month 33.

- Laboratory:

  a. Added pregnancy test at prestudy. "Δ" footnote describes that this test is to be performed 24-48 hours prior to initiation of treatment.
  b. Clarified that serum creatinine testing should be performed monthly for the first 6 months (starting with Month 2) and then once every three months until Month 36.
  c. Added "creatinine clearance (calculated)" test at prestudy.
  d. Clarified that other laboratory tests (excluding serum creatinine and pregnancy test) are to be performed at Months 2, 4, and 6 and then once every three months until Month 36.
  e. Added "§" footnote next to electrolytes (to remind reader that this test is suggested at prestudy for Good Medical Practice).

- Physical:

  a. Clarified that history, physical exam, weight, PS, and toxicity notation are to be performed at Months 2, 4, and 6 and then once every three months until Month 36.
  b. Clarified that disease assessments are to be performed every 6 months until Month 36.

- Footnotes:

  a. **"Ω" footnote**: "Zoledronic acid will be administered on Day 1 q 4 weeks for the first 6 months and then on Day 1 q 3 months for 30 months" has been changed to "Zoledronic acid will be administered by IV on Day 1 q 4 weeks for the first 6 months, *however, minor deviations are acceptable. It is suggested that the infusions be given within ± 2 days (2 days earlier or later). During the remaining period of dosing, zoledronic acid may be given within ± 7 days (7 days earlier or later).*"
  b. **"ψ" footnote**: Added the following sentence "Discontinue oral bisphosphonate on the first day of Month 36."
  c. **"α" footnote**: Added the following sentence "Discontinue oral bisphosphonate on the first day of Month 36."
  d. "***ƒ*" footnote**: "Patients off protocol treatment prior to recurrence should return at least every 6 months for disease assessment" has been changed to "Patients off protocol treatment prior to recurrence should return *for disease assessment at least every 6 months for 5 years and then annually for 5 years or until death (whichever occurs first).*"
  e. **"λ" footnote**: In the first sentence "Dental exam should be performed at the beginning and end of the study" has been changed to "Dental exam should be performed at the beginning and end of *treatment*". In the second sentence "Dental exam form to be completed" has been changed to "Complete the Dental Examination Form (Form# 30100)."
  f. **"√" footnote**: This footnote has been removed.
  g. Added **"Δ" footnote** (see description above).

16. (Page 34, Section 12.0): Formatting changes have been made to this section, but no changes have been made to the content.

17. (Pages 37-38, Section 14.0): The following changes have been made to these pages:

    - Section 14.4a: Removed "Breast Cancer" from the **S0307** Prestudy Form title.
    - Section 14.4b: "A completed copy of Section 5.0 of the protocol…" has been removed. Subsequent sections have been reorganized.
    - Section 14.4: Replaced item "d" (a copy of the consent form page documenting answers to the specimen consent questions) with "Dental Examination Form," now located in Section 14.4c.
    - Section 14.5: "WITHIN 90 DAYS OF REGISTRATION, submit the Dental Examination Form" has been removed. Subsequent sections have been renumbered. The **S0307** Treatment Summary Form has been updated. Final form numbers were added throughout new Section 14.5.
    - Section 14.8: "AFTER OFF TREATMENT – ANNUALLY UNTIL YEAR 10 OR DEATH..." has been changed to "AFTER OFF TREATMENT – EVERY 6 MONTHS UNTIL YEAR 5, THEN ANNUALLY UNTIL YEAR 10 OR UNTIL DEATH..."
    - Sections 14.9 and 14.10: "Southwest Oncology Group Follow-Up Form" has been renamed as "Follow-Up Form".
    - Section 14.11: "**S0307** Osteonecrosis Jaw Lesion Form" has been renamed as "Osteonecrosis Jaw Lesion Form."
    - Final form numbers were added throughout this section.

18. (Page 38, Section 15.1): "One block of fixed tissue will be banked for the purpose of investigating PTHrP and other markers of preferential bone metastasis in the future" has been replaced with "Institutions are encouraged to seek patient consent to submit tissue and serum for banking (see Sections 15.3 and 15.4)."

19. (Pages 38-39, Section 15.2c): The location of the Specimen Tracking laboratory ID numbers listed in the second paragraph has been updated. On page 39, the last paragraph that begins, "A copy of the Southwest Oncology Group Specimen Submission Form..." has been removed.

20. (Pages 39-41, Sections 15.3 and 15.4): The tissue and serum submission instructions for banking have been updated.

21. (Page 44, Table 16.1): Formatting changes have been made to this table, but no changes have been made to the content.

22. (Page 45, Section 16.1g): In the first paragraph, first sentence, "All cases of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and acute lymphocytic leukemia (ALL) that occur..." has been changed to "All cases of acute myeloid leukemia (AML) *and* myelodysplastic syndrome (MDS) that occur..." In the first bullet, "AML/MDS/ALL" has been changed to "AML/MDS". Additionally, the address for the Investigational Drug Branch has been removed as the AML/MDS report form and documentation should be only be faxed.

23. (Pages 47-49, Section 17.0): The bibliography has been updated per item #6 above.

24. (Page 50, Section 18.0): The following changes have been made to this page:

    - Section 18.1: The following new instructions have replaced the original section: "The Model Informed Consent Form is included in this section, preceded by "Notes for Local Institution Consent Form Authors" and "Notes for Local Investigators." The study – as well as the local consent form meeting the guidelines noted in these documents – must be reviewed and approved by the Institutional Review Board prior to registration and treatment of patients on this study."

- Section 18.2a: Added "Southwest Oncology Group Registration Form Code Sheet"
- Section 18.2b: Removed "Breast Cancer" from the **S0307** Prestudy Form title.
- Section 18.2c: The **S0307** Treatment Summary Form has been updated.
- Section 18.2e: Removed "Southwest Oncology Group" from Follow-Up Form.
- Section 18.2k: Removed "**S0307**" from Osteonecrosis Jaw Lesion Form.
- Added final form numbers and version dates throughout.

25. (Pages 51-52, Model Consent Form): Formatting changes have been made to these pages, but no changes have been made to the content.

26. (Page 54, Model Consent Form): Under During the study, fourth bullet, "If you are assigned to Arm 1 you will need to have your kidney function tested..." has been changed to "You will need to have your kidney function tested..." ("If you are assigned to Arm 1" has been removed from the sentence). Routine laboratory tests will be performed for all patients in all three arms of the study.

27. (Page 55, Model Consent Form, During the study…) After the first paragraph, the following was added: "If you are assigned to either Group 2 or 3, it is strongly encouraged that you record the number of pills you take each day on a calendar. During visits with your doctor (at Months 6, 12, 24, and 36) you will be asked how many pills were missed during the last month of protocol treatment. This will be done in order to determine if you are having any problems taking the drug and to confirm you are taking it as directed."

28. (Pages 55-55a, Model Consent Form, Study Chart): The following changes have been made to these pages (page 55a was added to prevent extensive repagination):

    - Second row: In the second column, fourth bullet, "Get tumor biopsy for research studies..." has been changed to "*Tissue from the original tumor biopsy will be submitted* for research studies..."
    - Third row: In the first column, "Within 7 days prior to starting study" has been changed to "Within *14* days prior to starting study." In the second column, "Get serum creatinine blood test" has been changed to "Get serum creatinine *and calculated creatinine clearance blood tests.*"
    - Fifth row: "Week 1" has been changed to "*Day 1 of Month 1*".
    - Sixth row: "Weeks 5, 13, 21, 37, 61, 85, 108, 132" has been changed to "*Day 1 of Months 2-6 and Months 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36*."
    - Seventh row: "Week 9, 17, 25, 49, 73, 97, 120, & 144" have been changed to "*Day 1 of Months 2, 4, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36*". "Return to your doctor's office...for your next physical examination (only for Weeks 25-144)" has been changed to "Return to your doctor's office...for your next physical examination (*only for Months 6, 12, 18, 24, 30, and 36).*
    - Last row: "Annually after completing study" has been changed to "*After completing study, every 6 months for 5 years, then annually until Year 10 or until death*."

29. (Page 56, Model Consent Form, Schema): The dose information for each bisphosphonate has been removed.

30. (Page 58, Model Consent Form, Risks): "Osteonecrosis of the jaw" has been added under the 'rare, but serious' category of risks for clodronate.

31. (Page 59, Model Consent Form, Risks): The following changes have been made to this page:

- "Osteonecrosis of the jaw" has been added under the 'rare, but serious' category of risks for ibandronate.
- The "Osteonecrosis of the jaw" paragraph has been replaced with the following updated text (This change was made at the recommendation of the CIRB):

  "Osteonecrosis of the jaw: Recent reports suggest an association between the use of intravenous bisphosphonates, such as zoledronic acid, and osteonecrosis of the jaw (permanent damage to the jawbone), a rare, but serious potential side effect. This condition may be painful and may happen after tooth extraction or other dental procedures such as tooth cleaning or when a patient is also getting chemotherapy while taking bisphosphonates. *Oral clodronate and ibandronate may also increase the risk of osteonecrosis of the jaw, although this link is not as well established.*"

32. (Page 62, Model Consent Form): In the additional research studies section a new question has been added that states the following: "I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study."

33. (Page 63, Model Consent Form): The following changes have been made to this page:

- Where will my specimens be kept: The contact information for the Southwest Oncology Group Serum Bank at the CLASS Laboratory, University of Michigan, has been removed. Also, the telephone and fax number for the Southwest Oncology Group Tissue Bank has been updated.
- About using specimens for research: The first paragraph that begins, "You have had a biopsy (or surgery) to see if you have cancer..." has been removed. In the paragraph that begins, "We would like to keep some of the specimens that are left over for future research..." the first sentence has been changed to "We would like to keep *leftover tissue and serum* for future research..."

34. (Page 64, Model Consent Form): The following changes have been made to this page:

- In the consent form for use of specimens for research, third question of "Making your choice", the sentence "Someone may contact me in the future to ask me to take part in more research" has been revised to "Someone may contact me in the future *for my permission to allow other uses of my specimens*".
- In the last paragraph of "Making your choice", the sentence that begins, "Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the treating physician" has been changed to "*If you decide to withdraw your permission from the banking part of the study, your tissue will be returned to the treating institution, and any blood specimens will be destroyed.*" (This change was made at the recommendation of the CIRB.)

35. (Page 65, Model Consent Form): Formatting changes have been made to this page, but no changes have been made to the content.

36. (Master Forms Set): The following forms have been updated.

- **S0307** Registration Form
- **S0307** Prestudy Form
- **S0307** Treatment Summary Form
- Due to the inclusion of new forms, repagination was required for pages 83-88, Section 19.0.

37. (Page 84, Section 19.1): Under CTSU requirements for patient enrollment on **S0307**, fourth bullet, "Specimen materials submitted per Section 15.0" has been replaced with "*Patients who wish to participate in the tissue and serum sample submissions for banking as outlined in Sections 15.3 and 15.4 must consent to the procedures. Written informed consent must be obtained prior to submitting samples*."

38. (Page 85, Section 19.1): Under specimen collection for serum banking, the second sentence, "prior to patient registration, contact the CLASS lab to order serum collection kits" has been removed.

39. (Page 86, Section 19.1, Drug Procurement): In the second paragraph, the name of "ibandronic acid" was misspelled and has been corrected. Also, "UintaVision" has been changed to "UVI, Inc." throughout this section.

Institutions should update their local consent forms to include the above-noted changes for future registrations. Patients currently being treated on this study should be informed of the changes in the manner determined by the local Institutional Review Board (IRB).

Please attach this memorandum and the attachments to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Christine McLeod
Lisa Gavigan
Amy Edwards
Jeri Jardine
Kendra Godfrey Barrow - CTSU
Edward McKenna, Pharm.D. - Roche
Hartwig H. Hennekes, Ph.D. - Berlex
Gail A. Larkins - Novartis

Southwest
Oncology Group
A National Clinical Research Group

August 1, 2006

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

We have recently received two safety reports via the National Surgical Adjuvant Breast and Bowel Project (NSABP) from Schering Oy, the manufacturer of Bonefos® (clodronate disodium tetrahydrate, IND# 71,481). These safety reports describes events of renal failure as discussed in the reports dated June 20, 2006.

The safety reports can be accessed via the **S0307** abstract page or the safety report link on the Southwest Oncology Group website (https://swog.org/safetyreports/safetyreports.asp).

The safety reports pertain to the following study:	Report:	
S0307 Breast	June 20, 2006	AE #2006015297
	June 20, 2006	AE #2006015298

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Lisa Gavigan
Jeri Jardine
Christine McLeod
Hartwig H. Hennekes, Ph.D. – Berlex
Gail A. Larkins - Novartis
Edward McKenna, Pharm.D. – Roche
Joyce Mull – NSABP
Kendra Godfrey Barrow – CTSU

Southwest
Oncology Group
A National Clinical Research Group

July 1, 2006

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

We have recently received a safety report via the National Surgical Adjuvant Breast and Bowel Project (NSABP) from Schering Oy, the manufacturer of Bonefos® (clodronate disodium tetrahydrate, IND# 71,481). This safety report describes osteonecrosis of the jaw on a patient from the Czech Republic as discussed in the report dated May 29, 2006.

The safety report can be accessed via the **S0307** abstract page or the safety report link on the Southwest Oncology Group website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Report:	
S0307 Breast	May 29, 2006	AE #2006-007626

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by FDA regulation. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

cc:
PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Amy Edwards
Lisa Gavigan
Jeri Jardine
Christine McLeod
Hartwig H. Hennekes, Ph.D. – Berlex
Gail A. Larkins - Novartis
Edward McKenna, Pharm.D. – Roche
Joyce Mull – NSABP
Kendra Godfrey Barrow – CTSU

Southwest
Oncology Group
A National Clinical Research Group

May 15, 2006

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

We have recently received a follow-up safety report via the National Surgical and Bowel Safety Project (NSABP) from Schering Oy, the manufacturer of Bonefos® (clodronate disodium tetrahydrate, IND# 71,481). This follow-up safety report describes a non-healing ulceration of the upper palate with a small area of exposed bone on a patient described in the report dated March 8, 2006.

The safety report can be accessed via the **S0307** abstract page or the safety report link on the Southwest Oncology Group website (https://swog.org/safetyreports/safetyreports.asp).

These safety report pertain to the following study:	Reports:	
S0307 Breast	April 21, 2006	AE #2006003410(1)

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by FDA regulation. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the Southwest Oncology Group Statistical Center.

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Kendra Godfrey Barrow – CTSU

Southwest
Oncology Group
A National Clinical Research Group

April 1, 2006

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

We have recently received several safety reports via the **National Surgical Adjuvant Breast and Bowel Project** (NSABP) from Schering Oy, the manufacturer of Bonefos® (clodronate disodium tetrahydrate, IND# 71,481). Three of these safety reports detail osteonecrosis of the jaw appearing in patients (one with metastatic renal cell carcinoma, one with myeloma, and one details unknown) who received oral clodronate after previous treatment with IV zoledronate or IV pamidronate. We have now received a fourth report (AE#2006003780) of a probable case from one of NSABP's sites of a patient enrolled on NSABP B-34 who has received two years of treatment with clodronate (the patient's study medication was unblinded following the diagnosis) with no previous exposure to other bisphosphonates.

This B-34 patient has had a small, non-healing area of bone exposure on the left palatal torus (a bony prominence on the anterior palatal bone). The lesion is currently painless and there is no history of recent dental extraction. Clodronate therapy has been stopped. The toxicity has been described as Grade 2.

This B-34 case suggests that osteonecrosis of the jaw and maxilla might be seen with all classes of bisphosphonates, although we continue to believe that the incidence with clodronate will be much lower than that seen with the more potent agents currently available. We have been informed that it is the practice in some countries for patients on potent bisphosphonates who develop osteonecrosis of the jaw or maxilla, or symptoms suggesting that this toxicity may be occurring, to be switched to oral clodronate. Therefore, we expect that there may be further reports of this potentially serious toxicity in patients receiving clodronate.

The Southwest Oncology Group, in accordance with the NSABP medical staff, agrees that this recent information does not require any change to the protocol or reconsent of the patients, but we do suggest continued vigilance in the routine clinical examination of the

patients (which should include examination of the oropharynx). We should also re-emphasize the importance of good dental hygiene and, where possible, the avoidance of dental extractions while patients are on bisphosphonates. Patients on **S0307** who develop any exposed area of bone in the mandible or maxilla should have study medication discontinued. Patients who have symptoms of jaw or maxillary pain should be investigated with this toxicity in mind although, of course, there are other possible diagnoses.

The safety reports can be accessed via the **S0307** abstract page or the safety report link on the Southwest Oncology Group website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S0307 Breast	February 27, 2006	AE #2006001006(1)
	March 1, 2006	AE #2006003411
	March 8, 2006	AE #2006003410
	March 9, 2006	AE #2006003780

Please append this notice and the reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by FDA regulation. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Southwest
Oncology Group
A National Clinical Research Group

March 1, 2006

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: IND Safety Reports for Clodronate (IND-71,481)

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

A safety report was submitted to our office via the National Surgical and Bowel Safety Project (NSABP) from Schering Oy, the manufacturer of Bonefos® (clodronate disodium tetrahydrate, IND# 71,481). The report, from French health authorities, describes a recent serious adverse event detailing the first confirmed case report of osteonecrosis of the jaw in a male patient receiving clodronate. Osteonecrosis of the jaw has been previously reported with more potent bisphosphonate drugs, but not in association with clodronate.

A description of osteonecrosis of the jaw is already included as a potential side-effect of all bisphosphonates in the **S0307** model informed consent. Additionally, because it appears that this particular serious adverse event was due to a pre-existing condition unlikely to be related to clodronate, we will not require modification of the protocol or consent form.

The safety report can be accessed via the **S0307** abstract page or the safety report link on the Southwest Oncology Group website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Report:
S0307 Breast	February 1, 2006 AE #2006001006

Please append this notice and the report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by FDA regulation. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

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Southwest
Oncology Group
A National Clinical Research Group

November 15, 2005

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; CTSU.

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer." Study Coordinators: J. Gralow, R. Livingston, W.E. Barlow.

STATUS NOTICE

Study Coordinator: Julie Gralow, M.D.
Phone number: 206/288-7722
E-mail: 206/288-2054

IRB Review Requirements

(√) Full board review required. Reason:
- (√) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

ACTIVATION

The study referenced above is now open for participation. Entire copies of the protocol are enclosed for your use.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William E. Barlow, Ph.D.
Danika Lew, M.A.
Christine McLeod
Lisa Gavigan
Amy Edwards
Kendra Godfrey Barrow - CTSU
Edward McKenna, Pharm.D. - Roche
Hartwid H. Hennekes, Ph.D. - Berlex
Gail A. Larkins - Novartis

SOUTHWEST ONCOLOGY GROUP
PROTOCOL FAST FACT SHEET

THIS FORM HAS BEEN DESIGNED AS A RESOURCE ONLY AND IS NOT INTENDED FOR USE IN THE FULFILLMENT OF PATIENT REGISTRATION AND TREATMENT REQUIREMENTS

S0307

PHASE III TRIAL OF BISPHOSPHONATES AS ADJUVANT THERAPY FOR PRIMARY BREAST CANCER

Treatment initiation: Within 5 working days

Drugs provided: Zoledronic acid (Novartis), Clodronate (Bayer Schering Pharma Oy), Ibandronate (Roche)

RANDOMIZE

Arm 1:	Zolendronic Acid	IV over 15 minutes on Day 1	→	q monthly for 6 months then q 3 months for 2.5 years.
Arm 2:	Clodronate	PO, start on Day 1	→	q day for 3 years
Arm 3:	Ibandronate	PO, start on Day 1	→	q day for 3 years

Eligibility	Ineligibility
Histologically confirmed primary invasive adenocarcinoma of the breast, Stage I, II, III, with no evidence of metastatic disease.	Pregnant or nursing women may not participate.
Must receive standard (systemic) adjuvant therapy for breast cancer. Chemotherapy, hormone therapy, or combined therapy permitted. Additional therapies are allowed including radiation therapy and biologic agents (e.g. Herceptin®, Avastin®, hematopoietic growth factors). Neoadjuvant therapy is permitted, but enrollment must occur after completion of surgery.	Use of biologic agents only or local radiation therapy only (without chemotherapy and/or hormone therapy). Patients who are at such a low risk of recurrence that adjuvant therapy will not be prescribed.
Patients may be enrolled prior to, simultaneously with, or after beginning adjuvant systemic therapy. Patients receiving hormonal therapy alone (no chemotherapy) or pre-operative chemotherapy should be enrolled within 84 days (12 weeks) after the date of final surgical procedure. Patients receiving adjuvant post-operative chemotherapy may be enrolled up to 8 weeks after completion of chemotherapy. Additional biological therapy or radiation therapy is allowed at any time before or after registration.	Esophageal stricture or motility disorder. Patients with a history of gastroesophageal reflux disorder (GERD) are eligible, but caution should be used when giving oral bisphosphonates.
Patients who wish to participate in the tissue and serum sample submissions for banking must consent to the procedures.	No other prior malignancy is allowed except treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated stage I or II cancer from which patient is currently in complete remission.
Zubrod performance status of 0-2.	No other use of bisphosphonates. Previous use OK as long as bisphosphonates are discontinued at registration.
Serum creatinine that is ≤ 2 X IULN and measured creatinine clearance of ≥ 30 ml/min within 7 days of registration.	Patients with skeletal pain if a bone scan and/or roentgenological exam shows metastatic disease.
Must undergo a dental examination within 6 months prior to registration.	Must not be co-enrolled on protocols that have bone density as an endpoint. If allowed by the protocol, can be enrolled on other locoregional or systemic therapy breast cancer study, including cooperative group studies.

PRESTUDY REQUIREMENTS:

≤ 6 months before initiation of treatment: Dental examination

≤ 7 days before registration: Serum creatinine and measured creatinine clearance

≤ 28 days before registration: History and physical exam, weight and height, performance status, and chest x-rays unless done for the original diagnostic workup. Bone Scan if patient has bone pain.

≤ 72 hours before initiation of treatment: Pregnancy test (for women of childbearing potential)

Suggested for Good Medical Practice

CBC/Diff/PLTS, bilirubin, SGOT/SGPT, alk phosph, calcium, phosphate, magnesium *albumin (only if serum calcium is drawn, not needed for ionized calcium), electrolytes including sodium, potassium, chloride and bicarbonate

*This form has been developed with the support of the SWOG Nurse Oncologists' Committee.

SWOG

PHASE III TRIAL OF BISPHOSPHONATES AS ADJUVANT THERAPY FOR PRIMARY BREAST CANCER

SWOG STUDY COORDINATORS:
Julie Gralow, M.D. (Medical Oncologist)
University of Washington School of Medicine
Seattle Cancer Care Alliance
825 Eastlake Ave East, MS G4-830
Seattle, WA 98109-1023
Phone: 206/288-7722
FAX: 206/288-2054
E-mail: pink@u.washington.edu

Robert B. Livingston, M.D. (Medical Oncologist)
Arizona Cancer Center
1515 N. Campbell Avenue
P.O. Box 245024, Hem/Onc Section
Tucson, AZ 85724-5024
Phone: 520/626-2816
FAX: 520/626-3754
E-mail: rlivingston@azcc.arizona.edu

AGENTS:
Clodronate (NSC-713466) (IND-71,481)
Supplied by Bayer Schering Pharma Oy
Ibandronate (NSC-722623) (IND-71,481)
Supplied by Roche
Zoledronic Acid (CGP 42446) (NSC-721517)
Supplied by Novartis

BIOSTATISTICIANS
William E. Barlow, Ph.D. (Biostatistics)
Cancer Research and Biostatistics
1730 Minor Avenue, Suite 1900
Seattle, WA 98101-1468
Phone: 206/652-2267
Fax: 206/652-4612
E-mail: williamb@crab.org

Danika Lew, M.A. (Biostatistics)
Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, M3-C102
P.O. Box 19024
Seattle, WA 98109-1024
Phone: 206/667-4623
FAX: 206/667-4408
E-mail: dlew@fhcrc.org

mb

(Version Date 12/19/14)

NCCTG STUDY COORDINATOR

James N. Ingle, M.D.
Professor of Oncology
Mayo Clinic
200 First Street SW
Rochester, MN 55905
Phone: 507/284-8432
FAX: 507/284-1803
E-mail: Ingle.james@mayo.edu

ECOG STUDY COORDINATOR

Carla Falkson, M.D.
Professor, Dept of Medicine
Division of Hematology/Oncology
University of Alabama at Birmingham
WTI 275 J1
1824 6th Ave South
Birmingham, AL 35294
Phone: 205/975-2691
FAX: 205/975-0805
E-mail: cfalkson@uab.edu

NSABP STUDY COORDINATOR

Alexander Paterson, M.D.
Tom Baker Cancer Center
Dept. of Medicine
1331 29th Street NW
Calgary, AB T2N 4N2, Canada
Phone: 403/944-1707
FAX: 403/283-1651
E-mail: alexpate@cancerboard.ab.ca

CALGB STUDY COORDINATOR

E. Claire Dees, M.D.
Assistant Professor of Medicine
Division of Hematology and Oncology
University of North Carolina at Chapel Hill
CB 7305, 3009 Old Clinic Bldg
Chapel Hill, NC 27514
Phone: 919/843-7714
FAX: 919/966-6735
E-mail: claire_dees@med.unc.edu

BIOLOGIC CORRELATES

Daniel F. Hayes, M.D.
Clinical Director, Breast Oncology Program
University of Michigan Comprehensive Cancer Center
6312 Cancer Center
1500 E. Medical Center Drive
Ann Arbor MI 48109-0942
Phone: 734/615-6725
FAX: 734/615-3947
E-mail: hayesdf@umich.edu

CO-COORDINATOR BONE HEALTH

Dawn Hershman, M.D., M.S.
Assistant Professor of Medicine
Columbia University College of Physicians & Surgeons
Herbert Irving Cancer Center
161 Ft Washington, Room 1068
New York, NY 10032
Phone: 212/305-1945
FAX: 212/05-0178
E-mail: Dlh23@columbia.edu

CO-COORDINATOR JAW/DENTAL HEALTH

Mark Schubert, D.D.S., M.D.S. (Special Consultant)
University of Washington School of Dentistry
Director and Professor of Oral Medicine
Seattle Cancer Care Alliance
825 Eastlake Ave East, Mailstop G6900
Seattle, WA 98109
Phone: 206/288-1331
FAX: 206/288-1332
E-mail: mschuber@seattlecca.org

CO-COORDINATOR STATINS

Alison T. Stopeck, M.D.
Medical Oncologist
Arizona Cancer Center
1515 N. Campbell Ave
P.O. Box 245024
Tucson, AZ 85724-0001
Phone: 520/626-2816
FAX: 520/626-3754
E-mail: astopeck@azcc.arizona.edu

CO-COORDINATOR PHARMOCOGENOMICS

Catherine H. Van Poznak, M.D.
Department of Internal Medicine
Division of Hem/Onc
1500 E Medical Center Drive
C346 MIB/Box 0848
Ann Arbor, MI 48109-0848
Phone: 734/936-9209
FAX: 734/615-2109
E-mail: cvanpoz@umich.edu

NCIC-CTG STUDY COORDINATOR:

Mark J. Clemons, M.D.
Medical Oncologist
Division of Medical Oncology
The Ottawa Hospital Cancer Centre
501 Smyth Road
Ottawa, ON K1H 8L6
Phone: 613/737-7700
FAX: 613/247-3511
E-mail: mclemons@toh.on.ca

For questions relating to treatment please contact the Southwest Oncology Group Coordinator (Dr. Gralow) or:

Kim Dammann,
Research RN
Seattle Cancer Care Alliance
Phone: 206/288-6900
Email: ADJBISJG@u.washington.edu

PARTICIPANTS

ALLIANCE/Alliance for Clinical Trials in Oncology

ECOG-ACRIN/ECOG-ACRIN Cancer Research Group

NCIC-CTG/NCIC Clinical Trials Group

NRG/NRG Oncology

SWOG/SWOG

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Institutions not aligned with SWOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

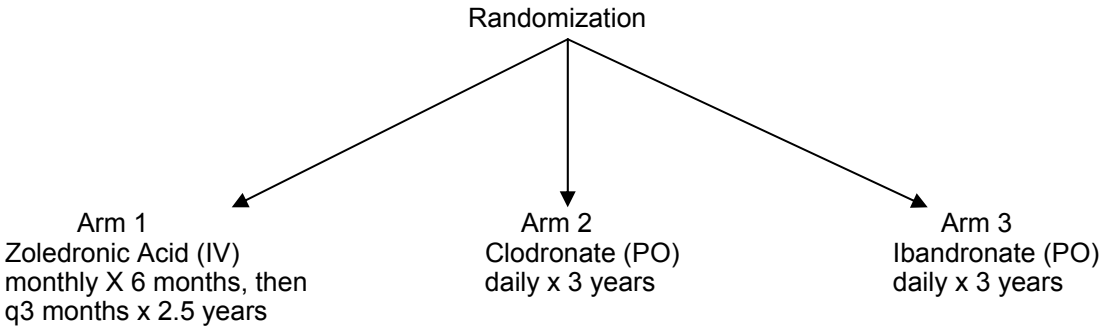
- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://members.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the Southwest Oncology Group. **Case report forms** (with the exception of patient enrollment forms)**, clinical reports, and transmittals** must be sent to the Southwest Oncology Group Data Operations Center unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the Southwest Oncology Group. Please send query responses and delinquent data to the Southwest Oncology Group Data Operations Center and do not copy the CTSU Data Operations.
- Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the SWOG data center.

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-888/823-5923 Fax: 215/569-0206	CTSU Patient Registration Voice Mail: 1-888/462-3009 Fax: 1-888/691-8039 Hours: 9:00 am – 5:30 pm EST, Monday – Friday (excluding holidays) [Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301/704-2376 between 9:00 am and 5:30 pm.]	Southwest Oncology Group Data Operations Center Fax: 1-800/892-4007 [Please do not use a cover sheet for faxed data.] Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
For treatment- or toxicity-related questions contact the Study PI of the Coordinating Group.		
For eligibility questions contact the Southwest Oncology Group Data Operations Center by phone or email: Phone: 206/652-2267; Email: breastquestion@crab.org		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line: 1-888/823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Public Web site is located at: www.ctsu.org **The CTSU Registered Member Web site is located at https://members.ctsu.org**		

CTSU logistical information is located in Appendix 19.1

SCHEMA



Patients will be followed for disease-free and overall survival, as well as sites of first recurrence.

1.0 OBJECTIVES

1.1 To compare disease-free survival in patients receiving clodronate versus ibandronate versus zoledronic acid as adjuvant therapy for breast cancer.

1.2 To compare overall survival in patients receiving clodronate versus ibandronate versus zoledronic acid as adjuvant therapy for breast cancer.

1.3 To compare the distributions of sites of first recurrence on the three arms.

1.4 To assess the adverse events of clodronate compared to ibandronate compared to zoledronic acid in this cohort of patients.

1.5 To assess the association of PTHrP status and serum N-telopeptide levels at baseline with disease-free survival and sites of first recurrence.

1.6 To test treatment-PTHrP and serum N-telopeptide levels interactions with respect to disease-free survival and sites of first recurrence.

1.7 To investigate whether there is an association between inherited germ-line single nucleotide polymorphisms (SNP, rs2297480) in farnesyl diphosphate sythase (FDPS) and the adverse event of acute phase reactions in this cohort of patients (see Appendix 19.3).

2.0 BACKGROUND

Bone metastases are very common in patients with breast cancer. The skeleton is the initial site of recurrence in 35 - 40% of patients. *(1)* Up to 60 - 80% of patients with metastatic breast cancer eventually develop signs and symptoms related to bone involvement. *(2)* Bone metastases are a major cause of morbidity in breast cancer, with complications including pain, pathologic fractures, hypercalcemia, bone marrow suppression, and spinal cord compression.

There is increasingly persuasive evidence that overactivation of osteoclasts is the primary process of neoplastic damage in bone. Breast cancer cells present in bone marrow appear to release factors that activate osteoclasts to resorb bone. *(3)* Stimulators of osteoclastic activity include tumor-derived factors such as parathyroid hormone related peptide (PTHrP) and transforming growth factor beta (TGF-β). Recent work has suggested that PTHrP may be the major mediator of osteoclastic hyperactivity in patients with lytic bone metastases. *(4, 5)*

Bisphosphonates are a diverse group of compounds, which have profound effects on bone mineralization and resorption. As a group, they are poorly absorbed from the gastrointestinal tract and when given orally are associated with reduced compliance due to gastrointestinal intolerance. They bind avidly to bone, altering the properties of hydroxyapatite crystals and rendering them resistant to hydrolysis by endogenous phosphates. *(4)* Bisphosphonates are a class of drugs capable of inhibition of osteoclast function. They are effective in treating conditions in which there is excessive bone resorption and osteoclast activity, including osteoporosis and Paget's disease of bone. Several randomized clinical trials in breast cancer patients with bone metastases have demonstrated the ability of bisphosphonates to reduce skeletal-related events and symptoms, including pathologic fractures, requirement for surgery or radiation, spinal cord compression, hypercalcemia, and pain. *(5-8)* Bisphosphonates have not shown improved survival in these patients. Clodronate (Bonefos®) and pamidronate (Aredia®) have been extensively evaluated in patients with metastatic cancer and are widely used in oncology. *(5-7)* Zoledronic acid (Zometa®) and ibandronate (Bondronat®) represent highly potent, newer generation bisphosphonates with recently demonstrated benefit in reducing skeletal-related events. *(9-13)*

Three randomized clinical trials of the oral bisphosphonate clodronate as adjuvant therapy in breast cancer have been reported, yielding conflicting results with respect to development of bone metastases and survival. A German trial of 302 breast cancer patients with immunocytochemical evidence of cancer cells in a bone marrow aspirate but no other evidence of metastatic disease showed a reduction in bone recurrence and an increase in overall survival with two years of clodronate. *(14, 15)* With almost 5 years of follow-up, bone metastases were

reduced in the clodronate group compared to a control group (14% versus 24%, p=0.044) and visceral metastases showed a trend toward reduction (17% versus 26%, p=0.091). Overall survival was higher in the clodronate arm (91% versus 77%, p=0.002). The effect of adjuvant clodronate appeared weakened with longer follow-up.

A Finnish trial involving 299 women with lymph node-positive breast cancer randomized to 3 years of adjuvant clodronate showed virtually the opposite result, with no effect on the rate of bone metastasis and a deleterious effect on relapse rates of non-bone metastasis as well as survival. *(16)* After 5 years of follow-up, bone metastases were detected equally in the clodronate group and placebo groups (21% versus 17%, p=0.27), and non-skeletal metastases were significantly more common in the clodronate group (43% versus 25%, p=0.0007). Overall survival was worse in the clodronate group (79% versus 83%, p=0.009).

Most recently, a randomized, multicenter trial involving 1,079 primary breast cancer patients evaluating 2 years of adjuvant clodronate reported a benefit in overall survival. *(17)* Within the two years of clodronate treatment, bone metastases were significantly lower in the group receiving clodronate compared to placebo (2.3% versus 5.2%, p=0.016); however, at 5 years of follow-up, bone metastasis were no longer significantly different between the two treatment arms (12% versus 15%, p=0.107). No effect was observed on visceral sites of metastasis (17% versus 20%, p>0.05), although reassuringly there was no trend toward an increase. Overall survival was significantly improved in the clodronate arm (82% versus 76%, p=0.047).

All three adjuvant clodronate trials were recently updated at the American Society of Clinical Oncology meeting in 2004. *(18-20)* The German trial continues to show a survival benefit for the clodronate arm (80% vs. 60%) overall survival at 103 months, p=0.04). *(18)* The final analysis of the larger UK-led trial shows a statistically significant survival benefit for the clodronate arm, with a hazard ratio for survival of 0.768 (p=0.048) that persists at 10 years of follow-up. *(19)* The Finnish study no longer shows a significant survival detriment at 10 years of follow-up. *(20)* The intriguing but contradictory results of these three adjuvant bisphosphonate studies highlight the need for further investigation to determine whether bisphosphonates can influence the development of bone metastases and improve survival in early stage breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) has recently completed accrual on a multicenter confirmatory trial. NSABP B34 is evaluating oral clodronate for 3 years versus placebo in addition to standard treatment in 3,200 patients with Stage I or II breast cancer. The North American Intergroup trial **S0307** will compare newer, more potent bisphosphonate agents to clodronate. It is noteworthy that this trial design will still be valid even if the B-34 study results are not able to show a benefit for clodronate. As long as the clodronate arm is not inferior to placebo in B-34 (which is fairly unlikely provided the weight of the available evidence), the clodronate arm of the proposed trial would serve as a "reference control" against which one could still study the two newer, more potent bisphosphonates.

Ibandronate is a highly potent aminobisphosphonate that is currently approved in Europe in intravenous (6 mg) and oral (50 mg) form in breast cancer patients with bone metastases. Placebo-controlled trials of both oral and intravenous ibandronate in metastatic breast cancer show significant activity in reducing skeletal related events. *(9, 10)*

A phase III placebo-controlled trial of 466 breast cancer patients with bone metastases compared either 2 mg or 6 mg ibandronate as a 1- or 2-hour infusion or placebo injections every 3 - 4 weeks for up to two years in addition to their antineoplastic therapy. *(9)* The primary study endpoint, skeletal morbidity period rate, was lower in both ibandronate groups compared to placebo (p=0.004 for ibandronate 6 mg versus placebo). Ibandronate 6 mg reduced the number for new bone metastases by 38% and increased time to first new bone event. Additionally, patients on ibandronate 6 mg experienced decreased bone pain cores and analgesic use.

An oral formulation of ibandronate has also been developed and Phase III clinical trials of oral ibandronate versus placebo in breast cancer patients with bone metastases have recently been reported. *(10)* Two pivotal studies were performed in which two doses of ibandronate (20 mg and 50 mg) were compared to placebo. Both oral ibandronate doses demonstrated significant treatment effects in breast cancer patients with metastatic bone disease compared to placebo. In a pooled analysis, oral ibandronate 50 mg significantly reduced the mean skeletal morbidity period rate, the primary study endpoint, compared to placebo (0.95 versus 1.18, p=0.004). Both the 20 and 50 mg ibandronate doses also demonstrated significant treatment effects on the secondary efficacy parameters, WHO performance status, bone pain and markers of bone resorption.

Zoledronic acid, another third-generation aminobisphosphonate, has been shown to be superior to pamidronate in treating hypercalcemia of malignancy, and is at least as effective as pamidronate in the prevention of SREs in breast cancer and multiple myeloma patients. *(11,12)* A major advantage of zoledronic acid is that it can be given safely over short infusion durations. A randomized Phase III non-inferiority trial comparing 4 mg and 8 mg of zoledronic acid versus pamidronate in breast cancer and multiple myeloma patients with documented bone metastases was conducted. (*12,13*) Partway through the trial, the 8 mg arm was eliminated and the infusion volume and time for the 4 mg arm was lengthened due to concerns about renal toxicity. For the primary study endpoint, the proportion of patients with at least one skeletal-related event, results were similar in patients treated with zoledronic acid and pamidronate. With a fifteen-minute infusion rate, zoledronic acid was more convenient to administer than pamidronate (90 mg), which requires a 2-hour infusion. Zoledronic acid has been approved by the FDA at a dose of 4 mg over 15 minutes every 3 - 4 weeks for reduction of skeletal complications in cancer patients with bone metastases.

Some patients may prefer oral formulations to IV formulations for reasons of comfort and convenience. Zoledronic acid is available only as an intravenous infusion, whereas ibandronate may be given either intravenously or as an oral tablet. While oral bioavailability of bisphosphonates is overall very low (≤ 0.5-4%), it has been shown that oral dosing of ibandronate resulting in comparable drug exposure to effective intravenous doses can be achieved, and that this dose is tolerable and efficacious in inhibiting skeletal-related events.

This study proposes to determine whether two newer, potentially more potent bisphosphonates, zoledronic acid and ibandronate, can delay or prevent the occurrence of metastases compared with the control arm containing oral clodronate. Breast cancer patients receiving standard adjuvant systemic therapy will be eligible. At registration, patients would be randomized to either zoledronic acid 4 mg IV to be given over 15 minutes every 4 weeks for the first six months, and then every 3 months for the following 2.5 years, clodronate 1,600 mg/day orally, or ibandronate 50 mg/day orally for three years. The proposed duration of bisphosphonate therapy is 3 years.

Bisphosphonates in Pre-Menopausal Women

All 3 bisphosphonates used in **S0307** are approved worldwide for treatment of bone metastases without restriction regarding menopausal status, and there is no data to support excluding premenopausal women from enrollment in **S0307**. Potential impact on fetal development is a concern in this population should the patient become pregnant, but with proper patient awareness and education regarding adequate contraception this should not be a reason to restrict studying the use of a potentially life-saving anti-cancer agent in premenopausal women.

It is possible that long-term effects on bone quality and bone health may differ in premenopausal versus postmenopausal women. None of the adjuvant bisphosphonate trials to date, all of which included large percentages of premenopausal women, have shown any trend toward increased long-term bone or other toxicities when compared to placebo. We plan on performing a substudy addressing bone health, including serial bone biopsies in a small number of patients enrolled on **S0307**, to further address this issue (we have submitted a grant to the NIH to fund this substudy). We will also be collecting detailed bone fracture follow-up data on all patients.

Clodronate is approved in Canada, Europe and Asia at the 1,600 mg per day dose for treatment of bone metastases and has been widely used for greater than a decade. It is on fast-track approval with the FDA in the U.S. The label does not restrict usage based on menopausal status. The three adjuvant European trials evaluating clodronate versus placebo were recently updated with 10-year follow-up data at ASCO 2004. *(18-20)* All three of these trials enrolled both pre- and post-menopausal early stage (non-metastatic) breast cancer patients. Thirty-seven percent of the women in the German trial were premenopausal (113 of 302 patients). *(19)* In the Finnish trial, 52% of the enrollees were pre-menopausal (148 of 282). *(18)* In the larger UK-led trial, 50 % of trial participants were pre-menopausal (520 out of 1069 patients). *(20)* None of these trials reported toxicity rates based on menopausal status, but none of the trials reported any major significant difference in toxicities between the clodronate and placebo arms.

A recent publication of the extended safety profile of oral clodronate in the UK adjuvant clodronate study concluded that clodronate was well-tolerated with no serious long-term sequelae. *(21)* The precursor trial to **S0307**, the 3,200 patient NSABP B-34 study, met accrual in March of 2004. B-34 randomized early stage breast cancer patients to 3 years of clodronate versus placebo. The study has not yet reached a sufficient number of events to allow analysis based on the statistical plan. The Data Safety and Monitoring board has not identified any adverse events worthy of reporting. B-34 did not restrict enrollment based on menopausal status.

Ibandronate has recently been approved in Europe, Central America and Asia for the treatment of bone metastases in both intravenous form (6 mg dose monthly) and oral form (50 mg daily). There is no restriction based on menopausal status in the labeling in any country, and the trials leading to the approval of this drug included breast cancer patients of all ages. It is approved, but not yet available, in the U.S. for an osteoporosis indication at a substantially lower dose than that used in bone metastases (and in **S0307**). Again, no restriction has been placed based on menopausal status. The breast cancer studies of intravenous and oral ibandronate performed to date collected patient age but not menopausal status, and therefore such a breakdown is impossible. Of the 435 patients with metastatic breast cancer treated on the pivotal oral ibandronate studies, the median age was 57, and the age range was 29 - 92. *(22)* Some of the younger women who would normally have been within a pre-menopausal age range were likely post-menopausal secondary to their anti-cancer therapies, but based on the age range at least some pre-menopausal women were undoubtedly treated on this study. The median age and age range are similar in the intravenous ibandronate trials. The metastatic ibandronate trials included follow-up reporting of up to 2 years of treatment, and have shown a statistical decrease in skeletal-related events and improvement in quality of life.

Zoledronic acid is approved in the United States at the dose to be used in **S0307** for the treatment of bone metastasis in multiple myeloma and all solid tumors. There is no restriction based on menopausal status. The **S0307** protocol background, drug information and toxicity sections do not limit discussion to post-menopausal women. There were 3 pivotal trials leading to approval of zoledronic acid for the bone metastasis indication: 1 in breast cancer and multiple myeloma, one in prostate cancer, and one in all other sold tumors. The breast and myeloma trial randomized between pamidronate and zoledronic acid. The other 2 trials randomized between placebo and zoledronic acid. Pre-menopausal status was not an exclusion criterion. In the breast cancer and myeloma study, 12.8% of patients were < 45 years of age, 11.8% were between ages 45-49, and 75.3% were > 49 years. In the solid tumor study, 7.4% of patients were less than 45, 6.3% were 45-49, and 86.3% were > 49 years (and at least half were male). All three studies showed a decrease in skeletal-related events with up to 24 months of treatment, and an improvement in quality of life scores.

Adjuvant Bisphosphonate Therapy

A recent study investigating the adjuvant use of zoledronic acid reported an improvement in disease-free survival, in addition to favorable effects on bone mineral density. The Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial, ABCSG-12, enrolled 1,800 pre-menopausal women with ER-positive breast cancer. *(66)* All patients received ovarian suppression for three years with a leutinizing hormone releasing hormone (LHRH) analogue, goserelin. Patients were randomized in a 2 x 2 design to receive tamoxifen versus anastrozole, and zoledronic acid (4 mg q 6 months) or not. At the first efficacy analysis, reported after 137 events (70 distant relapses) with approximately 60 months of follow-up, there was no difference in outcome with respect to the endocrine therapy randomization. There was, however, a statistically significant improvement in disease-free survival for the patients who received zoledronic acid (HR 0.64; p = 0.01), with a similar trend towards improved overall survival (HR 0.60, p = 0.10). While ABCSG-12 clearly provides additional support for the metastasis-suppressing potential of adjuvant bisphosphonates, this study enrolled only a narrow subset of breast cancer patients: pre-menopausal women with estrogen receptor-positive tumors who did not receive adjuvant chemotherapy. While promising, caution must be taken not to over-extrapolate these findings, or this dose schedule, to all breast cancer patients.

The Zometa-Femara Adjuvant Synergy Trials (Z-FAST and ZO-FAST) enrolled ER-positive, postmenopausal women receiving letrozole and randomized them to "upfront" versus "delayed" zoledronic acid therapy (every 6 months for 5 years) in an attempt to reduce bone loss-related morbidity. Time to recurrence was a secondary endpoint. A recent combined analysis of these trials showed lower recurrence rates in the group receiving upfront zoledronic acid therapy (1.1% versus 2.3%, p = 0.04). *(67)*

The results of ongoing and recently closed studies will aid in defining the optimal patient and tumor populations for the addition of adjuvant bisphosphonates, as well as optimal doses and schedules of administration, and long-term toxicities. Whether doses used in metastatic disease are required for prevention or whether lower doses will suffice is unknown. It is unclear whether adjuvant bisphosphonates should be given continuously and orally, whether intravenous therapy is preferable, and whether "less intensive" intravenous regimens will turn out to be as effective as "more intensive" regimens. The optimal duration of adjuvant bisphosphonate therapy is also unknown.

Bone density and bone quality

Bisphosphonates increase bone density and have been shown to reduce fracture rates in women with osteopenia and osteoporosis. *(23)* It may be that patients enrolled in **S0307** will have a fracture rate that is less than age and race matched controls. Osteoporotic fractures, an important cause of chronic disability and disfigurement in the elderly, result when stresses placed on the bone exceed the strength of the bone. *(24)* Bone density is one important determinant of the strength of bone. However, bone strength depends on both the quantity and the quality of bone. One factor that influences the bone quality is the mineralization density. *(25)* Bisphosphonates inhibit bone turnover, interfere with bone remodeling, and increase mineralization density, which could potentially make the bone more brittle.

Studies in beagles have shown increased bone density but also markedly decreased bone formation rates and development of fatigue damage after one year of high dose alendronate or risedronate. *(26)* Biomechanical testing showed increased bone strength, but decreased toughness. A case report was recently published of a boy who developed osteopetrosis (marble bone disease) after several years of treatment with high doses of pamidronate. Osteopetrosis is the result of defective remodeling and is characterized by dense, poorly-formed and brittle skeletal tissue. Although the bones in this patient became extremely dense, he fractured his radius with only minimal trauma, suggesting decreased bone strength. *(27,28)*

In this study, bisphosphonates will be used in much higher doses than currently recommended for treatment of postmenopausal osteoporosis, and the long-term effects of such high doses of bisphosphonates on the skeleton are not known. In order to determine if the effects of bisphosphonates are beneficial or detrimental to the skeleton, we will collect prospective data on traumatic and non-traumatic fractures. In addition, a separate companion study to **S0307** will evaluate bone density and turnover in a subset of patients, and a small, limited-institution companion study of bone quality on **S0307** will include bone biopsies and experimental measures of bone strength and elasticity.

Renal toxicity

As there are limited data on the long-term renal safety of high-dose bisphosphonates in healthy patients, **S0307** will be collecting data on renal function. Oral and short-term intravenous administration of bisphosphonates, when given according to recommended infusion doses, times, and intervals, are associated with a low risk of renal dysfunction. In a randomized comparison of monthly pamidronate (90 mg as a 2-hour infusion) versus zoledronic acid (4 mg as a 15-minute infusion), 6% to 8% of patients with breast cancer experienced deterioration of renal function during the first 12 months of bisphosphonate therapy. *(12)* Renal dysfunction was defined as a change in baseline serum creatinine ≥ 0.5 mg/dL or ≥ 2 times baseline value in patients with baseline normal creatinine (< 1.4 mg/dL), or a change from baseline serum creatinine ≥ 1.0 mg/dL or ≥ 2 times baseline value in patients with abnormal baseline creatinine. Rare case reports of more serious renal toxicity have been reported with long-term and/or high-dose use of pamidronate. *(29-31)*

The American Society of Clinical Oncology 2003 update on the role of bisphosphonates in women with breast cancer recommends that serum creatinine be monitored prior to each dose of zoledronic acid, in accordance with FDA-approved labeling. *(32)* In order to be able to compare renal toxicity between all three arms of the study, **S0307** will require a monthly serum creatinine in all patients for the first 6 months, increasing the creatinine assessment interval to q3 monthly at 6 months as the zoledronic acid arm moves to quarterly infusion intervals. Patients with baseline abnormal creatinine levels will be excluded from **S0307**. Patients who develop renal dysfunction on **S0307** will have their bisphosphonate held. Reassessment of renal function will occur every 3-4 weeks, and the bisphosphonate should be reinstituted cautiously when renal function returns to baseline.

The ASCO guidelines also recommend that serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin also be monitored regularly, although the time interval is not specified. In **S0307**, these laboratory values will be monitored on a q6 monthly basis.

Osteonecrosis of the jaw

Case reports of osteonecrosis of the jaw in cancer patients on high-dose bisphosphonates have been recently published. *(33,34)* In one series, 36 patients receiving pamidronate or zoledronate for bone metastases (evenly split between multiple myeloma and breast cancer) presented with painful bone exposure in the mandible, maxilla or both that was unresponsive to surgical or medical treatment. *(33)* Approximately two-thirds of these patients were also receiving steroids, and two-thirds were receiving chemotherapy. Seventy-eight percent of the patients in this series had a dental extraction preceding the diagnosis of osteonecrosis, while the remainder developed exposed bone spontaneously.

Although a cause and effect relationship has yet been definitively established, subsequent to the publication of these two case report series Novartis Pharmaceuticals has received over 80 adverse event reports of osteonecrosis of the jaw in cancer patients receiving pamidronate or zoledronate (personal communication, Novartis). Additionally, two large oral surgery practices in Florida and New York have each collected series of approximately 75-80 cancer patients with osteonecrosis of the jaw while on high dose bisphosphonates (personal communication, R. Marx and S. Ruggiero). Although the number of reported jaw osteonecrosis cases has steadily increased since this phenomenon was initially recognized and reported in 2003 and may at this point approach a few hundred patients, this is in the setting of over 2.5 million cancer patients worldwide having been treated with pamidronate or zoledronic acid in the past decade. Additionally, clinical trials of pamidronate and zoledronic acid in more than 3,000 cancer patients dating back to the early 1990s did not detect this complication. Osteonecrosis of the jaw appears to be a very rare complication of high-dose bisphosphonate use, and is not likely limited to intravenous bisphosphonate administration alone.

Toxicity data for the AZURE study (an adjuvant trial of control versus zoledronic acid) was recently presented. *(63)* In this study of 3,360 patients receiving standard adjuvant systemic therapy, patients were randomized to receive either no additional treatment or zoledronic acid monthly x 6, then every 3 months for 8 doses, followed by every 6 months for 5 doses to complete 5 years. Patients were enrolled between September 2003 and January 2006. There was no significant difference in SAEs or AEs reported. There was a small numerical difference in vomiting (1.1% vs 2.5%) and pyrexia (1.1% vs 2.3%), higher in the zoledronic acid arm. Seven cases of osteonecrosis of the jaw have been reported, all in the zoledronic acid arm, with a median of 8 doses received at the time of ONJ (range 1-12 doses). This represents 0.4% of patients on the zoledronic acid arm. Efficacy data for this trial are expected in 2008.

S0307 will attempt to further define the magnitude of the problem of osteonecrosis of the jaw related to bisphosphonate use, and identify risk factors for the development of this complication. Therefore, all patients enrolling on **S0307** will be asked to undergo a dental exam at baseline and completion of the study, to evaluate for periodontal disease and exposed bone. Any patient who develops dental complications while on study will be evaluated for risk factors and clinical course. Since q 6-12 monthly dental exams and cleaning are considered to be part of good oral hygiene practice, these exams will not be considered to be study-specific with respect to reimbursement purposes. A small pool of money will be available for financially-limited patients without dental insurance who would not have access to dental care by any other means.

It is worth noting that there are no reports in the literature of osteonecrosis of bone in any other site (other than the jaw) related to bisphosphonate use. This may be because the jaws are the only bones in the skeleton exposed to the external environment, via the teeth, which frequently have periodontal inflammation, dental abscesses, root canal treatments, and other pathologies that increase the demand for and rate of bone turnover.

Statins

There is increasing evidence that statin drugs, through interactions that are indirect of lipid controlling activity, may mediate suppression of a number of molecular pathways that may confer benefit in cancer. *(35)* At pharmacologic doses, statins inhibit prenylation of several isoforms of the small GTPase protein family including Ras, Rac, Rho, and cdc42 in a number of cell types including endothelial and epithelial cells, resulting in an abrogation of angiogenic factors VEGF, FGF, and hyperglycemia-stimulated angiogenesis. *(36-46)* Statins have also been associated with a reduction in PAI-I activity and phosphorylation of AKT by IP-3 kinase; as well as down-regulation of MMPs; key mediators of tumor invasion and spread. *(39,4245,46)*

In two large retrospective studies of over 60,000 patients, statin use was associated with a statistically significant decrease in newly diagnosed cancers. Graaf and colleagues in the Netherlands reported a 20% decrease in relative risk for all cancers among statin users. *(47)* In another study that included over 68,000 women over the age of 35 enrolled in a Health Care Plan from Virginia, Mortimer et al demonstrated lower breast cancer risk in those women concurrently taking statins. *(48)* Statins, while designed to target liver cholesterol biosynthesis, can also have bone and brain effects. Simvastatin (Zocor), in particular, has been demonstrated to accumulate in bone and has been associated with increased bone mineral density, positive changes in serum and urine bone formation and resorption factors and with a controversial decrease in risk of osteopenic fractures. In a randomized clinical trial comparing simvastatin 40 and 80 mg/day to atorvastatin (Lipitor) 20 and 40 mg/day, serum levels of bone specific alkaline phosphatase were significantly reduced by simvastatin in a dose-dependent fashion. *(49)*

Because of anti-tumor activity demonstrated in several preclinical models, statins are currently under investigation as anti-cancer agents in early phase clinical trials. No studies to date have evaluated the efficacy of long-term statin use for preventing or diminishing liver, bone or other organ specific metastasis when administered in low, chronic, and safe doses in patients with curable or early stage disease. *(50)*

Overall the epidemiologic, cell culture and animal studies, and early human clinical trial data suggest that statin agents, particularly those that are more systemically bioavailable (i.e., atorvastatin, simvastatin), may demonstrate anti-tumor activity at the sites of highest accumulated doses (liver, bone, brain). Therefore a strong rationale exists to collect data on statin use in the adjuvant Southwest Oncology Group trial **S0307** to test our hypothesis that statin use may decrease the risk of recurrence to liver, bone and brain and may act synergistically with bisphosphonate therapy to decrease the risk of recurrence to the bone.

Biologic Correlates

Tumor PTHrP and Bone Recurrence

Metastases involving the skeleton are the first site of recurrence in 25-40% of metastatic breast cancer patients. It would be useful to determine which patients were at particular risk for developing osseous metastasis and who therefore might be expected to benefit most by receiving a bisphosphonate agent. Although several classes of adhesion molecules and cell-cell interaction molecules have been suggested to play a role in determining sites of metastasis, the one factor for which there is the most practical (but still preliminary) evidence in breast cancer is parathyroid hormone related protein (PTHrP). *(51)* Work done by Powell et al. showed that PTHrP expression could be detected by immunohistochemistry (IHC) in 92% of breast cancer bone metastasis, but only 17% of metastasis at other sites. *(52)* Work using IHC by Rivkin et al, has shown that for patients whose tumors were low expressers of PTHrP, 33% of patients developed bone metastasis while for patients who were high expressers of PTHrP, 65% developed bone metastasis. *(53)* This study has been supported by nearly identical results obtained by IHC of PTHrP in study of breast cancer patients in Japan. *(54)* Taken together these studies suggest that PTHrP may help identify breast cancer patients at high and low risk for developing osseous metastasis.

These observations are consistent with work on PTHrP measured by other methods. For example, Bundred et al, found that approximately 60% of breast cancers overexpressed PTHrP as measured in breast tumor cytosols, and preliminary results suggested that patients with tumors overexpressing PTHrP had twice the risk of developing bone marrow metastases. *(55)* Expression of PTHrP in primary breast tumor has been reported to correlate with the subsequent incidence of bone metastases. *(56)* Overexpression of PTHrP mRNA detected by PCR also has been associated with an elevated risk of developing bone metastasis. (*56)* Measurement of PTHrP levels may also have other implications, as it has been suggested in model systems that PTHrP may serve as an autocrine growth factor. *(57, 58)*

The above studies are preliminary, but suggest that expression of PTHrP in primary tumors correlate with subsequent incidence of bone metastases. We propose to test the hypothesis that patients with PTHrP expressing tumors will have a higher rate of bone recurrence. We will prospectively evaluate for presence of PTHrP in the tumor by IHC and correlate with the occurrence of bone relapse.

Serum NTx and Bone Recurrence

The development of bone metastases involves complex interactions between cancer cells and the bone microenvironment. Circulating breast cancer cells 13have affinity for bone and exhibit chemotactic responses to areas of bone undergoing resorption. *(59)* The majority of disseminated tumor cells die, but a few are capable of proliferation or can remain dormant, with bone serving as a reservoir. In the early establishment of metastases, bone is destroyed by the osteoclast, which is activated by a variety of cytokines produced directly or indirectly by the tumor cell. *(60)* As bone matrix is broken down, a rich supply of mitogenic factors is released, which can in turn lead to increased proliferation of the breast cancer cells. *(61)*

We propose to test the hypothesis that elevated levels of biochemical markers of bone remodeling, such as the bone collage breakdown product N-telopeptide (NTx), will predict for future development of bone metastases. *(62)* We will collect baseline serum on patients enrolled on **S0307** for NTx evaluation and correlate with the occurrence of bone relapse.

We realize that since all patients on this study will receive a bisphosphonate, this could influence the site of future metastases and impact our ability to study both tumor PTHrP expression and serum NTx levels as predictors of bone recurrence. We hope that the large potency differences between the three bisphosphonates will allow us to still detect differences in the first site of recurrence between the most potent (zoledronic acid) and the least potent (clodronate), and to evaluate our proposed biologic correlates across treatment groups.

Pharmacogenomic Studies

Pharmacogenomics investigates the inherited variation in genes that dictate drug response and explores ways that these variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug, or perhaps, no response at all. In the practice of medical oncology, it is common to treat many patients, when only a few actually derive distinct benefit from a specific drug therapy. The admixing of pharmacology, genetics and oncology offers the opportunity to practice individualized medicine.

The objectives of the pharmacogenomic studies include to investigate whether there is an association between single nucleotide polymorphisms (SNPs) and the adverse event of acute phase reactions in patients with early stage breast cancer who have been randomly assigned to one of three adjuvant bisphosphonates on clinical trial **S0307**. This study will investigate SNPs within FDPS, CYP2C8, and the VEGF pathway as they associate with the efficacy and toxicity of the 3 adjuvant bisphosphonate therapies administered in **S0307**. The resource developed here will provide materials for present and future research as related to bisphosphonate and breast cancer therapies, as well as serve as a DNA repository for future investigations

It is strongly recommended that all **S0307** participants, new and existing patients already registered to the protocol at the time of Revision #5, be given the opportunity to consent to submission of whole blood specimen prior to the their next blood draw for routine laboratory testing. The **S0307** whole blood specimen may be drawn at any point of clinical care or planned study phlebotomy and at any time of study participation or follow up. Patients need not be in active therapy to donate the whole blood specimen for DNA.

Rationale for Banking of Tissue Specimens

An analysis of tumor markers in stored paraffin blocks from this study has the potential to allow the testing of proposed prognostic and predictive factors for bone recurrence. Additionally, evaluation of these markers may allow us to predict which patients are particularly likely to benefit from bisphosphonate therapy.

Rationale for Banking of Serum/Whole Blood Samples

Several studies have shown that a variety of circulating markers can provide insight into bone turnover. We propose to collect samples from this clinical trial and store them in the Southwest Oncology Group Solid Tumor Bank. We propose to test the hypothesis that elevated levels of markers of bone turnover (specifically serum NTx) at baseline will predict for future development of bone metastases. These specimens will also serve as a valuable resource for future studies of tumor/bone interaction and pharmacogenomics.

Inclusion of Women and Minorities:

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	270	0	270
Not Hispanic or Latino	5,130	0	5,130
Total Ethnic	5,400	0	5,400
Racial Category			
American Indian or Alaskan Native	14	0	14
Asian	134	0	134
Black or African American	444	0	444
Native Hawaiian or other Pacific Islander	7	0	7
White	4,801	0	4,801
Racial Category: Total of all Subjects*	5,400	0	5,400

Differences among treatment arms are not expected to be a function of race or ethnicity. Thus the study is not designed to detect differences within race or ethnicity subsets. This will be explored as part of the final analysis.

3.0 DRUG INFORMATION

3.1 Zoledronic Acid (Zometa®) (NSC-721517)

a. Description

1. Zoledronic acid is a third generation bisphosphonate which is a highly potent inhibitor of bone resorption and will decrease hypercalcemia of malignancy.

2. Molecular Formula C5H10N2O7P2 · H2O

3. Molecular Weight 290.1 g/Mol

b. Pharmacology

Zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factor released by tumors.

c. Pharmacokinetics

1. Distribution: Decline of zoledronic acid concentrations in plasma is consistent with a triphasic process showing a rapid decrease from peak concentrations at end of infusion to less than 1% of Cmax 24 hours post infusion with population half-lives of t1/2α 0.24 hours and t1/2β 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 post infusion, and a terminal elimination half-life t 1/2γ of 146 hours. The area under the plasma concentration versus time curve (AUC0-24h) of zoledronic acid was dose proportional from 2-16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean AUC0-24h ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively. *In-vitro* and *ex-vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. *In vitro,* mean zoledronic acid protein binding in human plasma ranged from 28% at 200 ng/mL to 53% at 50 ng/mL.

2. Metabolism: Zoledronic acid does not inhibit human P450 enzymes in vitro. Zoledronic acid does not undergo biotransformation in vivo. In animal studies, less than 3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. In animal studies, less than 3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney.

3. Elimination: In 64 patients with cancer and bone metastases, on average (± s.d.) 39 ± 16% of the administered zoledronic acid dose was recovered in the urine within 24 hours, with only trace amounts of drug

found in urine post-Day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h.

d. Adverse Effects

1. The most common adverse events (≥ 25%) are nausea, fatigue, anemia, bone pain, constipation, fever, vomiting, and dyspnea. In less than 10% of patients treated with zoledronic acid, the following adverse events were reported: asthenia, chest pain, leg edema, mucositis, dysphagia, granulocytopenia, thrombocytopenia, pancytopenia, nonspecific infection, dehydration, arthralgias, headache and somnolence. Electrolyte abnormalities, most commonly hypocalcemia, hypophosphatemia and hypomagnesemia, can occur with bisphosphonate use.

   Injection Site Reactions: Local reactions at the infusion site, such as redness or swelling, were observed infrequently. In most cases, no specific treatment is required and the symptoms subside after 24-48 hours.

   Renal Toxicity: Administration of zoledronic acid 4 mg given as a 5-minute intravenous infusion has been shown to result in an increased risk of renal toxicity, as measured by increases in serum creatinine, which can progress to renal failure. Preexisting renal insufficiency and multiple cycles of zoledronic acid and other bisphosphonates are risk factors for subsequent renal deterioration with zoledronic acid. Factors predisposing to renal deterioration, such as dehydration or the use of other nephrotoxic drugs, should be identified and managed, if possible.

   Musculoskeletal Pain: Severe an occasionally incapacitating bone, joint, and/or muscle pain has been reported. The time of onset of symptoms varied from one day to several months after starting the drug.

   Osteonecrosis of the Jaw: Cases of osteonecrosis (primarily involving the jaws) have been reported predominantly in cancer patients. The majority of the reported cases are following invasive dental procedures, such as tooth extraction.

   Ocular Adverse Events: Cases of uveitis, scleritis, epislceritis, conjunctivitis, iritis, and orbital inflammation including orbital edema have been reported during postmarketing use. In some cases, symptoms resolved with topical steroids.

   Hypersensitivity Reactions: There have been rare reports of allergic reaction with intravenous zoledronic acid including angioedema, and bronchoconstriction. Very rare cases of anaphylactic reaction/shock have also been reported.

2. Pregnancy and Lactation: Pregnancy Category D. ZOLEDRONIC ACID SHOULD NOT BE USED IN PREGNANCY. If a patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be

advised to avoid becoming pregnant. It is not known whether zoledronic acid is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from zoledronic acid, a decision should be made to discontinue nursing or to discontinue the drug, taking in to account the importance of the drug to the mother. Zoledronic acid binds to bone long term and may be released over weeks.

3. Drug interactions: In-vitro studies indicate that zoledronic acid is approximately 22% bound to plasma proteins. In-vitro studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. *In-vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug.

Aminoglycosides	Caution is advised as these agents may have an additive effect to lower serum calcium levels for prolonged periods. This effect has not been reported in clinical trials.
Loop diuretics	Caution is advised due to an increased risk of hypocalcemia.
Nephrotoxic drugs	Caution is advised with other potentially nephrotoxic drugs.
Thalidomide	No dose adjustment of zoledronic acid is needed when co-administered with thalidomide.

e. Administration & Dosing

1. See Treatment Plan Section 7.0

2. Vials of zoledronic acid concentrate for infusion contain overfill allowing for the withdrawal of 5 mL of concentrate (equivalent to 4 mg zoledronic acid). This concentrate should immediately be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP, following proper aseptic technique, and administered to the patient by infusion. Do not store undiluted concentrate in a syringe, to avoid inadvertent injection.

f. Storage/Stability

1. Zoledronic acid must not be mixed with calcium or other divalent cation-containing infusion solutions, such as Lactated Ringer's solution, and should be administered as a single intravenous solution in a line separate from all other drugs.

2. Cartons of zoledronic acid vials should be stored at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. If not used immediately after dilution with infusion media, for microbiological integrity, the solution should be refrigerated at 2-8°C (36-46°F). The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between dilution, storage in the refrigerator, and end of administration must not exceed 24 hours.

g. How Supplied

1. Zoledronic acid is available in a 4 mg / 5 mL single-use vial of concentrate. Each 5 mL vial contains 4.264 mg of zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, 220 mg of mannitol, USP, water for injection, and 24 mg of sodium citrate, USP.

2. Zoledronic acid is being supplied free-of-charge by Novartis. To obtain a supply of zoledronic acid, contact UVI, Inc at:

UVI, Inc
Phone: 800-370-2508
Fax: 650-745-3877

UVI, Inc. office hours are 8:00 a.m. to 1:00 p.m. PST; a phone message may be left at other times. Orders received by 12:00 p.m. PST Monday through Thursday will be shipped for next day delivery. Orders received by 3:00 p.m. PST on Friday will be shipped the following Monday for receipt Tuesday, unless institutions specifically request Saturday delivery and can guarantee their institution will accept delivery. Patients must be registered to the study before study drug can be obtained.

3. Drug handling and Accountability

a. Drug Accountability: The principal investigator, or authorized designee, must maintain careful record of the receipt, disposition, and return of all zoledronic acid using the NCI Investigational Drug Accountability Record Form available on the CTEP forms page http://ctep.cancer.gov/forms/. Institution specific electronic logs allowable if approved by NCI.

b. Drug Returns: All unused drug supplies should be returned to Novartis Pharmaceutical for destruction. Returned drug must be sent with the zoledronic acid return form, which can be requested by contacting Novartis Pharmaceuticals. The Novartis contact information can be found on the **S0307** abstract page of the SWOG website (www.swog.org).

3.2 Clodronate (Bonefos®) (NSC-713466) (IND-71,481)

a. DESCRIPTION

Clodronate (Bonefos®) is not FDA-approved for use in the U.S.

Manufacturer: Bayer Schering Pharma Oy, Pansiontie 47, FIN-20210 Turku, Finland.

Active Ingredient: One clodronate 800 mg tablet contains 800 mg disodium clodronate.

Inactive Ingredients: Clodronate 800 mg tablets: Silicified microcrystalline cellulose (consisting of microcrystalline cellulose and colloidal anhydrous silica), croscarmellose sodium, stearic acid, magnesium stearate, hypromellose, polyethylene glycol 400, titanium dioxide (E171).

Clodronate is intended for the treatment of bone diseases and for reduction of occurrence of bone metastases in primary breast cancer. Clodronate contains disodium clodronate as an active ingredient. Clodronate is chemically defined as bisphosphonate and is an analogue of the natural pyrophosphate. Clodronate has a strong affinity for mineralized tissues such as bone, where it inhibits bone resorption, which may be abnormally increased due to malignancy. Consequently, reduction in elevated serum calcium concentrations and a decrease in fracture risk have been observed in patients during clodronate

treatment. In patients with primary breast cancer clodronate treatment has been shown to reduce occurrence of bone metastases, and to be associated with reduced mortality.

Clodronate is indicated for the treatment of osteolysis and hypercalcemia due to malignancy and for reduction of occurrence of bone metastases in primary breast cancer.

Clodronate shall not be used concomitantly with other bisphosphonates or for patients with known hypersensitivity to bisphosphonates.

b. TOXICOLOGY

Adequate fluid intake shall be maintained during clodronate treatment. This is particularly important when clodronate is used in connection with hypercalcemia or renal failure.

Clodronate is eliminated mainly via the kidneys. Clodronate should therefore be used with caution in connection with renal failure; daily doses exceeding 1,600 mg should not be used continuously.

The following interactions with clodronate have been reported: Clodronate forms poorly soluble complexes with divalent cations. Therefore, if clodronate is taken simultaneously with food, liquids or drugs containing divalent cations, e.g. antacids or iron preparations, the bioavailability of clodronate is reduced significantly. This may in turn reduce the efficacy of clodronate. An interval of one hour is recommended after drug intake before eating or drinking other than plain water. In some cases when clodronate has been used simultaneously with anti-inflammatory analgesics (NSAIDs) renal dysfunction has been reported.

Due to increased risk of hypocalcemia, caution should be taken when using clodronate together with aminoglycoside antibiotics. Concomitant use of estramustine phosphate with clodronate has been reported to increase the serum concentration of estramustine phosphate.

The most frequently reported adverse reactions attributable to clodronate are gastrointestinal effects such as nausea, vomiting and diarrhea. These may occur in up to 10% of patients. However, such effects are usually mild and occur more commonly with high doses. Occasionally, clodronate treatment may elevate serum concentrations of parathyroid hormone and aminotransferases. These usually transient changes rarely exceed twice the laboratory reference range. Changes in serum concentrations of alkaline phosphatase have also been reported, as well as usually asymptomatic hypocalcemia. In addition, individual cases of impairment of respiratory function resembling hypersensitivity reaction or in patients with aspirin-sensitive asthma, as well as skin reactions have been reported. Reversible proteinuria, serum creatinine elevation, and renal dysfunction have been reported. However, most patients have been terminally ill and the causal role of clodronate treatment in the renal dysfunction has not been confirmed.

Pregnancy and lactation: It is not known if clodronate can cause damage to the fetus, or affect reproduction, or if it is secreted in human milk. Therefore, clodronate should not be used for pregnant or lactating women, unless the therapeutic advantages clearly outweigh any risks.

c. PHARMACOLOGY

Formulation: Clodronate 800 mg tablets: White, oval, scored, film-coated tablets, marked L134 on one side. Size of tablet 9 mm x 20 mm.

Storage and Stability: Clodronate 800 mg tablets shelf life: Three years. Do not store above 30°C (86°F). Keep the medicine out of the reach of children.

Expiration date: Check the expiration date on the package. Do not use the medicine after the expiration date or if there are any visible changes in the preparation.

Administration: Oral. A clodronate 800 mg tablet may be divided into two to ease swallowing, but the halves have to be taken at the same time of administration. Clodronate tablets should not be crushed or dissolved before intake.

When clodronate is taken as a single daily dose, it should preferably be taken in the morning on an empty stomach together with a glass of water. Thereafter, the patient should refrain from eating, drinking (other than plain water), and taking any other oral drugs for one hour.

If the daily dose of clodronate is taken as divided doses, the first dose should be taken as recommended above. The second dose should be taken between meals, more than two hours after and 30 minutes before eating, drinking (other than plain water), or taking any other oral drugs.

Clodronate should in no case be taken with milk, food or drugs containing calcium or other divalent cations, because they impair the absorption of clodronate.

Children: Safety and efficacy in pediatric patients have not been established.

Elderly: There are no special dosage recommendations for the elderly.

Adult patients with normal renal function: The dose is individual and depends on the indication clodronate is used for. The recommended starting dose is 1,600 mg/day taken as a single dose. If clinically necessary, the dose may be increased, but is not recommended to exceed 1,600 mg daily. For reduction of occurrence of bone metastases in primary breast cancer, the recommended dose is 1,600 mg daily.

Patients with renal failure: Clodronate is eliminated mainly via the kidneys. Therefore clodronate should be used with caution for patients with renal failure; daily doses exceeding 1,600 mg should not be used continuously.

Supplier: Clodronate is investigational for this study. This drug **will not** be supplied by the NCI. However, for this study it is being supplied free-of-charge by Bayer Schering Pharma Oy. To obtain a supply of clodronate (Bonefos®), contact UVI, Inc.:

UVI, Inc.
Phone: 800/370-2508
FAX: 650/745-3877

UVI, Inc. office hours are 8:00 a.m. to 1:00 p.m. PST; a phone message may be left at other times.

Orders received by 12:00 p.m. PST Monday through Thursday will be shipped for next day delivery. Orders received by 3:00 p.m. PST on Friday will be shipped the following Monday for receipt Tuesday, unless institutions specifically request Saturday delivery and can guarantee their institution will accept delivery. Clodronate (Bonefos®) orders from USA sites only will be accepted. Patients must be registered to the study before study drug can be obtained.

Drug Returns: Unused drug supplies should NOT be returned. Unused drug should be disposed of per local institutional guidelines.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return or disposal of all drugs received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

Questions about drug orders, transfers, returns, or accountability should be addressed to UVI at 800/370/2508.

3.3 Ibandronate (Ibandronic acid, Bondronat®) (NSC-722623) (IND-71,481)

a. DESCRIPTION

Manufacturer: Roche, Grenzacherstrasse 124, CH-4070 Basel, Switzerland.

Ibandronic acid, monosodium salt, monohydrate (Bondronat™) is a nitrogen-containing bisphosphonate that inhibits osteoclast-mediated bone resorption. The chemical name for ibandronate is 3-(*N*-methyl-*N*-pentyl)amino-1-hydroxypropane-1,1-diphosphonic acid, monosodium salt, monohydrate with the molecular formula $C_9H_{22}NO_7P_2Na \cdot H_2O$ and a molecular weight of 359.24.

Active Ingredient: Ibandronate is available as a white to off-white in colour, engraved L2/IT, 50 mg film-coated tablet for oral administration. One tablet contains 50 mg of ibandronic acid (as ibandronic sodium monohydrate).

Inactive Ingredients: lactose monohydrate, povidone, microcrystalline cellulose, crospovidone, purified stearic acid, colloidal silicon dioxide, and purified water. The tablet film coating contains hypromellose, titanium dioxide, talc, polyethylene glycol 6000, and purified water.

Metabolism: There is no evidence that ibandronate is metabolized in animals or humans.

Elimination: The absorbed fraction of ibandronate is removed from the circulation via bone absorption (estimated to be 40-50%) and the remainder is eliminated unchanged by the kidney. The unabsorbed fraction of ibandronate is eliminated unchanged in the faeces. The range of observed apparent half-lives is broad and dependent on dose and assay sensitivity, but the apparent terminal half-life is generally in the range of 10-60 hours. However, early plasma levels fall quickly, reaching 10% of peak values within 3 and 8 hours after intravenous or oral administration respectively. Total clearance of ibandronate is low with average values in the range 84-160 ml/min. Renal clearance (about 60 ml/min in healthy postmenopausal females) accounts for 50-60% of total clearance and is related to creatinine clearance. The difference between the apparent total and renal clearances is considered to reflect the uptake by bone.

b. TOXICOLOGY

Oral ibandronate has been studied in over 3,900 patients in postmenopausal osteoporosis trials of up to 3 years duration. The overall adverse event profile of ibandronic acid in these studies was similar to that of placebo. Most adverse events were mild or moderate and did not lead to discontinuation. The incidence of serious adverse events was 20% in the placebo group and 23% in the ibandronic acid group. The percentage of patients who withdrew from treatment due to adverse events was approximately 17% in both the ibandronate group and the placebo group. Overall, and according to body system, there was no difference between ibandronate and placebo, with adverse events of the digestive system being the most common reason for withdrawal. Caution should be used when administering oral bisphosphonates in patients with a medical history of gastroesophageal reflux disease (GERD). Patients should be

instructed to discontinue ibandronate therapy and seek medical attention if they develop symptoms of esophageal irritation such as worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn. Since NSAIDS and oral bisphosphanates are both associated with gastrointestinal irritation, caution should be taken during concomitant medication with ibandronate.

c. PHARMACOLOGY

Formulation: Ibandronate is a white- to off-white powder. It is freely soluble in water and practically insoluble in organic solvents.

Mechanism of Action: The action of ibandronate on bone tissue is based on its affinity for hydroxyapatite, which is part of the mineral matrix of bone. Ibandronate inhibits osteoclast activity and reduces bone resorption and turnover. In post-menopausal women, it reduces the elevated rate of bone turnover, leading to, on average, a gain in bone mass.

Drug Interactions: When co-administered with melphalan/prednisolone in patients with multiple myeloma, no interaction was observed. Other interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen or hormone replacement therapy (oestrogen). In healthy male volunteers and postmenopausal women, IV ranitidine caused an increase in ibandronate bioavailability of about 20% (which is within the normal variability of the bioavailability of ibandronate), probably as a result of reduced gastric acidity. However, no dosage adjustment is required when Bondronat is administered with H_2-antagonists or other drugs that increase gastric pH. In relation to disposition, no drug interactions of clinical significance are likely. Ibandronate is eliminated by renal secretion only and does not undergo any biotransformation. The secretory pathway does not appear to include known acidic or basic transport systems involved in the excretion of other active substances. In addition, ibandronate does not inhibit the major human hepatic P450 isoenzymes and does not induce the hepatic cytochrome P450 system in rats. Plasma protein binding is low at therapeutic concentrations and ibandronate acid is therefore unlikely to displace other active substances. Caution is advised when bisphosphonates are administered with aminoglycosides, since both agents can lower serum calcium levels for prolonged periods. Attention should also be paid to the possible existence of simultaneous hypomagnesaemia. In clinical studies, Bondronat has been administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring.

Calcium Supplements/Antacids: Products containing calcium and other multivalent cations (such as aluminum, magnesium, iron), including milk, food, and antacids are likely to interfere with absorption of ibandronate, which is consistent with findings in animal studies. Ibandronate should be taken at least 1 hour before any oral medications containing multivalent cations (including antacids, supplements, or vitamins).

Hormone Replacement Therapy: Oral bioavailability studies were used to demonstrate the lack of hormone replacement therapy (HRT) on ibandronate kinetics. However, the identity and dose of the HRT could not be identified. Mean serum ibandronate concentrations and pharmacokinetic parameters after IV and oral administration were essentially the same in postmenopausal women taking HRT as in those not on HRT. Hence, HRT did not alter the ibandronate pharmacokinetics after either IV or oral administration. However, HRT and ibandronate might have synergistic effects on bone turnover suppression, which has been observed in studies involving alendronate when co-administered with estrogen ± progestin.

Aspirin/Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): In the large, placebo-controlled osteoporosis Treatment Study, aspirin and nonsteroidal anti-inflammatory drugs were taken by 62% of the 2,946 patients. Among aspirin or NSAID users, the incidence of upper gastrointestinal adverse events in patients treated with ibandronate daily was similar to that in placebo-treated patients. However, since aspirin, NSAIDs, and bisphosphonates are all associated with gastrointestinal irritation, caution should be exercised in the concomitant use of aspirin or NSAIDs with ibandronate.

H2 Blockers and Proton Pump Inhibitors (PPIs): Of over 3,500 patients enrolled in the ibandronate osteoporosis Treatment and Prevention Studies, 15% used anti-peptic agents (primarily H2 blockers and PPIs). Among these patients, the incidence of upper gastrointestinal adverse experiences in the patients treated with ibandronate was similar to that in placebo-treated patients.

Absorption: The absorption of ibandronate in the upper gastrointestinal tract is rapid after oral administration. Maximum observed plasma concentrations were reached within 0.5 to 2 hours (median 1 hour) in the fasted state and absolute bioavailability was about 0.6%. The extent of absorption is impaired when taken together with food or beverages (other than plain water). Bioavailability is reduced by about 90% when ibandronic acid is administered with a standard breakfast in comparison with bioavailability seen in fasted subjects. When taken 30 minutes before a meal, the reduction in bioavailability is approximately 30%. There is no meaningful reduction in bioavailability provided ibandronic acid is taken 60 minutes before a meal. Bioavailability was reduced by approximately 75% when Bondronat tablets were administered 2 hours after a standard meal. Therefore, it is recommended that the tablets should be taken after an overnight fast (minimum 6 hours) and fasting should continue for at least 30 minutes after the dose has been taken.

Distribution: After initial systemic exposure, ibandronate rapidly binds to bone or is excreted into urine. In humans, the apparent terminal volume of distribution is at least 90 l and the amount of dose reaching the bone is estimated to be 40 - 50% of the circulating dose. Protein binding in human plasma is approximately 87% at therapeutic concentrations, and thus drug-drug interaction due to displacement is unlikely.

Animal Pharmacology and/or Toxicology: Animal studies have shown that ibandronate is an inhibitor of osteoclast-mediated bone resorption. In the Schenk assay in growing rats, ibandronate inhibited bone resorption and increased bone volume, based on histologic examination of the tibial metaphyses. There was no evidence of impaired mineralization at the highest dose of 5 mg/kg/day (subcutaneously), which is 1,000 times the lowest antiresorptive dose of 0.005 mg/kg/day in this model, and 5,000 times the optimal antiresorptive dose of 0.001 mg/kg/day in the aged ovariectomized rat. This indicates that ibandronate administered at the therapeutic doses is unlikely to induce osteomalacia.

Administration: Oral. Ibandronate should be taken at least 30 minutes before the first food or drink (other than water) of the day or any oral medication or supplementation, including calcium, antacids, or vitamins. To facilitate delivery to the stomach, ibandronic acid should be swallowed whole while the patient is in an upright position and with a full glass of plain water (6 to 8 oz). Patients should not lie down for 30 minutes after taking the medication.

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate. Calcium supplements and calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of ibandronate and should be taken at a different time of the day. Ibandronate is not recommended

for use in patients with severe renal impairment (creatinine clearance < 30 mL/min). No dosage adjustments are necessary in patients with a creatinine clearance ≥ 30 mL/min or in the elderly.

Storage and Stability: Store at controlled room temperature 20°-25° C (68°-77° F)

Supplier: Ibandronate is investigational for this study. This drug **will not** be supplied by the NCI. However, for this study it is being supplied free-of-charge by Roche. To obtain a supply of ibandronate, contact UVI, Inc.:

UVI, Inc.
Phone: 800/370-2508
FAX: 650/745-3877

UVI, Inc. office hours are 8:00 a.m. to 1:00 p.m. PST; a phone message may be left at other times.

Orders received by 12:00 p.m. PST Monday through Thursday will be shipped for next day delivery. Orders received by 3:00 p.m. PST on Friday will be shipped the following Monday for receipt Tuesday, unless institutions specifically request Saturday delivery and can guarantee their institution will accept delivery. Ibandronate orders from USA sites only will be accepted. Patients must be registered to the study before study drug can be obtained.

Drug Returns: Unused drug supplies should NOT be returned. Unused drug should be disposed of per local institutional guidelines.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return or disposal of all drugs received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

Questions about drug orders, transfers, returns, or accountability should be addressed to UVI at 800/370/2508.

4.0 STAGING CRITERIA, AJCC 6th Edition, 2002

DEFINITION OF TNM

Primary Tumor (T)

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2 or T3). If other measurements, such as mammographic or pathologic measurements are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1 cm increment.

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease of the nipple with no tumor

NOTE: Paget's disease associated with a tumor is classified according to the size of the tumor.

T1	Tumor 2 cm or less in greatest dimension
T1mic	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumor more than 0.1 cm but no more than 0.5 cm in greatest dimension
T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c	Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension

T4	Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below:
T4a	Extension to chest wall, not including pectoralis muscle
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Regional Lymph Nodes (N)

Clinical

N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph node(s)
N2	Metastasis in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis
N2a	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastasis
N3	Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

**Clinically apparent* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

Pathologic (pN)[a]

pN0	No regional lymph node metastasis histologically, no additional examination for isolated tumor cells (ITC)

NOTE: Isolated tumor cells (ITC) are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but which may be verified on H&E stains. ITCs do not usually show evidence of malignant activity e.g., proliferation or stromal reaction.

pN0 (i-)	No regional lymph node metastasis histologically, negative IHC
pN0 (i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
pN0(mol-)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)[b]
pN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)[b]

[a]Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," e.g., pN0 (i+) (sn).

[b]RT-PCR: reverse transcriptase/polymerase chain reaction.

pN1	Metastasis in 1 to 3 axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN1mi	Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
pN1a	Metastasis in 1 to 3 axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.**
pN1c	Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.** (If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden)
pN2	Metastasis in 4 to 9 axillary lymph nodes or in clinically apparent* internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
pN2a	Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastasis in clinically apparent* internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent**
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

**Clinically apparent* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

***Not clinically apparent* is defined as not detected by imaging studies (excluding lympho-seintiography) or by clinical examination.

Distant Metastasis (M)

M0 No distant metastasis

STAGE GROUPING

Stage I	T1*	N0	M0
Stage IIA	T0	N1	M0
	T1*	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0

*T1 includes T1mic

NOTE: Stage designation may be changed if post-surgical imaging studies reveal the presence of distant metastases, provided the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please complete the Prestudy Form and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

____ 5.1 Patients must be women with histologically confirmed primary invasive adenocarcinoma of the breast (Stage I, II, III) with no evidence of metastatic disease. Primary disease within the breast must be resected, either with mastectomy or breast sparing surgery. An axillary node evaluation should be performed per the standard of care specified at each institution.

____ 5.2 Patients must receive standard (systemic) adjuvant therapy for their breast cancer. Chemotherapy, hormone therapy, or combined chemo/hormone therapy is permitted. Additional therapies are allowed including radiation therapy and biologic agents (e.g. Herceptin®, Avastin®, hematopoietic growth factors). Patients who receive biologic agents only or local radiation therapy only (without chemotherapy and/or hormone therapy) are not eligible. Patients who are at such a low risk of recurrence that adjuvant therapy will not be prescribed are ineligible. Neoadjuvant therapy is permitted, but enrollment must occur after completion of surgery.

____ 5.3 Patients may be enrolled prior to, simultaneously with, or after beginning adjuvant systemic therapy. Patients receiving hormonal therapy alone (no chemotherapy) or pre-operative chemotherapy should be enrolled within 84 days (12 weeks) after the date of final surgical procedure for the cancer. Patients receiving adjuvant post-operative chemotherapy may be enrolled up to 8 weeks after the last administration of chemotherapy. Additional biological therapy or radiation therapy is allowed at any time before or after registration.

____ 5.4 Institutions are encouraged to seek patient consent to submit tissue, whole blood and serum for banking. Patients who wish to participate in the tissue, whole blood and serum submissions for banking as outlined in Section 15.3 and 15.4 must consent to the procedures. Written informed consent must be obtained prior to submitting samples.

____ 5.5 Patients must have a Zubrod performance status of 0 - 2 (see Section 10.5).

____ 5.6 Patients must not be co-enrolled on protocols that have bone density as an endpoint. Patients may be registered to any other locoregional or systemic therapy breast cancer study, including cooperative group studies, as long as the protocol does not specifically exclude co-enrollment.

____ 5.7 Patients must have a serum creatinine that is $\leq$ 2 times the institutional upper limit of normal and a calculated creatinine clearance of $\geq$ 30 ml/min within 7 days prior to enrollment. Patients with renal failure are ineligible for this study.

____ 5.8 Patients who have previously been or are currently being treated with a bisphosphonate for bone density are eligible, as long as the bisphosphonate is discontinued at registration. No other forms of bisphosphonates, other than those prescribed in this study, may be used or planned during protocol treatment, either as an adjuvant or for the treatment of osteoporosis. (Note: This study has no placebo arm, so all patients will be receiving a bisphosphonate.)

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

____ 5.9 Patients must undergo a dental examination within 6 months prior to initiation of treatment per Section 7.4.

____ 5.10 A patient with skeletal pain is eligible for inclusion in the study if bone scan and/or roentgenological examination fails to disclose metastatic disease. Suspicious finding must be confirmed as benign by x-ray, MRI, or biopsy.

____ 5.11 Patients must not have a medical history of esophageal stricture or motility disorders. Patients with a history of gastroesophageal reflux disorder (GERD) are eligible, but caution should be used when administering oral bisphosphonates.

____ 5.12 Pregnant or nursing women may not participate due to the possibility of fetal harm or harm to nursing infants from this treatment regimen (see Section 3.0). Women of reproductive potential may not participate unless they have agreed to use an effective contraceptive method while on this trial. Women of child-bearing potential must have a pregnancy test performed within 72 hours prior to initiation of treatment (see Section 7.2).

____ 5.13 No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.

5.14 If Day 14, 28, or 84 falls on a weekend or holiday, the limit may be extended to the next working day.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday two weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines.

____ 5.15 All patients must be informed of the investigational nature of this study and give written informed consent in accordance with institutional and federal guidelines. At the time of registration, the date of informed consent must be provided.

____ 5.16 At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

6.0 STRATIFICATION FACTORS

Balancing on patient characteristics will not be necessary due to the large sample size. Thus, stratification factors are not applicable to this study.

7.0 TREATMENT PLAN

For treatment or dose modification related questions, please contact Dr. Julie Gralow at 206/288-7722 or Dr. Robert Livingston at 520/626-2816 or Kim Damman, BSN at 206/288-6900 (e-mail: ADJBISJG@u.washington.edu).

7.1 Good Medical Practice

The following pre-study tests should be obtained within 28 days prior to registration in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations would be acceptable if they do not impact on patient safety in the clinical judgment of the treating physician. The Study Coordinator must be contacted if there are significant deviations in the values of these tests.

a. Chest x-ray that is negative for metastatic disease. If a chest x-ray was done as part of the original diagnostic and/or preoperative workup and was negative, it does not need to be repeated.

b. CBC (WBC ≥ 3,000/µl, ANC ≥ 1,000/µl, platelets ≥ 100,000/µl).

c. Total bilirubin that is ≤ 2 x the institutional upper limit of normal and SGOT or SGPT that is ≤ 3 x the institutional upper limit of normal.

d. Calcium, albumin, magnesium and phosphate within institutional normal limits.

e. Electrolytes (sodium, potassium, chloride, bicarbonate)

f. Alkaline phosphatase within institutional normal limits.

g. Ultrasound or CT scan of the abdomen if liver function tests (alkaline phosphatase, bilirubin, SGOT or SGPT) are elevated without a clear cause.

h. CT scan of the chest and abdomen and a bone scan are recommended in patients at high risk for harboring metastatic disease, such as patients with Stage III disease or those with 10 or more lymph nodes involved by malignancy. The combination of chest x-ray, liver ultrasound and bone scan (with CTs only for abnormal chest x-ray or ultrasound) will also be considered acceptable in these high risk patients.

7.2 Pre-Treatment Guidelines

Patients will be randomized to zoledronic acid (Arm 1) or to clodronate (Arm 2) or to ibandronate (Arm 3). The duration of bisphosphonate therapy is 3 years. After three years, patients may receive non-protocol therapy at the physician's discretion.

Investigators are encouraged to begin bisphosphonate therapy as soon as possible after surgery. Patients may be registered and begin bisphosphonate therapy prior to, simultaneously, or after systemic therapy. Patients receiving hormonal therapy alone (no chemotherapy) or pre-operative chemotherapy should be enrolled within 84 days (12 weeks) after the date of final surgical procedure. Patients receiving adjuvant post-operative chemotherapy may be enrolled up to 8 weeks after completion of chemotherapy (see Section 5.3).

Women of child-bearing potential must have a pregnancy test performed within 72 hours prior to initiation of treatment.

7.3 Treatment Schedule

For patients receiving zoledronic acid, peripheral or central intravenous access may be used. During the first 6 months of dosing, zoledronic acid should be administered to patients in Arm 1 monthly (i.e. if treatment begins on the 1st of the month, then the subsequent doses are given on the 1st of each month thereafter), however minor deviances from this dosing interval are acceptable. It is suggested that the infusions be given within ± 2 days (2 days earlier or later). During the remaining period of dosing, zoledronic acid may be given within ± 1 week (7 days earlier or later). The last dose of zoledronic acid in Arm 1 should be administered at Month 33. Oral bisphosphonates given in Arms 2 and 3 are to continue daily until the first day of Month 36 and are then discontinued.

NOTE: For Arm 1, monthly dosing of zoledronic acid is given for 6 doses, q 3 monthly dosing is given for 9 doses.

DRUG	DOSE	RX ROUTE	DAY	INTERVAL
Arm 1				
Zoledronic acid	*4 mg	IV over 15 minutes	1	q monthly x 6 months then q 3 months for 2.5 years
Arm 2				
Clodronate	1,600 mg	PO	1	q day x 35 months
Arm 3				
Ibandronate	50 mg	PO	1	q day x 35 months

* Upon treatment initiation, the recommended zoledronic acid doses for patients with reduced renal function (mild and moderate renal impairment) are listed below. These doses are calculated to achieve the same AUC as that achieved in patients with creatinine clearance of 75 ml/min. Creatinine clearance (CrCl) is calculated using the Cockcroft-Gault formula:

$$\frac{(140\text{-age}) \times \text{wt (kg} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dL)}}$$

Baseline Creatinine Clearance (ml/min)	Zoledronic Acid recommended dose. (Calculated assuming AUC of 0.66 mg/hr/L) (CrCl = 75 ml/min)
> 60	4 mg
50 - 60	3.5 mg
40 - 49	3.3 mg
30 - 39	3 mg

7.4 Dental Examination

Patients will undergo a dental exam within 6 months prior to initiation of treatment. The Dental Examination Form (Form #30100) should be completed by a dental health professional (may be retrospectively completed if the exam was prior to initiation of treatment). The exam should include visual inspection and periodontal probing. Specifically, evaluation of risk factors for osteonecrosis of the jaw should be evaluated. X-rays are not required, but should be performed, if indicated to assess degree of periodontal involvement and endodontic (root canal) problems.

Patients on chemotherapy, who have the potential to develop neutropenia, should avoid undergoing teeth cleaning or elective restorative procedures due to possible increased risk of infection. Patients are expected to undergo standard dental examinations and care while on study. Financial assistance will be available for baseline dental exams for patients with severe financial need and without dental insurance who would not have access to dental care by any other means. Contact the Southwest Oncology Group Operations Office at 210/614-8808 for further information. X-rays are not required by this study and will not be covered unless significant baseline problems are identified.

7.5 Patients may receive radiation therapy to breast/chest wall/lymph node groups while on protocol treatment at the treating physician's discretion.

7.6 Patients should have supplemental administration of oral calcium and vitamin D. Recommended dose of calcium for premenopausal women is 1,000 mg PO daily, and range for postmenopausal women is 1,200-1,500 mg PO daily. The recommended daily dose of vitamin D is 400-800 units/day. These supplements should not be taken within 30 minutes of oral bisphosphonates.

7.7 Oral bisphosphonates should be taken at least one hour before the first food or drink of the day other than water. To facilitate delivery to the stomach, oral bisphosphonates should be swallowed while the patient is in an upright position and with a full glass of plain water (6 to 8 oz). Patients should not lie down for 30 minutes after taking the medication.

Calcium supplements and calcium-, aluminum-, and magnesium-containing medications may interfere with the absorption of oral bisphosphonates and should be taken at a different time of the day.

7.8 Pill Compliance: Patients are encouraged to keep their own pill diary and should bring the diary with them to each follow-up visit. Diaries will not be collected, but any missed pills during the last month of treatment should be reported on the **S0307** Treatment Summary Form (Form #31453).

7.9 Treatment Evaluations

Physical exams and labs (including CBC, electrolytes, calcium, phosphate, magnesium, albumin, and LFTs) should be performed prior to dosing (ideally Day 1) of Month 2, 4, 6, then q 3 months until Month 36.

For Arm 1, serum creatinine testing must be performed within 7 days prior to administering subsequent zoledronic acid dosing q monthly for Months 2-6, then q 3 months until Month 36.

For Arms 2 & 3, serum creatinine testing should be performed ± 7 days (7 days earlier or later) q monthly for Months 2-6, then q 3 months until Month 36.

7.10 End of Treatment Evaluation

An end of treatment physical examination and a bone scan will be obtained in all patients at the end of protocol treatment, on Day 1 of Month 36 or up to 14 days after Day 1 of Month 36. Patients who have had a bone scan within 6 months prior to ending treatment will not be required to have the scan repeated. Additionally, a dental examination will also be required at the end of protocol treatment (within 6 months after study completion or removal from protocol treatment, see Section 7.11). The end of treatment dental examination must be performed regardless of how long the patient was on treatment (including one month or less). For patients without insurance to cover these examinations, financial assistance will be available. Contact the Southwest Oncology Group Operations Office at 210/614-8808 for further information.

7.11 Evaluation at the time of recurrence

a. Recurrence of disease must be adequately demonstrated. Suspected recurrence should be biopsied or otherwise confirmed if at all possible. Good medical practice requires biopsy proof of recurrent disease, as such documentation helps avoid the occasional mistake of misidentification of a benign lesion as recurrence or of second primary cancers as recurrence. If biopsy proof of recurrence cannot be obtained, radiologic diagnosis will be allowed at the discretion of the treating physician.

b. Patients must be restaged at the time of recurrence. All patients with recurrence must have the following studies within 30 days of diagnosis and/or biopsy documentation of recurrence.

1. Nucleotide bone scan, CT of chest and abdomen (MRI, CAT or ultrasound of the liver may be substituted for abdomen CT if desired).

2. For patients experiencing bone pain with other sites of recurrence, plain films will be obtained on the painful sites if the bone scan is negative.

3. For patients with other possibly tumor related symptoms, appropriate radiologic or other studies should be obtained to document the sites of disease.

7.12 Criteria for Removal from Protocol Treatment:

a. Invasive recurrence of disease or diagnosis of new invasive breast primary. A new diagnosis of ipsilateral or contralateral DCIS without an invasive component is not considered to be a recurrence or a second primary.

b. Unacceptable toxicity (see Section 8.0).

c. Greater than 3 months in delay of protocol treatment.

d. Completion of three years of protocol treatment.

e. The patient may withdraw from the study at any time for any reason.

7.13 All reasons for discontinuation of treatment must be documented on the Off-Treatment Notice.

7.14 All patients will be followed until death or for 10 years, whichever is first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE DELAY AND MODIFICATIONS

8.1 **Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.**

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 will be utilized **for SAE reporting only**. The CTCAE Version 4.0 is identified and located at the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 3.0 for routine toxicity reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.

8.2 Bisphosphonate therapy must be held for any Grade 3 or greater toxicity (that is attributed to the bisphosphonate by the treating physician). If toxicity has not resolved within 3 months, then the patient must be removed from protocol treatment. If toxicity resolves (Grade 0-1) within 3 months, the protocol treatment should be restarted. If Grade 3 or greater toxicity reoccurs, then the patient must be removed from protocol treatment.

8.3 Renal Toxicity: For any increase of 0.5 mg/dL from normal baseline creatinine that is > IULN, or any increase of ≥ 1 mg/dL from an abnormal baseline creatinine that is > IULN, bisphosphonate therapy should be held, and serum creatinine must be monitored until it returns to within 10% of baseline. Once creatinine returns to within 10% of baseline, bisphosphonate therapy can be reinitiated at the same dose prior to treatment interruption.

For patients in the zoledronic acid arm with an increased creatinine, consider increasing the infusion duration to 30 minutes in subsequent cycles.

Grade 3 or higher creatinine elevations (> 3 x the institutional upper limit of normal) that is attributed to the bisphosphonate by the treating physician will require removal of the patient from protocol treatment.

8.4 Bisphosphonates from any of the 3 arms may be held or delayed for up to 3 months for any reason without requiring removal from protocol treatment. The total duration of treatment will be 35 months (through Day 1 of Month 36) for the clodronate and ibandronate arms regardless of how many doses may have been missed during this period. The last dose on the zoledronic acid arm should be administered at Month 33, but no later than 36 months after registration due to treatment delays. If treatment is delayed for more than one week during the first 6 months of treatment on zoledronic acid, the schedule should be adjusted so that there is at least 3 weeks between successive doses, until all 6 monthly doses have been given, after which every 3 months dosing can begin. Otherwise, the original schedule on the zoledronic acid arm should be adhered to following treatment delays.

8.5 Osteonecrosis of the jaw: Completion of the Osteonecrosis Jaw Lesion Form (Form #52641) will be required for any patient diagnosed with osteonecrosis of the jaw. Because of the long half-life of bisphosphonates in bone, it is not clear that stopping the bisphosphonate therapy will aid in healing. Consultation with the **S0307** Jaw/Dental Health Coordinator, Dr. Mark Schubert (206/288-1331), is recommended in this situation.

8.6 For treatment or dose modification related questions, please contact Dr. Julie Gralow at 206/288-7722 or Dr. Robert Livingston at 520/626-2816 or Kim Dammann, BSN at 206/288-6900 (e-mail: ADJBISJG@u.washington.edu).

8.7 Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Coordinator and the NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR **S0307**, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer"

REQUIRED STUDIES	PRE STUDY	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	Month 27	Month 30	Month 33	End of Treatment € Month 36	ƒ Follow Up
PHYSICAL																		
History and Physical Exam @	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X
Weight and Performance Status	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X
Disease Assessment	X						X		X		X		X		X		X	X
Toxicity Notation			X		X		X	X	X	X	X	X	X	X	X	X	X	
Dental Exam λ	X																X	
LABORATORY																		
CBC/Differential/Platelets §	X		X		X		X	X	X	X	X	X	X	X	X	X	X	
Calcium, phosphate, magnesium, albumin § *	X		X		X		X	X	X	X	X	X	X	X	X	X	X	
Electrolytes (Na^+, K^+, Cl^-, HCO_3^-) §	X		X		X		X	X	X	X	X	X	X	X	X	X	X	
Liver function tests § π	X		X		X		X	X	X	X	X	X	X	X	X	X	X	
Serum Creatinine ◊	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Creatinine clearance (calculated)	X																	
Preganancy test Δ	X																	
X-RAYS AND SCANS																		
Chest X-ray §	X																	
Bone Scan or roentgenological exam £	X†																Xδ	
CT Scan Chest and Abdomen	X†																	
SPECIMENS																		
Tumor block for PTHrP & banking	X																	
Serum for N-telopeptide & banking	X																	
Whole Blood for Pharmacogenomics and Banking β	X																	
TREATMENT																		
Arm 1: Zoledronic Acid Ω		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Arm 2: Clodronate ψ		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Arm 3: Ibandronate α		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

NOTE: Forms are found in Section 18.0. Forms submission guidelines may be found in Section 14.0.

@ Patient height should also be assessed at prestudy.

§ Results of these tests do not determine eligibility but are suggested at prestudy for Good Medical Practice (see Section 7.1). These tests are required during treatment as scheduled to assess toxicity.

* Albumin is needed only if a serum calcium is drawn. It is not needed for an ionized calcium.

π Liver function tests: SGOT or SGPT, Bilirubin, and Alkaline Phosphatase

Ω Arm 1: **Zoledronic Acid** will be administered by IV on Day 1 q monthly for the first 6 months, however minor deviations are acceptable. It is suggested that the infusions be given within ± 2 days. During the remaining period of dosing, zoledronic acid may be given within ± 1 week (7 days earlier or later). NOTE: Monthly dosing of zoledronic acid is given for 6 doses, q 3 monthly dosing is given for 9 doses (see Section 7.3 for definition of monthly).

ψ Arm 2: **Clodronate** will be given PO q day . Discontinue on the first day of Month 36.

α Arm 3: **Ibandronate** will be given PO q day. Discontinue on the first day of Month 36.

£ Bone scan should be done at baseline if the patient has bone pain (see Section 5.10), after 3 years of study drug treatment, or when the patient goes off study if it is prior to 3 years. Patients who have had a bone scan within six months of ending treatment will not be required to have the scan repeated.

β It is strongly recommended that patients already registered to the protocol at the time of Amendment #3 be given the oppportunity to consent to submission of whole blood specimen prior to their next blood draw for routine laboratory testing. The whole blood specimen may be drawn at any time during the patient's clinical care or planned phlebotomy and at any time during study particpation or follow-up. Patients need not be on protocol treatment at the time of this draw.

† CT scan of the chest and abdomen and bone scan are recommended for some patients at prestudy according to Good Medical Practice as outlined in Section 7.1f,g.

ƒ All patients including patients off protocol treatment prior to recurrence should return for disease assessments at least every 6 months for 5 years and then annually for 5 years or until death (whichever occurs first). See Section 7.11 for restaging at recurrence.

λ Dental exam should be performed at the beginning and end of the treatment (regardless of how long the patient was on protocol treatment, see Section 7.10). Complete the Dental Examination Form (Form# 30100). To keep in line with patient's normal dental exam schedule, exams 6 months pre-enrollment and 6 months post-completion of study (or removal from protocol treatment, see Section 7.12) are required.

◊ Arm 1: To be performed within 7 days prior to registration, and within 7 days prior to administering all subsequent doses.
Arm 2/Arm 3: To be performed within 7 days prior to registration and within ± 7 days (7 days earlier or later) of q monthly for Months 2-6 and q 3 month patient visits.

Δ To be performed within 72 hours prior to initiation of treatment.

€ All end of treatment-evaluations occur on Day 1 of Month 36, or up to 14 days after Day 1 of Month 36.

δ Only a bone scan is acceptable at End of Treatment (see Section 7.10)

Revised 6/12/06
Revised 9/25/06
Revised 1/25/07
Amended 6/18/07
Amended 3/11/08
Revised 7/25/08
Revised 7/13/09
Revised 1/21/10
Revised 4/21/11
Revised 10/11/11

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 **Invasive Recurrence:** Appearance of any new invasive lesions during or after protocol treatment. Whenever possible recurrences should be documented histologically. A new diagnosis of ipsilateral or contralateral DCIS without an invasive component is not considered to be a recurrence.

10.2 **Sites of first invasive recurrence:** All sites of invasive disease documented within 30 days of first documentation of invasive recurrence.

10.3 **Disease-Free Survival:** Time from date of registration to date of first observation of recurrence or death due to any cause. Patients last known to be alive who have not experienced recurrence of disease are censored at their last contact date.

10.4 **Overall Survival:** Time from date of registration to date of death due to any cause. Patients last known to be alive are censored at their last contact date.

10.5 **Performance Status**: Patients will be graded according to the Zubrod performance status scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

11.1 At registration, patients will be randomized to receive zoledronic acid (Z), clodronate (C) or ibandronate (I) for three years. Simple randomization will be used with equal allocation to the treatment groups due to the large sample size planned.

11.2 The final target accrual is 5,400 patients distributed as follows: 2,000 zoledronic acid, 2000 clodronate, and 1,400 ibandronate. After the trial began, plans to market ibandronate in North America were abandoned so we have concentrated remaining accrual in the other two arms. Nonetheless, ibandronate remains of interest since it is a highly active oral agent and may provide an effective treatment where IV administration would be difficult. The expected accrual rate currently is 286 per month. The former accrual target was 4,500 patients equally allocated to the three groups with an assumed accrual rate of 63 per month. That accrual goal was established in 2007 under CTEP guidelines for reassessing accrual at one year. Accrual increased dramatically after that reassessment which then shortened the trial duration and lowered power. Consequently, the accrual was increased to 5,400 to restore power to desired levels. The original sample size goal was 6,000 patients over a four year accrual period or 125 per month. The final sample size is 5,400 accrued over an approximate four year period. At the end of the accrual period, there will be an additional 5 years of follow-up before the scheduled final analysis. However, all patients will be followed for 10 years from randomization to assess long-term outcomes.

11.3 The primary outcome is disease-free survival (see Section 10.3). The complete Statistical Analysis Plan may be found in Appendix 19.4 as a separate document. Only a summary is provided here. The primary analysis is a log-rank survival comparison of the three groups followed by three pairwise comparisons if the overall omnibus test is statistically significant at the designated level. The analysis will be stratified by time period of randomization (3 Arms versus 2 Arms) as described in the **S0307** Statistical Analysis Plan (see Appendix 19.4). Each pairwise comparison is performed at the same α level as the overall comparison. Given that the overall comparison is significant, this preserves the experiment-wise error rate at the designated level. (*64*) Since three active treatments are being compared, we assume that clodronate is the "standard" treatment that the newer agents are being compared against. Clodronate and placebo are being directly compared in NSABP trial B-34. A secondary analysis of overall survival (see Section 10.4) will also be performed. Stratified Cox regression will be used to estimate the hazard ratios and confidence intervals for the treatment comparisons, both unadjusted and adjusted for tumor and patient characteristics related to prognosis.

11.4 The sample size targets assumes a cumulative α=0.05 for the omnibus comparison of the three groups. The least effective treatment is assumed to have disease-free survival of 80% at 5 years. The least effective treatment compared to the most effective treatment is assumed to have a hazard ratio of 1.25. The third treatment is varied from 1.00 to 1.25. Power is computed by simulation assuming exponential distributions, 4.17 years of accrual, and an additional 5 years of follow-up. Power of the omnibus test depends on the distribution of the three hazard ratios with power lowest if the middle group is midway between the high and low groups (i.e. HR=1.125). Given a significant omnibus test, pairwise comparisons will be performed..

HR = 1.0, 1.25, 1.25 (zoledronic acid (Z) = ibandronate (I) > clodronate (C))

	Power	Power	Power	Power
	Omnibus	Z vs C	I vs C	Z vs I
Equal allocation (n=1500, 1500, 1500)	86%	78%	78%	NA
Equal allocation (n=1800, 1800, 1800)	91%	86%	86%	NA
Unequal allocation (n=2000, 1400, 2000)	93%	89%	84%	NA

HR = 1.0, 1.0, 1.25 (zoledronic acid > ibandronate = clodronate)

	Power	Power	Power	Power
	Omnibus	Z vs C	I vs C	Z vs I
Equal allocation (n=1500, 1500, 1500)	85%	78%	NA	78%
Equal allocation (n=1800, 1800, 1800)	91%	86%	NA	86%
Unequal allocation (n=2000, 1400, 2000)	92%	89%	NA	84%

HR = 1.0, 1.125, 1.25 (zoledronic acid > ibandronate > clodronate)

	Power	Power	Power	Power
	Omnibus	Z vs C	I vs C	Z vs I
Equal allocation (n=1500, 1500, 1500)	73%	72%	32%	27%
Equal allocation (n=1800, 1800, 1800)	81%	80%	39%	29%
Unequal allocation (n=2000, 1400, 2000)	86%	85%	36%	28%

HR = 1.0, 1.25, 1.125 (ibandronate > zoledronic acid > clodronate)

	Power	Power	Power	Power
	Omnibus	Z vs C	I vs C	Z vs I
Equal allocation (n=1500, 1500, 1500)	74%	33%	72%	25%
Equal allocation (n=1800, 1800, 1800)	81%	39%	80%	30%
Unequal allocation (n=2000, 1400, 2000)	78%	42%	77%	27%

These examples show that omnibus power under unequal allocation ranges from 78% to 93%, but that a comparison of zoledronic acid to clodronate would be enhanced in the unequal allocation scheme. It further demonstrates that restoration to an increased sample size is necessary due to faster than expected accrual than at the time of the previous sample size amendment.

11.5 Under the null hypothesis, a total of 1,314 events would be expected by the end of the trial. We propose to have annual interim analyses beginning when about 31% of the failures have been observed which should occur shortly after the close of accrual. P-values for each analysis are determined using the Lan-DeMets spending function with bounds such that the minimal *p*-value is 0.001. (*65*) The table below shows the expected percentage of events and the *p*-value at each analysis.

If the omnibus analysis is statistically significant at an interim analysis, then pairwise comparisons will be performed using the same alpha level. If one treatment group is clearly superior to the other two, consideration will be given to stopping the trial. If one treatment group is clearly inferior to the other two, consideration will be given to stopping accrual to that arm (if accrual is incomplete) or having patients change to other treatments (if treatment is ongoing). The exact decision will depend on the full information available including adverse events and efficacy. It is also possible that the interim analysis will show that it is unlikely the trial will find a statistically significant difference among the three groups. Conditional power will be conducted at each interim analysis to determine the probability of finding a significant difference at the end of the trial. Additionally, the hazard ratio of the worst treatment versus the best treatment will be computed with a 99% confidence interval. If the upper limit of the confidence interval is lower than the alternative hypothesis of HR=1.25, consideration will be given to stopping the trial due to futility. If it is determined that there are justifiable reasons for early termination, a recommendation will be made to the Data and Safety Monitoring Committee.

Year	Analysis	Percent of Events (n=1,314)	Alpha Level for Test	Cumulative probability
4	Interim 1	31%	0.0010	0.0010
5	Interim 2	46%	0.0012	0.0022
6	Interim 3	60%	0.0068	0.0077
7	Interim 4	74%	.0158	0.0158
8	Interim 5	87%	.0265	0.0265
9	Final	100%	.0391	0.0500

11.6 A sample of 2,000 patients on an arm is sufficient to estimate the probability of specific toxicities to within at least $\pm$ 0.022. A difference in toxicities of 0.05 between two arms can be detected with 90% power (2-sided α=0.05) if the mean prevalence of the adverse event is 20%.

11.7 Percent of patients with bone as a site of first recurrence will be compared. Approximately 4% of all randomized patients are expected to have bone as the site of first recurrence. Bone is the site of first metastases in 40% of the patients who become metastatic. If two-thirds of the patients have measured markers (e.g. PTHrP, serum N-teleopeptide levels) and the markers are dichotomized at the median, then a difference of 0.024 (0.052 vs. 0.028) in bone recurrence rates in all patients could be detected with 90% power (2-sided α=0.05).

11.8 A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the Southwest Oncology Group, three Southwest Oncology Group members, three non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every six months from the Southwest Oncology Group Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study

12.0 DISCIPLINE REVIEW

There will be no discipline review for this study.

13.0 REGISTRATION GUIDELINES

13.1 Patients must be registered prior to initiation of treatment (no more than five working days prior to planned start of treatment).

13.2 For either phone or web registration, the individual registering the patient must have completed the appropriate Southwest Oncology Group Registration Form. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The individual registering the patient must also be prepared to provide the treating institution's name and ID number in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base. Patients will not be registered if the IRB approval date has not been provided or is > 365 days prior to the date of registration.

13.3 Registration procedures

a. You may register patients from Member, CCOP and approved Affiliate institutions to a therapeutics study using the SWOG Registration program. To access the Registration program go to the SWOG Web site (http://swog.org) and click on the *Logon* link to go to the SWOG Members Area logon page (https://swog.org/visitors/logon.asp). This Web program is available at any time except for periods listed **under *Down Times*.** Log on as an Individual User using your SWOG Roster ID Number and individual web user password. Help for the logon process may be found at https://swog.org/visitors/logonhelp.asp. After you have logged on, click on the *Clinical Trials* link and then the *Patient Reg* link to go to the Entry Page for the Patient Registration program. If you are a Registrar at an institution with Internet access you are encouraged to register this way. For new users, the link to a "Starter Kit" of help files may be found by clicking on **Starter Kit link at the logon page.**

To register a patient the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN to the institution where a registration is occurring, and

3. You are granted permission to use the Patient Registration program at that institution.

For assistance with points 1 and 2 call the SWOG Operations Office at 210/614-8808. For point 3 you must contact your Web User Administrator. Each SWOG institution has one or more Web User Administrators who may set up Web Users at their institution and assign permissions and passwords to these users. For other password problems or problems with the Patient Registration program, please e-mail webreghelp@crab.org. Include your name, Roster ID Number, and telephone number, when the problem occurred, and exactly what you were doing.

b. If the Web Reg program is not used, the registration must be done by phone.

Member, Affiliate and CCOP Institutions

Registration by phone of patients from member, affiliate and CCOP institutions must be done through the Southwest Oncology Group Data Operations Center in Seattle by telephoning 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.

13.4 For either method of registration, exceptions to Southwest Oncology Group registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

13.5 Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to Appendix 19.1.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master forms are included in Section 18.0 and (with the exception of the sample consent form and the Registration Form) must be submitted to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see Section 14.3a for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).

14.3 Data Submission Procedures.

a. Southwest Oncology Group institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email *technicalquestion@crab.org*.

b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data. Please make sure that each page of all faxed data includes the SWOG patient number, study ID, and patient initials.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to Appendix 19.1.

14.4 WITHIN 14 DAYS OF REGISTRATION:

Submit copies of the following:

a. **S0307** Prestudy Form (Form #20161)

b. All pre-registration breast cancer pathology reports.

c. Dental Examination Form (Form #30100)

14.5 DURING TREATMENT AT 6 MONTHS, 1 YEAR, 2 YEARS, AND 3 YEARS:

Submit copies of the following:

a. **S0307** Treatment Summary Form (Form #31453)

b. **S0307** Adverse Event Summary Form (Form #22831)

c. **S0307** Serum Creatinine Reporting Form (Form #60188)

14.6 WITHIN 6 MONTHS OF DISCONTINUATION OF PROTOCOL TREATMENT:

Submit the Dental Examination Form (Form #30100).

14.7 WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit copies of the following:

a. Off Treatment Notice (Form #8756)

b. **S0307** Supplementary Off Treatment Form (Form #24801)

c. Final **S0307** Treatment Form (Form #31453) for current reporting period

d. Final **S0307** Adverse Event Summary Form (Form #22831)

e. **S0307** Serum Creatinine Reporting Form (Form #60188)

14.8 AFTER OFF TREATMENT- EVERY 6 MONTHS UNTIL YEAR 5, AND THEN ANNUALLY UNTIL YEAR 10 OR UNTIL DEATH, WHICHEVER COMES FIRST:

Submit the Follow-Up Form (Form #64587) and **S0307** Supplementary Follow-Up Form (Form #36846).

14.9 WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit the following:

a. Follow-up Form (Form #64587) documenting date, site and method for determining malignancy

b. **S0307** Supplementary Follow-Up Form (Form #36846)

c. If patient was still on treatment, final **S0307** Treatment Form (Form #31453) for current reporting period

d. If patient was still on treatment, final **S0307** Adverse Event Summary Form (Form #22831)

14.10 WITHIN 4 WEEKS OF KNOWLEDGE OF SECOND MALIGNANCY:

Submit the Follow-Up Form (Form #64587) documenting date, site and method of determining malignancy.

14.11 WITHIN 4 WEEKS OF KNOWLEDGE OF OSTEONECROSIS OF THE JAW:

Submit the Osteonecrotic Jaw Lesion Form (Form #52641) (see Section 8.4).

14.12 WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death (Form #49467) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Institutions are encouraged to seek patient consent to submit tissue, whole blood and serum for banking (see Sections 15.3 and 15.4).

15.2 General specimen submission instructions

a. All submitted specimens must be labeled with the protocol number (**S0307)**, SWOG patient number, patient's initials, and date of specimen collection.

b. **The federal guidelines for shipment are as follows**:

1. The specimen must be wrapped in an absorbable material.

2. The specimen must be placed in an AIRTIGHT container (like a resealable bag.)

3. Pack the resealable bag and specimen in a Styrofoam shipping container.

4. Pack the Styrofoam shipping container in a cardboard box.

5. The cardboard box must be labeled as "BIOHAZARD".

c. Specimen Tracking System

All specimen submissions for this protocol must be entered and tracked using the Southwest Oncology Group online Specimen tracking system. Southwest Oncology Group Members may log on to the specimen tracking system via the CRA Workbench (https://gill.crab.org/txwb/logon.aspx) using their Southwest Oncology Group roster identification numbers and passwords. First-time non-Southwest Oncology Group users must refer to start-up instructions located at https://gill.crab.org/SpecTrack/.

In the online Specimen Tracking system laboratory ID numbers are used to identify the laboratories to which specimens are shipped. The laboratory numbers for specimen submission on this study are listed in Sections 15.3e and 15.4d.3.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://gill.crab.org/SpecTrack/Documents/Instructions.pdf); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

15.3 Tissue Bank Submission Instructions

a. **Institutions are encouraged to seek additional patient consent to submit tissue for banking.** The Southwest Oncology Group plans to collect one block of fixed tissue for the purpose of investigating PTHrP and other markers of preferential bone metastasis in the future.

b. For medical/legal reasons, the blocks will remain at the tissue repository while slides may be cut from them to send to labs doing approved research. The blocks will only leave the tissue repository at the request of the originating institution; blocks are guaranteed to be returned within 48 hours of a written request. Materials to be submitted are as follows:

1. One block of the primary tumor should be submitted.

2. If the institution is not able to release the block, a punch of the block plus 25 unstained 5 micron sections on plus slides would be acceptable. The bank will send a disposable punch instrument at the request of the submitting institution.

3. At minimum, if no other tissues are available for submission, the tissue bank will accept 25 unstained 5 micron sections of the tumor block on plus slides.

c. A copy of the shipment packing list produced by the Specimen Tracking System should be printed and sent with the blocks in a separate resealable bag. A copy of the surgical pathology report should also be sent.

d. If shipping slides, wait 24 hours prior to shipping. Label all slides with protocol number (**S0307**), patient number, and date sectioned. Place in slide mailer and send overnight to the address below.

e. Tissue specimens should be submitted in a crush-proof mailing container (e.g. Styrofoam box or mailing tube). Please ship tissue blocks on cold packs to prevent heat damage in warm climates. Ship tissue samples (Monday through Thursday only) by overnight delivery to:

SpecTrack Lab #78: **SWOG Solid Tumor Tissue Bank**
University of Colorado HSC at Fitzsimons
Department of Pathology
RC-1 South, Room L18-5400A
12801 East 17th Avenue
Aurora, CO 80045

Contact: Miguel Martinez
Phone: 303/724-3086
E-mail: miguel.martinez@uchsc.edu

15.4 Instructions for submission of serum and whole blood for banking

a. **Institutions are encouraged to seek additional patient consent to submit serum and whole blood for banking**. The Southwest Oncology Group plans to collect, process, and store baseline serum samples for analysis of circulating bone turnover-related proteins and for future studies such as proteomics as the technology advances; and to collect, process and store whole blood for pharmacogenomics.

b. Blood collection: Obtain a 10 mL serum sample (red-top tube, Vacutainer®) at prestudy (prior to initiation of treatment).

Whole blood collection: Obtain a 10 mL whole blood sample (EDTA, lavender top Vacutainer®) obtained at any single timepoint when blood is otherwise being drawn for laboratory assessments.

c. Procedures:

1. Prepare participant's paper work to include SWOG STUDY NUMBER (**S0307**), participant ID number, visit number, collection date and time, and initials of the phlebotomist.
2. Prepare collection material and make sure the ID of the participant to be drawn matches the demographics on the requisition of the draw.
3. Seat the participant for at least five minutes prior to blood collection.
4. Collect sample preferably under fasting conditions.
5. Using the appropriate Vacutainer® blood collection tube (plastic vacutainer tubes preferred) and a double-ended Vacutainer® needle, draw blood. Place the tube in a rack at room temperature for at least one hour and not more than two hours. See **Table 1** for basic guide on frequently requested samples.
6. Label specimen with SWOG STUDY NUMBER (**S0307**), visit number, collection date and time, initials of the phlebotomist, participant study ID number, and treatment cycle number.

Reference

1. CAP. So you are going to collect a blood specimen. An Introduction to Phlebotomy, 6th Ed., 1994
2. Ernst, DJ, Calan, R. NCCLS simplifies order of draw: a brief history, MLO, 2004
3. Chance, J. Blood testing, Choosing the right specimen, Clinical Laboratory News, AACC 2001, vol 27, No. 7

Table 1

Type of Specimen	Vacutainer® Collection Tube	Anticoagulant	Mix	USE
Serum	Red Top or Serum Separator Tube (SST)	None	Do not mix	Biomarkers
Whole Blood	Lavender Top	EDTA	Mix (by gentle inversion)	Cells Nucleic acid

Fill the red top tube (serum) prior to the EDTA tube (whole blood). If drawn by syringe, fill applicable tubes with anticoagulant first.

NOTES TO AVOID HEMOLYSIS:

Do not use small-bore needles.
Invert filled tubes gently.
Do not keep tourniquet on too long.
Allow the cleaned venipuncture site to dry completely before skin puncture.
Do not expose to extreme heat or cold.
Do not draw blood from a difficult site such has a hematoma or IV line.

d. Shipping Instructions:

1. Sample should be shipped within 24 hours of collection. Sample can be stored at 4^{o}C until ready for shipment. Be sure tube is closed securely.

2. Place specimen in a sealed biohazard bag and include absorbent material.

3. Ship sample with an ice pack and the specimen collection form overnight in an appropriate shipping container (Monday through Thursday only. **Do not collect sample on Friday or day before a holiday**). Ship sample to:

SpecTrack Lab #78: **SWOG Solid Tumor Tissue Bank**
University of Colorado HSC at Fitzsimons
Department of Pathology
RC-1 South, Room L18-5400A
12801 East 17th Avenue
Aurora, CO 80045

Contact: Miguel Martinez
Phone: 303/724-3086
E-mail: miguel.martinez@ucdenver.edu

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 19.2 for general and background information about expedited reporting.

b. Reporting methods

This study requires that expedited adverse event reporting use the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the Southwest Oncology Group Operations Office electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events may require 24-hour notification (refer to Tables 16.1 and 16.2) via CTEP-AERS.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the events as specified in Table 16.1 or 16.2, as applicable.

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable must also be reported according to local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

e. **Expedited reporting for <u>investigational</u> agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agents used in this study are **<u>clodronate and ibandronate</u>**. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND or Non-CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days[1,3] of the Last Dose of the Investigational Agents Clodronate and Ibandronate in this Study (Arm 2 and Arm 3, respectively).

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND or Non-CTEP IND require reporting as follows:**

CTEP-AERS 24-hour notification (**via CTEP-AERS for CTEP IND agents; via email to *adr@swog.org* for agents in non-CTEP IND studies**) followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although a CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

[3] **Protocol-specific reporting requirements:** The adverse events listed below also require expedited reporting for this trial:

- *Osteonecrosis of the jaw (regardless of grade, attribution or expectedness)*

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within <u>24 hours</u> of learning of the event followed by a complete CTEP-AERS report within <u>5 calendar days</u> of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within <u>10 calendar days</u> of the investigator learning of the event.
- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND:**

1) **Group-specific instructions.**

Within **10 calendar days (5 calendar days if 24-hour reporting was required)**, submit the following to the Operations Office by fax to 210-614-0006 or mail to the address below:

- Printed copy of the first page of the CTEP-AERS report
- Copies of clinical source documentation of the event
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

g. **Expedited reporting for <u>commercial</u> agents**

Commercial reporting requirements are provided in Table 16.2. The commercial agent used in this study is **<u>zoledronic acid</u>**. If there is any question about the reportability of an adverse event, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced by patients who have received zoledronic acid on this study.

Attribution	**Grade 4**		**Grade 5[a]**		***(Option)* Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**	***See footnote (b,c) for special requirements***
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**	

CTEP-AERS: Indicates an expedited report is to be submitted using the CTEP-AERS Commercial Drug pathway within 7 working days of learning of the event[b].

24-Hr Report: Indicates a report must be sent to [desired recipient of the report] and [method of reporting, e.g., phone or fax].

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent by fax to 210-614-0006.

[c] **Protocol-specific expedited reporting requirements:** The adverse events listed below also require expedited reporting for this trial: *Osteonecrosis of the jaw (regardless of grade, attribution or expectedness)*

[d] ***Any Group-specific instructions.*** The SWOG Operations Office will notify Novartis as required.

h. **Reporting secondary AML/ALL/MDS**

1. All cases of acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following chemotherapy for cancer must be reported in CTEP-AERS.

   i. In protocols using CTCAE Version 4.0 for SAE reporting, three options are available to describe treatment-related events:

   - Leukemia secondary to oncology chemotherapy
   - Myelodysplastic syndrome. NOTE: The only grading option for "Myelodysplastic syndrome" is Grade 4, life-threatening. If reporting MDS that is other than Grade 4, use “Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, (specify,__)” and insert MDS as the specify term.
   - Treatment related secondary malignancy

   ii. In protocols using CTCAE Version 3.0 for SAE reporting, the event(s) can be reported as “Secondary malignancy-Other (specify, ___)”. Report MDS as “Myelodysplasia,” in the BLOOD/BONE MARROW category.

   iii. Secondary malignancies other than AML/ALL/MDS that are related to protocol treatment must also be reported in CTEP-AERS.

   iv. Non-treatment related cases of AML/ALL/MDS must be reported as follows:

   In protocols using CTCAE Version 4.0 for SAE reporting, report as “Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify”

   In protocols using CTCAE Version 3.0 for SAE reporting, report MDS as “Myelodysplasia” and Leukemias as “Blood/Bone Marrow - Other (Specify, __)”

   For more information see:
   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

2. The following supporting documentation must also be submitted within 30 days:

   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   Submit the Report and documentation to:

   Investigational Drug Branch **and** Southwest Oncology Group
   by fax at 301-230-0159 ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, Texas 78229

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

17.0 BIBLIOGRAPHY

1. Rubens R, Coleman R. Bone metastases. In Clinical Oncology (Abeloff et al, eds), Churchill Livingston Inc. New York 643-665, 1995.

2. Coleman RC, Rubens RD. The clinical course of bone metastases from breast cancer. Br J Cancer 55:61-66, 1987.

3. Mundy GR. Bone resorption and turnover in health and disease. Bone 8:S9-S16, 1987.

4. Lipton A, Theriault RL, Hortobagyi GN, et al. Pamidronate prevents skeletal complications and is effective treatment in women with breast carcinoma and osteolytic bone metastases. Cancer 88:1082-1090, 2000.

5. Paterson AHG, Powles TJ, Kanis JA, et al. Double-blind controlled trial of oral clodronate in patients with bone metastases from breast cancer. J Clin Oncol 11:59-65, 1993.

6. van Holten-Verzantvort ATM, Kroon HM, Bijvoet OLM, et al. Palliative pamidronate treatment in patients with bone metastases from breast cancer. J Clin Oncol 11:491-498, 1993.

7. Body JJ, Lichinitser I, Diehl K, et al. Double-blind placebo-controlled trial of intravenous ibandronate in breast cancer metastatic to bone. Proc Am Soc Clin Oncol 19:abstract 2222, 1999.

8. Body JJ, Diel IJ, Lichinitser MR, et al. Intravenous ibandronate reduces the incidence of skeletal complications in patients with breast cancer and bone metastases. Ann Oncol 12:1399-1405, 2003.

9. Body JJ, Diel IJ, Lichinitzer M, et al. Oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomized, placebo-controlled phase III studies. Br J Cancer 90:1133-1137, 2004.

10. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol 19:558-567, 2001.

11. Rosen LS, Gordon D, Kaminski M, et al. Zoledronic Acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: a phase III, double-blind, comparative trial. Cancer J 7:377-387, 2001.

12. Rosen LS, Gordon D, Kaminski M, et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma and breast cancer: a randomized, double-blind, multicenter comparative trial. Cancer 98:1735-1744, 2003.

13. Diel IJ, Solomayer EF, Costa SD, et al. Reduction in metastases in breast cancer with adjuvant clodronate treatment. N Eng J Med 339:357-363, 1998.

14. Diel IJ, Solomayer EF, Gollan C. Bisphosphonates in the reduction of metastases in breast cancer – Extended follow-up results. Proc Am Soc Clin Oncol abstract 314, 2000.

15. Saarto T, Blomqvist C, Virkkunen P, et al. Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomized controlled trial. J Clin Oncol 19(1):10-17, 2001.

16. Powles T, Paterson S, Kanis J, et al. Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. JCO 20:3219 – 24, 2002.

17. Prestwood KM, Raisz LG. Prevention and treatment of osteoporosis. Clin Cornerstone 4:31-41, 2002.

18. Jaschke A, Bastert G, Solomayer EF, et al. Adjuvant clodronate treatment improves the overall survival of primary breast cancer patients with micrometastases to bone marrow -a longtime follow-up. Proc Am Soc Clin Oncol abstract 529, 2004.

19. Powles T, McCloskey E, Kurkilahti M. Oral clodronate for adjuvant treatment of operable breast cancer: Results of a randomized, double-blind, placebo-controlled multicenter trial. Proc Am Soc Clin Oncol abstract 528, 2004.

20. Saarto T, Vehmanen L, Blomqvist C, et al. Ten-year follow-up for a randomized controlled trial of adjuvant clodoronate treatment in node-positive breast cancer patients. Proc Am Soc Clin Oncol abstract 527, 2004.

21. Atula S, Powles T, Paterson S, et al. Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. J Clin Oncol 20(15):3219-3224, 2002.

22. Tripathy D, Lichinitzer M, Lazarev A, et al. Oral ibandronate for the treatment of metastatic bone disease in breast cancer: efficacy and safety results from a randomized, double-blind, placebo-controlled trial. Ann Oncol 15(5):743-750, 2004.

23. Hodgson SF, Watts NB, Bilezikian JP, et al. American Association of Clinical Endocrinologists 2001 Medical Guidelines for Clinical Practice for the Prevention and Management of Postmenopausal Osteoporosis. Endocr Pract 7:293-312, 2001.

24. Ott K. Osteoporosis and bone densitometry. Radiol Technol 70:129-148, 1998.

25. Mashiba T, Turner CH, Hirano T, et al. Effects of suppressed bone turnover by bisphosphonates on microdamage accumulation and biomechanical properties in clinically relevant skeletal sites in beagles. Bone 28:524-531, 2001.

26. Whyte MP, Wenkert D, Clements KL, et al. Bisphosphonate-induced osteopetrosis. NEJM 349:457-463, 2003

27. Marini JC. Do bisphosphonates make children's bones brittle? NEJM 349:423-426, 2003.

28. Janssen van Doorn K, Neyns B, Van der Niepen P, et al. Pamidronate-related nephrotoxicity (tubulointerstitial nephritis) in a patient with osteolytic bone metastases. Nephron 89:467-468, 2001.

29. Markowitz GS, Appel GB, Fine PL, et al. Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. J Am Soc Nephrol 12:1164-1172, 2001.

30. Desikan R, Veksler Y, Raza S, et al. Nephrotic proteinuria associated with high-dose pamidronate in multiple myeloma. Br J Hematology 119:496-499, 2002.

31. Hillner B, Ingle J, Chlebowski R, Gralow J, et al. American Society of Clinical Oncology 2003 update on the role of bisphophonates and bone health issues in women with breast cancer. J Clin Oncol 21: 4042-57, 2003.

32. Marx RE. Pamidronate and zoledronate induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillo Surg 61:1115-1117, 2003.

33. Migliorati CA. Bisphosphonates and oral cavity avascular bone necrosis. J Clin Oncol 21:4253-4254, 2003.

34. Jakobisiak M., Golab J. Potential antitumor effects of statins. Int J Oncol 23:1055-1069, 2003.

35. Assmus B, Schachinger V, Teupe C, et al. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction (TOPCARE-AMI). Circulation 106:3009-3017, 2002.

36. Denoyelle C, Vasse M, Korner M, et al. Cerivastatin, an inhibitor of HMG-CoA reductase, inhibits the signaling pathways involved in the invasiveness and metastatic properties of highly invasive breast cancer cell lines: an in vitro study. Carcinogenesis 22:1139-1148, 2001.

37. Eto M, Kozai T, Cosentino F, et al. Statin prevents tissue factor expression in human endothelial cells: role of Rho/Rho-kinase and Akt pathways. Circulation 105:1756-1759, 2002.

38. Klein P, Glaser E, Grogan L, et al. Biomarker assays in nipple aspirate fluid. Breast J 7:378-387, 2001.

39. Park HJ, Kong D, Iruela-Arispe L, et al. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors interfere with angiogenesis by inhibiting the geranylgeranylation of RhoA. Circ Res 91:143-150, 2002.

40. Vincent L, Chen W, Hong L, et al. Inhibition of endothelial cell migration by cerivastatin, an HMG-CoA reductase inhibitor: contribution to its anti-angiogenic effect. FEBS Lett 495:159-166, 2001.

41. Bell RM, Yellon DM. Atorvastatin, administered at the onset of reperfusion, and independent of lipid lowering, protects the myocardium by up-regulating a pro-survival pathway. J Am Coll Cardiol 41:508-515, 2003.

42. Wilson SH, Herrmann J, Lerman LO, et al. Simvastatin preserves the structure of coronary adventitial vasa vasorum in experimental hypercholesterolemia independent of lipid lowering. Circulation 105:415-418, 2002.

43. Danesh FR, Sadeghi MM, Amro N, et al. 3-Hydroxy-3-methylglutaryl CoA reductase inhibitors prevent high glucose-induced proliferation of mesangial cells via modulation of Rho GTPase/ p21 signaling pathway: Implications for diabetic nephropathy. Proc Natl Acad Sci 99:8301-8305, 2002.

44. Umekita Y, Ohi Y, Sagara Y, et al. Expression of maspin predicts poor prognosis in breast-cancer patients. Int J Cancer 452-455, 2002.

45. Urbich C, Dernbach E, Zeiher AM, et al. Double-edged role of statins in angiogenesis signaling. Circ Res 90:737-44, 2002.

46. Fenton JW, Jeske WP, Catalfamo JL, e al. Statin drugs and dietary isoprenoids downregulate protein prenylation in signal transduction and are antithrombotic and prothrombolytic agents. Biochemistry 67:85-91, 2002.

47. Graaf MR, Beiderbeck AB, Egberts ACG, et al. The risk of cancer in users of statins. Proc Am Soc Clin Oncol, 2003

48. Mortimer JE, Axelrod, R and Zimbro K. Effect of statins on breast cancer incidence; Findings from the Sentara Health Plan. Proc Am Soc Clin Oncol 2003.

49. Stein EA, Farnier M, Waldstreicher J, et al. Effects of statins on biomarkers of bone metabolism: a randomised trial. Nutr Metab Cardiovasc Dis 11:84-7, 2001.

50. Chan KK, Oza AM, Siu LL. The statins as anticancer agents. Clin Cancer Res 9:10-9, 2003.

51. Walker RA, Jones JL, Chappell S, et al. Molecular pathology of breast cancer and its application to clinical management. Cancer & Metastasis Reviews 16(1-2): 5-27, 1997.

52. Powell GJ, Southby J, Danks JA. Localization of parathyroid hormone-related protein in breast cancers increased incidence in bone compared with other sites. Cancer Res 51, 3059-3061, 1991.

53. Rivkin SE, Gown A, Tickman R. Parathyroid-related Protein (PTHrP) expression in breast cancer patients and its relationship to subsequent bone metastasis. Proc Am Soc Clin Oncol 17:abs 656, 1998.

54. Kohno N, Kitazawa S, Fukase M, et al. The expression of parathyroid hormone-related protein in human breast cancer with skeletal metastases. Surgery Today 24(3): 215-220, 1994.

55. Bundred NJ, Walls J, Ratcliffe WA. Parathyroid hormone-related protein, bone metastases and hypercalcaemia of malignancy. Ann Roy Coll Surg of Eng 78(4):354-358, 1996.

56. Bouizar Z, Spyratos F, Deytieux S, de Vernejoul MC, Jullienne A. Polymerase chain reaction analysis of parathyroid hormone-related protein gene expression in breast cancer patients and occurrence of bone metastases. Cancer Res 53(21):5076-5078, 1993.

57. Downey SE, Hoyland J, Freemont AJ, et al. Expression of the receptor for parathyroid hormone-related protein in normal and malignant breast tissue. J Path 183(2):212-217, 1997.

58. Carron JA, Fraser WD, Gallagher JA. PTHrP and the PTH/PTHrP receptor are co-expressed in human breast and colon tumours. Br J Cancer 78(8):1095-1098, 1997.

59. Orr FW, Varani J, Gondetz MD, et al. Chemotactic responses of tumor cells to products of resorbing bone. Science 203:176-179, 1979.

60. Hauschka PV, ChenTL, Mavrakos AE. Polypeptide growth factors in bone matrix. Ciba Found Symp 136:207-225, 1988.

61. van der Pluijm G, Lowik C, Papapoulos S, et al. Tumor progression and angiogenesis in bone metastases from breast cancer: New approaches to an old problem. Cancer Treat Rev 26:11-27, 2000.

62. Demers LM, Costa L, Lipton A. Biochemical Markers and Skeletal Metastases. Cancer Supplement 88(12); 2919-2926, 2000.

63. Coleman R, Thorpe H, Cameron D, et al. Zoledronic acid is well tolerated and can be safely administered with adjuvant chemotherapy-first safety data from the AZURE trial (BIG 01/04). Br Cancer Res Treat 100, Abstract 2080, 2006.

64. Liu PY, Dahlberg S. Design and analysis of multiarm clinical trials with survival endpoints. Control Clin Trials, 16:119-130, 1995.

65. Lan KG, DeMets DL. Discrete sequential boundaries for clinical trial. Biometrika, 70:659-663, 1983.

66. Gnant M, Mlineritsch B, Schippinger W, et al. Adjuvant ovarian suppression combined with tamoxifen or anastrozole, alone or in combination with zoledronic acid, in premenopausal women with endocrine-responsive, stage I and II breast cancer: First efficacy results from ABCSG-12. Proc Am Soc Clin Oncol, 26:1006S (Abstract# LBA4), 2008.

67. Brufsky A, Bundred N, Coleman R, et al. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. Oncologist, 13:503-514, 2008.

18.0 MASTER FORMS SET

18.1 The Model Informed Consent Form is included in this section, preceded by "Notes for Local Institution Consent Form Authors" and "Notes for Local Investigators." The study - as well as the local consent form meeting the guidelines noted in these documents - must be reviewed and approved by the Institutional Review Board prior to registration and treatment of patients on this study.

18.2 This section includes copies of all data forms which must be completed for this study. These include:

a. **S0307** Registration Form (Form #46563) and Southwest Oncology Group Registration Form Code Sheet (10/24/06)

b. **S0307** Prestudy Form (Form #20161) (8/15/06)

c. **S0307** Treatment Summary Form (Form #31453) (8/15/06)

d. **S0307** Adverse Event Summary Form (Form #22831)

e. Follow-Up Form (Form #64587) (9/15/03)

f. **S0307** Supplementary Follow-Up Form (Form #36846) (6/1/08)

g. Off Treatment Notice (Form #8756) (9/1/03)

h. **S0307** Supplementary Off Treatment Form (Form #24801) (11/15/05)

i. Notice of Death (Form #49467) (9/1/03)

j. Dental Examination Form (Form #30100) (11/15/05)

k. Osteonecrotic Jaw Lesion Form (Form #52641) (10/15/04)

l. **S0307** Serum Creatinine Reporting Form (Form #60188) (6/1/08)

Informed Consent Model for S0307

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the Southwest Oncology Group Operations Office.

Readability Statistics:	*(Statistics updated 6/18/07)*
Flesch Reading Ease	57.6 (targeted above 55)
Flesch-Kincaid Grade Level	9.3 (targeted below 8.5)

- Instructions and examples for informed consent authors are in [italics].
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and the Southwest Oncology Group.

The "Southwest Oncology Group" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to the Southwest Oncology Group. This includes consent forms for studies where all patients are registered directly through the Southwest Oncology Group Data Operations Office, all intergroup studies for which the registration is being credited to the Southwest Oncology Group (whether

the registration is through the SWOG Data Operations Office or directly through the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to the Southwest Oncology Group. *(format change 6/12/06)*

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at http://cissecure.nci.nih.gov/ncipubs/details.asp?pid=1035 or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

S0307, "Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer"

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have Stage I, II, or III breast cancer that is currently in remission.

Why is this study being done?

This study is investigational and is being done to find out if adding a drug (a bisphosphonate) to hormonal therapy or chemotherapy will help prevent cancer from spreading to the bones or other parts of the body. "Bisphosphonates" are a group of drugs that have strong effects on the bones and have been shown to strengthen the bones in many patients who take them.

How many people will take part in the study?

About 5,400 women will take part in this study. *(6/18/07)(7/13/09)*

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical History and Physical Exam
- Weight and Performance Status
- Disease Assessment
- Routine laboratory tests: including a serum creatinine blood test (to measure kidney function) will be performed within 7 days prior to starting study
- CT and bone scans (as needed for disease assessment): a series of detailed pictures of areas inside the body from different angles; the pictures are created by a computer linked to an x-ray machine
- Dental examination: to be performed within 6 months prior to registration.
- Women of child-bearing potential must have a pregnancy test performed within 72 hours prior to initiation of treatment. *(6/18/07) (3/11/08)*

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Medical History and Physical Exam
- Weight and Performance Status
- Disease Assessment
- Routine laboratory tests (to measure your liver and kidney function): You will need to have your kidney function tested every month for the first 6 months, and then once every 3 months while on treatment. *(6/12/06)*
- CT and bone scans (as needed for disease assessment); and at the end of treatment: series of detailed pictures of areas inside the body from different angles; the pictures are created by a computer linked to an x-ray machine
- Dental examination (at the end of treatment): It is important to undergo routine dental exam and care while on the study. Be sure to discuss with your study doctor before having dental procedures while on chemotherapy.

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body. A sample of your tumor tissue and your blood will be requested for current and further scientific studies. At the end of this form you can indicate your preferences related to the use of these samples.

- Tumor block for PTHrP testing and banking: a sample of your tumor from the original biopsy will be removed and analyzed for parathyroid hormone related protein (PTHrP) to see if this predicts the risk of your breast cancer spreading to the bones. *(7/25/08)* If you consent, any remaining sample will be stored frozen for future scientific studies.
- Serum for N-telopeptide testing and banking: an additional blood sample (approximately 10 mL or 2-3 teaspoons) will be collected at prestudy and analyzed for the substance n-telopeptide to see if high levels will predict if breast cancer will spread to the bones. If you consent, any remaining sample will be stored frozen for future scientific studies.
- Whole blood for genetic studies related to the development of side-effects to the kinds of drugs used on this study. An additional blood sample (approximately 10 mL or 2-3 teaspoons) will be collected. With your additional agreement, any remaining sample will be stored for future scientific studies. *(added 7/13/09)*

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance to be put in any treatment group that has not yet reached its goal. *(sentence updated 7/13/09)* Group 3 (ibandronate) is limited to 1,400 patients while Groups 1 (zoledronic acid) and 2 (clodronate) will recruit 2,000 patients, each. *(sentence added 7/13/09)*

If you are in Group 1 (often called "Arm 1") you will be given 4 mg (or less based on how your kidneys are working) of **zoledronic acid** through a needle in your vein every month for the first six months and then once every three months after that for thirty months. *(7/25/08)*

If you are in Group 2 (often called "Arm 2") you will take 1,600 mg of **clodronate** by mouth once a day, every day for thirty-six months.

If you are in Group 3 (often called "Arm 3") you will take **ibandronate** once a day, every day for thirty-six months.

If you are assigned to either Group 2 or 3, it is strongly encouraged that you record the number of pills you take each day on a calendar. During visits with your study doctor (at Months 6, 12, 24, and 36) you will be asked how many pills were missed during the last month of protocol treatment. This will be done in order to determine if you are having any problems taking the drug and to confirm you are taking it as directed. *(paragraph added 6/12/06)*

Study Chart

The chart below shows what will happen to you during this study, as explained previously. The left-hand column shows the weeks in the study, and the right-hand column tells you what to do during that week.

Day	What you do
Within 6 months before starting study	• Get routine dental examination.
Within 28 days before starting study	• Get routine blood tests. • Get chest x-ray; chest CT and bone scans (as needed for disease assessment). • Get medical history, physical examination, and performance status. • Tissue from the original tumor biopsy will be submitted for research studies (if consent is established). *(6/12/06)*
Within 7 days prior to starting study *(6/12/06) (1/25/07)*	• Get kidney function test. *(6/12/06, 1/25/07)*
Within 72 hours prior to starting study *(6/18/07) (3/11/08)*	• If you are a woman of child-bearing potential, you will need to have a pregnancy test.
Day 1 of Month 1 *(6/12/06)*	• If using Zoledronic acid, you will receive an IV infusion at your clinical site. • If using Clodronate, begin taking until the end of study, unless told to stop by your health care team. • If using Ibandronate, begin taking until the end of study, unless told to stop by your health care team.
Day 1 of Months 2-6 and Months 9, 12, 15, 18, 21, 24, 27, 30, 33 and 36 *(6/12/06) (9/25/06)*	• Get kidney function test. *(1/25/07)*
Day 1 of Months 2, 4, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36 *(6/12/06)*	• Get routine blood tests (including kidney function test). *(1/25/07)* • Return to your doctor's office at _____ (insert appointment time) for your next physical examination. *(6/12/06, 9/25/06, 1/25/07)*

Day	**What you do** (contd.)
Within 14 days of end of treatment	• Return to your doctor's office at _____ (insert appointment time) for your next physical examination • Get bone scan.
Within 6 months after completing study or ending the study early *(6/18/07)*	• Get routine dental examination.
After completing study, every 6 months for 5 years, then annually until year 10 or until death *(6/12/06)*	• Return to your doctor's office at _____ (insert appointment time) for your next physical examination

Study Plan

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.

Randomization *(section revised 6/12/06)*

Arm 1	Arm 2	Arm 3
Zoledronic acid (IV) monthly for 6 months, then once every 3 months for 2.5 years	Clodronate daily (by mouth) for 3 years	Ibandronate daily (by mouth) for 3 years

When you are finished taking study drugs…

You will need to see your study doctor for a physical examination and bone scan. Additionally, you will need to have a dental examination within 6 months of completing treatment or being removed from treatment. *(3/11/08)*

How long will I be in the study?

You will be asked to take bisphosphonates for 3 years. After you are finished taking bisphosphonates, the study doctor will ask you to visit the office for follow-up exams every year for a length of ten years from the time you entered the study. *(1/21/10)* The follow-up evaluation tests that are standard to cancer care will include a medical history, physical examination, and performance status.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the zoledronic acid, clodronate, or ibandronate can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the zoledronic acid, clodronate, or ibandronate. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the zoledronic acid include the following:

Likely

- **Fever**
- **Nausea**
- **Constipation**
- **Shortness of breath**
- **Low red blood cell counts which may cause fatigue or pale appearance**
- **Loss of appetite**
- **Muscle or bone pain**
- **Fatigue or tiredness** *(added 4/21/11) (moved from Less Likely 10/11/11)*

Less Likely

- **Vomiting**
- **Diarrhea**
- **Alteration of serum calcium and phosphate levels in your blood (This can result in numbness and tingling sensations in the fingers and toes, muscle cramps, irritability or depression, seizures, symptoms of heart failure, and anemia.**
- **Joint pain, arthritis**
- **Bone pain/tingling**
- **Rash**
- **Abdominal pain**
- **Swelling of the legs**
- **Cough**
- **Headache**
- **Dizziness**
- **Insomnia**
- **Depression**
- **Anxiety**
- **Confusion**
- *(added 4/21/11) (deleted 10/11/11)*
- *(added 4/21/11) (moved to likely 10/11/11)*

Rare, But Serious *(updated 3/11/08)*

- **Seizures**
- **Abnormal kidney function or failure**
- **Osteonecrosis of the jaw (permanent damage to the jawbone)**
- **Atypical bone fractures** *(added 5/29/12)*
- **Inflammation of the eyes can occur with zoledronic acid use. Symptoms can include red eye, eye pain, and/or decreased/blurry vision. In some cases, these events did not improve until the zoledronic acid was discontinued.**
- **Allergic reaction: There have been rare reports of allergic reaction with intravenous zoledronic acid including swelling in the mouth or throat making it difficult to breath. Very rare cases of anaphylactic reaction/shock have also been reported.**

Irregular heartbeat: In a recent study in post-menopausal women with osteoporosis, a small number of patients treated with zoledronic acid experienced an irregular heartbeat called atrial fibrillation. More patients who received zoledronic acid experienced this kind of irregular heartbeat than patients who did not receive zoledronic acid. So far, this symptom has not been seen in cancer patients taking zoledronic acid. Atrial fibrillation is a common condition which can be treated; however, more research is needed before the importance of this finding becomes clear. *(paragraph added 6/18/07)*

Risks and side effects related to the clodronate include the following:

Likely

- **Nausea**

Less Likely

- **Vomiting**
- **Diarrhea or constipation**
- **Alteration of serum calcium in your blood (This can result in numbness and tingling sensations in the fingers and toes, muscle cramps, irritability or depression, seizures, and symptoms of heart failure.)**
- **Rash**
- **Alterations of liver enzymes in your blood (a possible result of injury to the liver).**

Rare, But Serious

- **Abnormal kidney function or failure**
- **Respiratory effects in patients with aspirin-sensitive asthma**
- **Osteonecrosis of the jaw (permanent damage to the jawbone).** *(added 6/12/06)*

Risks and side effects related to the ibandronate include the following:

Likely

- **Diarrhea**
- **Pain in extremities (arms or legs)**
- **Upset stomach**
- **Back pain**

Less Likely

- **Pain or trouble with swallowing**
- **Chest pain (non-cardiac)**
- **Very bad heartburn or heartburn that does not get better**
- **Low calcium levels in the blood which could cause shakiness and abnormal heart rhythms**
- **Nausea**
- **Myalgia (muscle pain)**

Rare, But Serious

- **Stomach ulcers (hole in the lining of the stomach) which may bleed and be life-threatening**
- **Increase of symptoms associated with gastroesophageal reflux disease, including difficulty swallowing, inflammation of the esophagus, and development of ulcers within the esophagus**
- **Osteonecrosis of the jaw (permanent damage to the jawbone)** *(6/12/06)*

Reproductive risks: You should not become pregnant while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Women of child-bearing potential will have a pregnancy test.

Osteonecrosis of the jaw: Recent reports suggest a possible association between the use of intravenous bisphosphonates, such as zoledronic acid, and osteonecrosis of the jaw (permanent damage to the jawbone), a rare, but serious potential side effect. *(6/12/06)* **This condition may be painful and may happen after tooth extraction or other dental procedures such as tooth cleaning or when a patient is also getting chemotherapy while taking bisphosphonates. A recent study of 3,360 patients receiving standard treatment with or without zoledronic acid reported seven cases of osteonecrosis of the jaw, all in the zoledronic acid arm, with an average of eight doses received at the time of the event. This represented 0.4% of patients on the zoledronic acid arm.** *(6/18/07)* **Oral clodronate and ibandronate may also increase the risk of osteonecrosis of the jaw, although this link is not as well established.** *(6/12/06)*

Severe bone pain: Rare reports of severe and occasionally disabling bone, joint, and/or muscle pain has been reported with bisphosphonate use. The severe bone, joint, and/or muscle pain may occur within days, months, or years after starting a bisphosphonate. Some patients have reported complete relief of symptoms after discontinuing the bisphosphonate, whereas others have reported slow or incomplete recovery. The risk factors that contribute to severe bone, joint, and/or muscle pain associated with bisphosphonates are unknown. *(paragraph added 3/11/08)*

For more information about risks and side effects, ask the study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope zoledronic acid, clodronate, and ibandronate will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about bisphosphonates as a treatment for cancer. This information could help future cancer patients.

Some small trials of clodronate have suggested some possible benefit for that drug, although with conflicting results, and now a study with zoledronic acid showed benefit for dosing twice a year in pre-menopausal women, with estrogen-receptor positive breast cancer receiving ovarian suppression and not chemotherapy. However, at present, it is not standard of care to give these drugs in the majority of breast cancer patients. *(paragraph added 7/25/08)*

What other choices do I have if I do not take part in this study?

Your other choices may include:

- **Getting treatment or care for your cancer without being in a study.**
- **Taking part in another study involving bisphosphonate treatments.**
- **Getting no treatment.**

There is currently no standard treatment for the prevention of bone metastasis in breast cancer. Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Local Institutional Review Board (IRB)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Southwest Oncology Group
- Qualified representatives from the drug manufacturers for the three drugs used in this study.

    - *[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]*

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Administration of the drug will be *(provided free of charge/charged in the usual way).* The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be *(charged in the usual way/provided at a reduced rate). (local institutions must choose the option that best fits the hospital's situation)*

The drug manufacturers, Bayer Schering Pharma Oy and Roche, will provide you with the investigational agents, free of charge for this study. *(6/18/07)* Although zoledronic acid is commercially available, Novartis will provide this drug to you free of charge for this study. If during this study any of these drugs becomes approved for use in your cancer, you and/or your health plan may have to pay for drugs as needed to complete the study.

You will not be paid for taking part in this study.

If you have a severe financial need, lack dental insurance, and do not have access to dental care by any other means, then financial assistance will be available for dental exams.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at ***http://cancer.gov/clinicaltrials/understanding/insurance-coverage*** . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about important new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people

who review the research to protect your rights) at _____ *(telephone number).* *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

Future Contact *(section added 6/12/06)*

Occasionally, researchers working with the Southwest Oncology Group (SWOG) may have another research idea that relates to people who were on a SWOG study. In some cases, to carry out the new research, we would need to contact participants in a particular study. You can agree or not agree to future contact. *(paragraph added 6/18/07)*

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes No

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

I agree to submit a tissue specimen for the analysis of the substance parathyroid hormone related protein (PTHrP) to see if this predicts the risk of my breast cancer spreading to the bones. *(7/25/08) This is an experimental test that may indicate a higher chance that breast cancer has spread to the bones. Since the significance of this test is not proven, neither you nor your doctor will be given the results of this test. (paragraph updated 1/25/07) (sentences italicized 7/25/08)*

YES NO

I agree to submit a blood sample to be analyzed for the substance n-telopeptide to see if high levels will predict the risk of my breast cancer spreading to the bones. *(7/25/08) This is an experimental test that may indicate a higher chance that breast cancer has spread to the bones. Since the significance of this test is not proven, neither you nor your doctor will be given the results of this test. (paragraph updated 1/25/07) (sentences italicized 7/25/08)*

YES NO

I agree to submit a whole blood sample for genetic studies related to the development of side-effects to the kinds of drugs used in this study. *(added 7/13/09)*

YES NO

Should any tissue or blood remain from these studies, we would like to store your specimens for future research studies. The remaining sections of the informed consent document apply to specimens for research purposes.

Consent Form for Use of Specimens for Research

Where will my specimens be kept?

(address updated 9/25/06, 1/25/07, 3/11/08)

Southwest Oncology Group Solid Tumor Tissue Bank:
University of Colorado HSC at Fitzsimons
RC-1 South, Room L18-5400A
12801 East 17th Avenue
Aurora, CO 80045
Phone: 303/724-3086

(section deleted 6/12/06)

About Using Specimens for Research

(paragraph deleted 6/12/06)

We would like to keep leftover tissue, whole blood and serum for future research. *(6/12/06) (7/13/09)* If you agree, these specimens will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How Are Specimens Used for Research" to learn more about specimen research.

Your specimens may be helpful for research whether you do or do not have cancer. The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then any specimens that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Southwest Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. **My specimens may be kept for use in research to learn about, prevent, or treat cancer.**

   Yes No

2. **My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).**

   Yes No

3. **Someone may contact me in the future for my permission to allow other uses of my specimens.** *(6/12/06)*

   Yes No

If you decide to withdraw your specimens from a Southwest Oncology Group Specimen Repository in the future, a written withdrawal of consent should be submitted through your treating physician to the Southwest Oncology Group Operations Office. If you decide to withdraw your permission from the banking part of the study, your tissue will be returned to the treating institution, and any remaining blood specimens will be destroyed. *(bolded 6/12/06)*

Where can I get more information?

(section bolded 6/12/06)
You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/**

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

(section bolded 6/12/06)
I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by the Southwest Oncology Group. Your doctor does not work for the Southwest Oncology Group, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact the Southwest Oncology Group and request samples for their studies. The Southwest Oncology Group reviews the way that these studies will be done, and decides if any of the samples can be used. The Southwest Oncology Group gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. The Southwest Oncology Group will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to the Southwest Oncology Group. If more information is needed, the Southwest Oncology Group will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

The Southwest Oncology Group is in charge of making sure that information about you is kept private. The Southwest Oncology Group will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person, which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).

Southwest Oncology Group Data Operations Center
C/o Cancer Research And Biostatistics
1730 Minor Ave Suite 1900
Seattle, WA 98101-1468
Patient Registration:
via WebReg at: http://swog.org
(24 hours a day, 7 days a week, excluding downtimes for maintenance)
or call 206-652-2267 (Mon-Fri, 6:30am-4:00pm Pacific Time, excluding holidays)

Southwest Oncology Group Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3217
Phone: (210) 450-8808
Fax: (210) 677-0006

Southwest Oncology Group Registration Form

SWOG Study No. S0307 | **Registration Step** 1 | **Assigned Treatment Arm** ☐ | **Activation Date: November 15, 2005** | **Last Amended Date: September 1, 2009**

Phase III Trial of Bisphosphonates as Adjuvant Therapy for Primary Breast Cancer

Patient's Name _____

SWOG Patient ID ☐☐☐☐☐☐

Other Group Patient Number ☐☐☐☐☐☐☐☐☐☐

Participating Group/ Protocol Number _____

INSTRUCTIONS: All of the information on this Registration Form and the Protocol Eligibility Section must be answered appropriately for a patient to be considered eligible for registration. This Registration Form must be entirely filled out and referred to during the registration. **Do NOT submit this form as part of the patient data.**

Caller's SWOG Roster ID ☐☐☐☐☐

IRB Approval Date ☐☐/☐☐/☐☐☐☐

Projected Start Date of Treatment ☐☐/☐☐/☐☐☐☐

Date Informed Consent Signed ☐☐/☐☐/☐☐☐☐

SWOG Investigator Number ☐☐☐☐☐

OR

Other Group Investigator Name and Number _____ / _____

SWOG Treating Institution Number ☐☐☐☐☐

OR

Other Group Institution Name and Number _____ / _____

Date HIPAA Authorization signed: ☐☐/☐☐/☐☐☐☐ ***(Not required for non-American sites)***

Please indicate how the patient answered the following questions on the consent form:

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer. ☐ Yes ☐ No

2. My specimens may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease). ☐ Yes ☐ No

3. Someone may contact me in the future to ask me to allow other uses of my specimens. ☐ Yes ☐ No

4. I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study. ☐ Yes ☐ No

5. I agree to submit a tissue specimen for analysis of the substance parathyroid hormone related protein (PTHrP) to see if this predicts the risk of my breast cancer spreading to the bones. ***This is an experimental test that may indicate a higher chance that breast cancer has spread to the bones. Since the significance of this test is not proven, neither you nor your doctor will be given the results of this test.*** ☐ Yes ☐ No

6. I agree to submit a blood sample for analysis of the substance n-telopeptide to see if high levels will predict the risk of my breast cancer spreading to the bones. ***This is an experimental test that may indicate a higher chance that breast cancer has spread to the bones. Since the significance of this test is not proven, neither you nor your doctor will be given the results of this test.*** ☐ Yes ☐ No

7. I agree to submit a whole blood sample for genetic studies related to the development of side-effects to the kinds of drugs used in this study. ☐ Yes ☐ No

Patient's Date of Birth: ☐☐/☐☐/☐☐☐☐

Patient Gender: ☒ Female ☐ Male **Method of Payment:** _____ **Patient's Ethnicity:** _____

Patient's Race (select all that apply):

☐ White ☐ Native Hawaiian or Other Pacific Islander ☐ American Indian or Alaska Native
☐ Black or African American ☐ Asian ☐ Unknown

If a U.S. resident: **Patient Social Security Number:** ☐☐☐-☐☐-☐☐☐☐ **Patient's ZIP Code:** ☐☐☐☐☐

Country of Residence (if not USA): _____

If a resident of Canada: **Social Insurance Number:** ☐☐☐-☐☐☐-☐☐☐ **Postal Code:** ☐☐☐-☐☐☐

Southwest Oncology Group Registration Form Code Sheet

Patient's race definitions:

White or Caucasian: a person having origins in any of the original peoples of Europe, Middle East, or North Africa.

Black or African American: a person having origins in any of the black racial groups of Africa.

Native Hawaiian or Other Pacific Islander: a person having origins in any of the original peoples of Hawaii, Guam, Samoa and other Pacific islands.

Asian: a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent. Including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam.

American Indian or Alaskan Native: a person having origins in any of the original peoples of North, Central or South America, and who maintains tribal affiliations or community attachment.

Patient's ethnicity (Spanish/Hispanic Origin) options:

Unknown
No (not Spanish)
Yes, Mexican
Yes, Puerto Rican
Yes, Cuban
Yes, Central American
Yes, South American
Yes, Other
Yes, NOS

Method of Payment codes:

Private
Medicare
Medicare and Private
Medicaid
Medicaid and Medicare
No insurance (self-pay)
No insurance (no means)
Other, specify at registration
Unknown
Veterans Admin
Military

Other Group codes for use in the Web Registration program:

9977 – ACOSOG
9982 – CALGB
9976 – CTSU
9995 – ECOG
9984 – GOG
9987 – MDACC
9996 – NCCTG
9981 – NCIC
9983 – NSABP
9997 – RTOG

SOUTHWEST ONCOLOGY GROUP
S0307 PRESTUDY FORM

SWOG Patient ID [ ][ ][ ][ ][ ][ ] **SWOG Study No.** [S][0][3][0][7] **Registration Step** [1]

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Submit this form within 14 days of registration. All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

ELIGIBILITY VERIFICATION:

Each of the fields below corresponds to a criterion in Section 5 and must be completed for patient to be eligible.

DISEASE DESCRIPTION

Performance status: ☐ 0 ☐ 1 ☐ 2

Histologically confirmed primary invasive adenocarcinoma of the breast:

☐ Stage I ☐ Stage II ☐ Stage III

LABORATORY VALUES

Document values in units listed

Renal: **Collection date:**

Serum creatinine [ ][ ].[ ][ ] mg/dL **ULN** [ ][ ].[ ][ ] mg/dL [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Calculated creatinine clearance [ ][ ][ ].[ ] ml/min [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Previous bisphosphonate: ☐ IV ☐ Oral ☐ None **Date discontinued:** [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Date of dental examination: [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Bone pain: ☐ Yes ☐ No **If Yes, bone metastasis?** ☐ Yes ☐ No

CONSENT FOR SUBMISSION AND BANKING

☐ Accepted tissue submission ☐ Declined tissue submission

☐ Accepted serum submission ☐ Declined serum submission

continued on next page

SOUTHWEST ONCOLOGY GROUP
S0307 PRESTUDY FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S0307 **Registration Step** 1

Patient Initials _____ (L, F M)

ADDITIONAL PRESTUDY DATA:

PATIENT CHARACTERISTICS

Menopausal status (select one):

- ☐ Pre (< 6 mo since LMP and no prior bilateral ovariectomy and not on estrogen replacement)
- ☐ Post (prior bilateral ovariectomy OR > 12 mo since LMP with no prior hysterectomy)
- ☐ Above categories not applicable AND age < 50 (pre)
- ☐ Above categories not applicable AND age≥ 50 (post)

Height: ☐☐☐ cm **Weight:** ☐☐☐.☐ kg **BSA:** ☐.☐☐ m^2

DISEASE DESCRIPTION

Date of Initial Diagnosis of Primary Tumor: ☐☐ / ☐☐ / ☐☐☐☐

Tumor Laterality (select one): ☐ Left ☐ Right ☐ Bilateral

Pathologic Primary Tumor Size: ☐☐.☐ cm *(Maximum diameter of the invasive component; if multiple lesions, use longest lesion)*

Number of Positive Lymph Nodes: ☐☐ *(If sentinel node biopsy and axillary node dissection were performed, enter the sum of positive nodes.)*

Receptor Status: *(≥10 is positive if measured in fmols/mg cytosol protein. Otherwise use institutional standards; borderline results should be reported as positive.)*

ER Status: ☐ Negative ☐ Positive

PgR Status: ☐ Negative ☐ Positive

Was HER-2/neu status determined? ☐ No ☐ Yes

If Yes, HER-2/neu final diagnosis: ☐ Positive* ☐ Negative ☐ Equivocal

** (Positive is DAKO3+, FISH+, or institutional standard.)*

TREATMENT WITH STATINS

Is the patient currently taking a statin: atorvastatin (Lipitor), pravastatin (Pravachol), simvastatin (Zocor), lovastatin (Mevacor), fluvastatin (Lescol), rosuvastatin (Crestor)? ☐ Yes ☐ No

Length of time on statin: ☐ < 1 yr ☐ 1-2 yrs ☐ 2-3 yrs ☐ 3-4 yrs ☐ >4 yrs

PATIENT PREFERENCE

If oral and intravenous bisphosphonates are equally effective in preventing breast cancer recurrence in the bone, which would the patient prefer to receive? *Note that the answer to this question will not in any way affect which treatment the patient is randomly assigned to on this study*.

- ☐ Oral (taken daily)
- ☐ Intravenous (by vein - given once a month for the first 6 months, and once every 3 months after)

continued on next page

SOUTHWEST ONCOLOGY GROUP
S0307 PRESTUDY FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S0307 **Registration Step** 1

Patient Initials _____ (L, F M)

PRIOR TREATMENT RELATED TO THIS CANCER:

PRIOR TREATMENT RELATED TO THIS CANCER

Most Extensive Primary Surgery (select one):
- ☐ Partial mastectomy/lumpectomy/excisional biopsy
- ☐ Mastectomy, NOS

Date of Most Extensive Primary Surgery: ☐☐ / ☐☐ / ☐☐☐☐ *(If required, use last re-excision date)*

Was sentinel node sampling performed? ☐ Yes ☐ No

Sentinel Node Biopsy Date: ☐☐ / ☐☐ / ☐☐☐☐

Sentinel Node Biopsy Results: ☐ Positive ☐ Negative

Was axillary dissection performed? ☐ Yes ☐ No

Date of Axillary Dissection: ☐☐ / ☐☐ / ☐☐☐☐

SYSTEMIC TREATMENT FOR THIS CANCER

Chemotherapy (select one):
- ☐ Currently receiving
- ☐ Planned
- ☐ Not planned
- ☐ Completed **If completed, Date chemotherapy ended:** ☐☐ / ☐☐ / ☐☐☐☐

Hormone therapy (select one):
- ☐ Currently receiving
- ☐ Planned
- ☐ Not planned

If currently receiving:
- ☐ SERM (e.g., tamoxifen, raloxifene)
- ☐ Aromatase inhibitor (e.g., anastrazole, letrozole, exemustane)
- ☐ Ovarian suppression

Comments:

SOUTHWEST ONCOLOGY GROUP
S0307 TREATMENT SUMMARY FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S 0 3 0 7 **Registration Step** 1

Patient Initials _____ (L, F M) **Reporting Period:** ☐ 0-6 months ☐ 6 mo-1 yr ☐ 1 yr-2 yr ☐ 2 yr-3 yr

Institution/Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Please complete this form at 6 months, 1 year, 2 years, and 3 years. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

DISEASE STATUS

Date of Last Clinical Assessment: ☐☐ / ☐☐ / ☐☐☐☐ *(submit Follow Up form if patient has relapsed)*

Date of Last Contact or Death: ☐☐ / ☐☐ / ☐☐☐☐

Vital Status: ☐ Alive ☐ Dead *(submit Notice of Death form)*

TREATMENT STATUS

Assigned Treatment Arm: ☐ Arm 1 ☐ Arm 2 ☐ Arm 3

Was the patient treated on the assigned arm during this reporting period?

☐ Yes ☐ No, specify reason in comments

Treatment Begin Date (for this reporting period): ☐☐ / ☐☐ / ☐☐☐☐

Treatment End Date (for this reporting period): ☐☐ / ☐☐ / ☐☐☐☐

Were there any dose modifications or additions/omissions to protocol treatment (during this reporting period)?

☐ No

☐ Yes, planned (per protocol guidelines), specify in comments

☐ Yes, unplanned (not per protocol guidelines), specify in comments

For Arms 2 and 3: **In the past month, how many pills did the patient miss?** ☐☐

Did the patient receive any chemotherapy during this reporting period? ☐ Yes ☐ No

Did the patient receive radiation therapy during this reporting period? ☐ Yes ☐ No

Did the patient receive any hormone therapy during this reporting period? ☐ Yes ☐ No

If yes, ☐ SERM (e.g., tamoxifen, raloxifene)

☐ Aromatase inhibitor (e.g., anastrazole, letrozole, exemestane)

☐ Ovarian suppression

Is the patient currently taking a statin: atorvastatin (Lipitor), pravastatin (Pravachol), simvastatin (Zocor), lovastatin (Mevacor), fluvastatin (Lescol), rosuvastatin (Crestor)? ☐ Yes ☐ No

Has the patient experienced a bone fracture since submission of the last treatment summary form? ☐ Yes ☐ No

If yes, indicate site: ☐ Hip ☐ Spine ☐ Pelvis ☐ Wrist ☐ Arm ☐ Leg ☐ Ankle

Was the fracture traumatic (from greater than standing height)? ☐ Yes ☐ No

Has the patient had osteonecrosis or osteomyelitis of the jaw since submission of the last treatment summary form? ☐ No ☐ Yes *If yes, submit Osteonecrotic Jaw Lesion Form*

Has the patient had any grade of renal toxicity since the submission of the last treatment summary form?

☐ No ☐ Yes **If yes, Grade** ☐

Comments:

8/15/2006

SOUTHWEST ONCOLOGY GROUP
S0307 ADVERSE EVENT SUMMARY FORM

SWOG Patient ID [ ][ ][ ][ ][ ][ ] **SWOG Study No.** S 0 3 0 7 **Registration Step** 1

Patient Initials _____ (L, F M)

Institution/Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Please complete this form after 6 months, 1 year, 2 years, and 3 years. Report all adverse events observed. Document the worst Grade seen during the reporting period. Do not code a condition existing prior to registration as an adverse event unless it worsens. Category lists may not include all adverse events from that category. Record any observed adverse events not listed on the blank lines at the end. ***NOTE: If osteonecrosis of the jaw (ONJ) is detected, also submit the Osteonecrotic Jaw Lesion Form.*** All dates are MONTH, DAY, YEAR. Explain any blank dates or fields in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

ADVERSE EVENTS **Reporting period start date:** [ ][ ] / [ ][ ] / [ ][ ][ ][ ] *(Day 1 of this period)*

Reporting period end date: [ ][ ] / [ ][ ] / [ ][ ][ ][ ] *(Day one of next period. If final period, date of first visit or contact after resolution of acute adverse events.)*

Were adverse events assessed during this report period?

☐ No ☐ Yes, but no reportable adverse events occurred

☐ Yes, and reportable adverse events occurred (report below)

	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
FL01	Fever	☐	☐
SK11	Rash/desquamation	☐	☐
GI81	Dental: periodontal disease	☐	☐
GI20	Diarrhea	☐	☐
GI61	Esophagitis	☐	☐
GI00	Nausea	☐	☐
GI10	Vomiting	☐	☐
ME03	ALT, SGPT	☐	☐
ME04	AST, SGOT	☐	☐
ME05	Bilirubin	☐	☐
ME60	Calcium, serum-low	☐	☐
ME06	Creatinine	☐	☐
ME12	Proteinuria	☐	☐

	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
MS31	Arthritis	☐	☐
MS09	Fracture	☐	☐
MS20	Osteonecrosis (avascular necrosis)	☐	☐
NR30	Seizure	☐	☐
	Pain		
PAM02	Bone	☐	☐
PAM11	Joint	☐	☐
GU53	Renal failure	☐	☐
	CTC Adverse Event Term, Other *(specify using CTCAE 3.0 terminology)*		
	_____	☐	☐
	_____	☐	☐
	_____	☐	☐

* **Attribution codes:** 1-unrelated 2-unlikely 3-possible 4-probable 5-definite

Comments: (Please explain any "other" adverse events reported above, e.g., PA99 Pain-other)

SOUTHWEST ONCOLOGY GROUP
FOLLOW UP FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S☐☐☐☐ **Registration Step** ☐

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Please submit at each follow up after completion of treatment until relapse or progression, at time of relapse or progression, and at protocol-specified intervals after relapse or progression. Also submit at time of diagnosis of second primary. All dates are **MONTH, DAY, YEAR**. Answer all questions and explain any blank fields or blank dates in the **Comments** section. Place an [X] in appropriate boxes. Circle AMENDED items in red.

VITAL STATUS

Vital Status: ☐ Alive ☐ Dead Date of last contact or death: ☐☐ / ☐☐ / ☐☐☐☐

If vital status is Dead, complete and submit Notice of Death form.

DISEASE FOLLOW UP STATUS

Has the patient had a documented clinical assessment for this cancer (since submission of the previous follow-up form)?

☐ No ☐ Yes If Yes, Date of Last Clinical Assessment: ☐☐ / ☐☐ / ☐☐☐☐

NOTICE OF FIRST RELAPSE OR PROGRESSION

Has the patient developed a first relapse or progression that has not been previously reported?

☐ No ☐ Yes If Yes, Date of Relapse or Progression: ☐☐ / ☐☐ / ☐☐☐☐

Site(s) of Relapse or Progression: _____

NOTICE OF NEW PRIMARY

Has a new primary cancer or MDS (myelodysplastic syndrome) been diagnosed that has not been previously reported?

☐ No ☐ Yes If Yes, Date of Diagnosis: ☐☐ / ☐☐ / ☐☐☐☐

New Primary Site: _____

NON-PROTOCOL TREATMENT

Has the patient received any non-protocol cancer therapy (prior to progression/relapse) not previously reported?

☐ No ☐ Yes If Yes, Date of First Non-Protocol Therapy: ☐☐ / ☐☐ / ☐☐☐☐

Agent Name(s): _____

LONG TERM ADVERSE EVENT

Has the patient experienced (prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment) any severe (grade ≥ 3) long term toxicity that has not been previously reported?

☐ No ☐ Yes If Yes, Adverse Events and Grades: _____

Comments:

SOUTHWEST ONCOLOGY GROUP
S0307 SUPPLEMENTARY FOLLOW UP FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S0307 **Registration Step** 1

Patient Initials _____ (L, F M) **Date of Patient Visit:** ☐☐ / ☐☐ / ☐☐☐☐

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Please submit at each follow up after completion of treatment until recurrence, at time of recurrence, and at protocol specified intervals after recurrence. All dates are **MONTH, DAY, YEAR**. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

NOTICE OF PROGRESSION - ADJUVANT

Has the patient been diagnosed with opposite breast cancer since submission of last follow-up form?

☐ No ☐ Yes Date of diagnosis: ☐☐ / ☐☐ / ☐☐☐☐

Has the patient been diagnosed with first local-regional recurrence (since submission of last follow-up form)?

☐ No ☐ Yes Date of First Local-Regional Progression: ☐☐ / ☐☐ / ☐☐☐☐

Site(s) of First Local-Regional Progression: *(select all that apply)*

☐ Ipsilateral breast ☐ Chest wall ☐ Axilla
☐ Axillary nodes ☐ Internal mammary nodes
☐ Supraclavicular nodes ☐ Infraclavicular nodes

How was this progression information obtained? ☐ Clinical assessment ☐ Patient self-report only

Has the patient been diagnosed with first distant recurrence/progression (since submission of last follow-up form)?

☐ No ☐ Yes Date of First Distant Progression: ☐☐ / ☐☐ / ☐☐☐☐

Site(s) of First Distant Progression: *(select all that apply)*

☐ Bone ☐ Liver ☐ Lung/pleura
☐ Brain ☐ Nodes ☐ Skin
☐ Other CNS ☐ Other Soft Tissue ☐ Other Visceral
☐ Other, NOS: _____

If the patient has been previously diagnosed with first distant recurrence/progression at a site other than bone, has the patient been diagnosed with a subsequent bone recurrence since submission of last follow-up form?

☐ No ☐ Yes Date of Subsequent Bone Progression: ☐☐ / ☐☐ / ☐☐☐☐

How was this progression information obtained? ☐ Clinical assessment ☐ Patient self-report only

Has the patient experienced a bone fracture since submission of the last follow-up form? ☐ Yes ☐ No

If yes, indicate site: ☐ Hip ☐ Spine ☐ Pelvis ☐ Wrist ☐ Arm ☐ Leg ☐ Ankle

Was the fracture traumatic (from greater than standing height)? ☐ Yes ☐ No

Has the patient had osteonecrosis or osteomyelitis of the jaw since submission of the last follow-up form?

☐ No ☐ Yes *If yes, submit Osteonecrotic Jaw Lesion Form*

Comments: ***6/1/2008***

(FUS0307)

SOUTHWEST ONCOLOGY GROUP
OFF TREATMENT NOTICE

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S☐☐☐☐ **Registration Step** ☐

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: For each registration step, submit this form within 2 weeks after completion (or discontinuation) of treatment.

Systemic Therapy: List regimens, start and end dates. For multidrug regimens, do not list individual drugs separately; end date would be the date all drugs in the regimen were discontinued.

Surgery: List type of surgery, and in the "end date" column, the date of surgery.

Radiation: List sites, start and end dates (inclusive of boosts and implants).

All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section.
Place an [X] in appropriate boxes. Circle **AMENDED** items in red.

Treatment Start Date	Treatment End Date	Regimen or Procedure or Site(s)
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	

(If more room is needed, please continue on a separate page)

Off Treatment Reason (select one):

- ☐ Treatment completed per protocol criteria
- ☐ Medically required, due to toxicity, specify: _____
- ☐ Patient refused, due to toxicity, specify: _____
- ☐ Patient refused, other than toxicity, specify: _____
- ☐ Progression or relapse. Sites: _____
- ☐ Death (submit Notice of Death form)
- ☐ Other, specify: _____

Off Treatment Date

Date of completion, progression, death or decision to discontinue therapy: ☐☐ / ☐☐ / ☐☐☐☐

Will patient receive further treatment?

☐ No ☐ Yes, specify: _____ ☐ Unknown

Date of Last Contact (or death): ☐☐ / ☐☐ / ☐☐☐☐

Vital Status: ☐ Alive ☐ Dead (submit Notice of Death form)

Comments:

SOUTHWEST ONCOLOGY GROUP
S0307 SUPPLEMENTARY OFF TREATMENT FORM

SWOG Patient ID | | | | | | | **SWOG Study No.** S 0 3 0 7 **Registration Step** 1

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Submit this form after completion of end-of-study bone scan. If bone scan was not done, explain in Comments. All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

BONE SCAN

Did the patient have a bone scan after completion or discontinuation of protocol therapy? ☐ Yes ☐ No

If yes, date of bone scan: | | / | | / | | | | **Is a bone metastasis present?** ☐ Yes ☐ No

Note: After completion or discontinuation of protocol therapy, patient should also receive a dental check-up and submit the Dental Examination Form.

PATIENT PREFERENCE

If oral and intravenous bisphosphonates are equally effective in preventing breast cancer recurrence in the bone, which would the patient prefer to receive?

☐ Oral (taken daily)

☐ Intravenous (by vein - given once a month for the first 6 months, and once every 3 months after)

Comments:

SOUTHWEST ONCOLOGY GROUP
NOTICE OF DEATH

SWOG Patient ID ☐☐☐☐☐☐ **Most Recent SWOG Study No.** S☐☐☐☐

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Answer all questions and explain any blank fields or blank dates in the **Comments** section.
Place an [X] in appropriate boxes. Circle **AMENDED** items in red.

Date of Death: ☐☐ / ☐☐ / ☐☐☐☐ (month / day / year)

CAUSES OF DEATH

Any cancer (select one):

☐ No ☐ Primary Cause ☐ Contributory ☐ Possible ☐ Unknown

If cancer was the primary cause or if cancer possibly or definitely contributed to death, and the patient had had multiple tumor types, specify those which were causes of death:

☐ Cancer of most recent SWOG study, specify cancer: _____

☐ Cancer of other SWOG study, specify cancer: _____

☐ Other cancer, specify: _____

Toxicity from disease related treatment (select one):

☐ No ☐ Primary Cause ☐ Contributory ☐ Possible ☐ Unknown

If Primary Cause, Contributory or Possible, specify treatment and toxicity:

Non-cancer and non-treatment related causes (select one):

☐ No ☐ Primary Cause ☐ Contributory ☐ Possible ☐ Unknown

If Primary Cause, Contributory or Possible, specify:

Autopsy? ☐ No ☐ Yes ☐ Unknown

Source(s) of death information:

☐ Autopsy report
☐ Medical record / Death certificate
☐ Physician
☐ Relative or friend
☐ Other, specify: _____

Comments:

SOUTHWEST ONCOLOGY GROUP
DENTAL EXAMINATION FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S☐☐☐☐ **Registration Step** ☐

Patient Initials _____ (L, F M) **Time:** ☐ Prestudy ☐ End of protocol treatment

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Submit this form after dental examination at prestudy and at end of protocol treatment. All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

Examination date: ☐☐ / ☐☐ / ☐☐☐☐

PERIODONTAL EXAMINATION

Dental plaque levels: ☐ None ☐ Mild ☐ Moderate ☐ Severe

Calculus: ☐ None ☐ Mild ☐ Moderate ☐ Severe

Gingivitis: ☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Patchy ☐ Generalized

Periodontis: ☐ All pockets 4 mm or less ☐ Pockets > 6 mm Teeth numbers: _____

☐ Pockets ≥ 4 mm ≤ 6 mm Teeth numbers: _____

Overall periodontal disease level: ☐ None ☐ Mild ☐ Moderate ☐ Severe

DENTITION EXAMINATION ☐ None

Deep carries (within 3 mm or pulp): (List teeth numbers) _____

Fractured teeth / restorations: (List teeth numbers) _____

ENDODONTIC EXAMINATION ☐ None

Endodontically treated teeth: (List teeth numbers) _____

Failing root canals: (List teeth numbers) _____

REMOVABLE DENTURES ☐ None ☐ Complete dentures ☐ Removable partial dentures

Age of dentures: ☐☐ years **Last reline/adjustment date:** ☐☐ / ☐☐ / ☐☐☐☐

Upper: Stability: ☐ Good ☐ Fair ☐ Poor **Retention:** ☐ Good ☐ Fair ☐ Poor

Lower: Stability: ☐ Good ☐ Fair ☐ Poor **Retention:** ☐ Good ☐ Fair ☐ Poor

Evidence of denture sores/denture stomatitis: ☐ None ☐ Mild ☐ Moderate ☐ Severe

continued on next page

SOUTHWEST ONCOLOGY GROUP
DENTAL EXAMINATION FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S☐☐☐☐ **Registration Step** ☐

Patient Initials _____ (L, F M) **Time:** ☐ Prestudy ☐ End of protocol treatment

OSTEONECROTIC JAW LESIONS

Site: _____ **Size:** _____ **Date of onset:** ☐☐ / ☐☐ / ☐☐☐☐

Site: _____ **Size:** _____ **Date of onset:** ☐☐ / ☐☐ / ☐☐☐☐

Associated factor(s):

☐ Periodontal infection ☐ Dental extraction ☐ Denture trauma ☐ Other dental surgery ☐ No identified factor

_____ _____

Signature of examining dentist date

Comments:

SOUTHWEST ONCOLOGY GROUP
OSTEONECROTIC JAW LESION FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S☐☐☐☐ **Registration Step** ☐

Patient Initials _____ (L, F M) **Date Form Completed:** ☐☐ / ☐☐ / ☐☐☐☐

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Submit this form each time a new osteonecrotic lesion(s) is detected. All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

Number of osteonecrotic lesions: ☐ 1 ☐ 2 ☐ 3 **Date of onset:** ☐☐ / ☐☐ / ☐☐☐☐

Any signs/symptoms of infection (e.g., mucosal erythema, swelling, pus, bad taste)? ☐ Yes ☐ No

Lesion 1:

Site of lesion *(select all that apply):*

Maxilla: ☐ Anterior ☐ Posterior ☐ Buccal ☐ Lingual ☐ Alveolar ridge ☐ Palate

Mandible: ☐ Anterior ☐ Posterior ☐ Buccal ☐ Lingual ☐ Alveolar ridge ☐ Mylohyoid plate

Size of lesion: ☐☐ mm

Associated factor(s) *(select all that apply)*:

☐ Periodontal infection ☐ Dental extraction ☐ Denture trauma ☐ Other dental surgery ☐ No identified factor

Lesion 2:

Site of lesion *(select all that apply):*

Maxilla: ☐ Anterior ☐ Posterior ☐ Buccal ☐ Lingual ☐ Alveolar ridge ☐ Palate

Mandible: ☐ Anterior ☐ Posterior ☐ Buccal ☐ Lingual ☐ Alveolar ridge ☐ Mylohyoid plate

Size of lesion: ☐☐ mm

Associated factor(s) *(select all that apply)*:

☐ Periodontal infection ☐ Dental extraction ☐ Denture trauma ☐ Other dental surgery ☐ No identified factor

Lesion 3:

Site of lesion *(select all that apply):*

Maxilla: ☐ Anterior ☐ Posterior ☐ Buccal ☐ Lingual ☐ Alveolar ridge ☐ Palate

Mandible: ☐ Anterior ☐ Posterior ☐ Buccal ☐ Lingual ☐ Alveolar ridge ☐ Mylohyoid plate

Size of lesion: ☐☐ mm

Associated factor(s) *(select all that apply)*:

☐ Periodontal infection ☐ Dental extraction ☐ Denture trauma ☐ Other dental surgery ☐ No identified factor

STEROID USE

Did the patient receive steroids within 12 months of occurrence of the current jaw lesion(s)? ☐ Yes ☐ No

If Yes, agent name: _____

Agent begin date: ☐☐ / ☐☐ / ☐☐☐☐ **Agent end date:** ☐☐ / ☐☐ / ☐☐☐☐

Comments: ***10/15/2004***

(OSTEOLES)

52641

SOUTHWEST ONCOLOGY GROUP
S0307 SERUM CREATININE REPORTING FORM

SWOG Patient ID | | | | | | | **SWOG Study No.** S 0 3 0 7 **Registration Step** 1

Patient Initials _____ (L, F M) **Reporting Period:** ☐ 0-6 months ☐ 6 mo-1 yr ☐ 1 yr-2 yr ☐ 2 yr-3 yr

Institution/Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Please complete this form at 6 months, 1 year, 2 years, and 3 years. All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

CREATININE VALUES

Please report all serum creatinine values obtained during this reporting period, and date obtained.

	Collection Date	Serum Creatinine	ULN
1.	__ __ / __ __ / __ __ __ __	__ __ . __ __ mg/dL	__ __ . __ __ mg/dL
2.	__ __ / __ __ / __ __ __ __	__ __ . __ __ mg/dL	__ __ . __ __ mg/dL
3.	__ __ / __ __ / __ __ __ __	__ __ . __ __ mg/dL	__ __ . __ __ mg/dL
4.	__ __ / __ __ / __ __ __ __	__ __ . __ __ mg/dL	__ __ . __ __ mg/dL
5.	__ __ / __ __ / __ __ __ __	__ __ . __ __ mg/dL	__ __ . __ __ mg/dL
6.	__ __ / __ __ / __ __ __ __	__ __ . __ __ mg/dL	__ __ . __ __ mg/dL
7.	__ __ / __ __ / __ __ __ __	__ __ . __ __ mg/dL	__ __ . __ __ mg/dL
8.	__ __ / __ __ / __ __ __ __	__ __ . __ __ mg/dL	__ __ . __ __ mg/dL

Comments:

19.0 APPENDIX

19.1 Cancer Trials Support Unit (CTSU) Participation Procedures

19.2 Determination of Expedited Adverse Event Reporting Requirements

19.3 Translational Medicine Study – Germ-line Single Nucleotide Polymorphisms in Farnesyl Diphosphate Sythase and the Adverse Event of Acute Phase Reactions

19.4 **S0307** Statistical Analysis Plan

19.1 Cancer Trials Support Unit (CTSU) Participation Procedures

Registration/Randomization

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an 'active' investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member website or by calling the PMB at 301/496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. EST.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at http://members.ctsu.org

All forms and documents associated with this study can be downloaded from the **S0307** web page on the CTSU registered member Web site (https://members.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for **S0307 site registration**:
- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Prestudy requirements for **patient enrollment** on **S0307**:
- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed.
- Patients who wish to participate in the tissue and serum submissions for banking as outlined in Sections 15.3 and 15.4 must consent to the procedures. Written informed consent must be obtained prior to submitting samples.

CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888/462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 301/704-2376.

2. Complete the following forms:
   - CTSU Patient Enrollment Transmittal Form
   - Eligibility Criteria Checklist (Section 5.0 of the protocol)
   - SWOG Registration Form (Complete all sections of form except for SWOG-specific data fields)

3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays). The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.

4. Once investigator eligibility is confirmed and enrollment documents deemed complete, the CTSU registrar will contact the Southwest Oncology Group to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will convey this information to the enrolling site and follow up with a confirmation via e-mail or fax.

Patients must begin study treatment within five working days of registration.

Data Submission and Reconciliation

1. All case report forms (CRFs) associated with this study must be downloaded from the **S0307** web page located on the CTSU registered member website (https://members.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the SWOG Data Operations Center. The preferred method of sending data is via fax at 800/892-4007, (large volumes of data may be sent via post, see contacts table for mailing address). Do NOT include a cover sheet for faxed data.

3. The SWOG Data Operations Center will send query notices and delinquency reports directly to the site for reconciliation. Please fax query responses and delinquent data to the SWOG Data Operations Center and do not copy the CTSU Data Operations. When faxing data, include the query sheet that was originally sent from SWOG.

4. Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP AMS account contact information current**. This will ensure timely communication between the clinical site and the SWOG data center.

Special Materials or Substudies

1. All specimens submitted for this study must be entered and tracked using the SWOG on-line Specimen Tracking System, as specified in protocol Section 15.2c.

2. You can also access the Tracking System from the CTSU Member Web Site. Go to the **S0307** protocol page and click on the link provided under the Case Report Forms header.

3. Specimen collection for correlative studies (see protocol Section 15.0)
   - **Tissue banking**: Tissue blocks for banking should be submitted with patient's consent. Submit materials as specified in Section 15.3.
   - **Serum banking**: Serum for banking should be submitted with patient's consent. Submit materials as specified in Section 15.4.

Serious Adverse (AE) Reporting (Section 16.0)

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Reporting System (CTEP-AERS) from either the Adverse Events tab of the CTSU member homepage (https://members.ctsu.org) or by selecting Adverse Event Reporting Forms from the document center drop down list on the **S0307** web page.

3. Do not send adverse event reports to the CTSU.

4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of CTEP-AERS. Submit the completed form and supporting documentation as outlined in the protocol.

Drug Procurement (Section 3.0)

Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in Section 3.0 of the protocol.

Investigational agents: Clodronate (Bonefos®), Ibandronate (Ibandronic acid, Bonedronat®).

Clodronate and ibandronate will be provided free of charge by Bayer Schering Pharma Oy and Roche, respectively. Both drugs will be distributed by UVI, Inc.

Commercial Agents: Zoledronic Acid (Zometa®)

Zoledronic acid will be provided free of charge by Novartis and distributed by UVI, Inc.

Regulatory and Monitoring

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. (e.g., NSABP members may only request credit for protocols pertaining to breast or colorectal cancers). Registrations to protocols for other disease sites may still take place through CTSU without receiving credit for your NSABP activities. Per capita reimbursement will be issued directly from CTSU.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member website.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the privacy rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA privacy rule does not affect participants from outside the United States. Authorization to release protected health information is NOT required from patients enrolled in clinical trials at non-U.S. sites.

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

19.2 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.0.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (I, II, or III) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm, but the commercial agent(s) is given for a period of time prior to starting the investigational agent(s), expedited reporting of adverse events that occur prior to starting the investigational agent(s) would follow the guidelines for commercial agents. Once therapy with the investigational agent(s) is initiated, all expedited reporting of adverse events should follow the investigational guidelines.

Steps to determine if an adverse event is to be reported in an expedited manner

Step 1: *Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE).* The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov)**.** Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: *Grade the event using the NCI CTCAE version specified.*

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event. Expected* events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in

- the current NCI Agent-Specific Adverse Event List (for treatments using agents provided under an NCI-held IND);
- the drug package insert (for treatments with commercial agents only);
- Section 3.0 of this protocol.

Step 5: *Review Tables 16.1 and 16.2 in the protocol to determine if there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included an investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.*

NOTE: If the patient received at least one dose of investigational agent, follow the guidelines in Table 16.1. If no investigational agent was administered, follow the guidelines in Table 16.2.

NOTE: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the agent(s) must be reported according to the instructions above.

19.3 Translational Medicine Study – Germ-line Single Nucleotide Polymorphisms in Farnesyl Diphosphate Synthase and the Adverse Event of Acute Phase Reactions

Primary study objective:

- To investigate whether there is an association between inherited germ-line single nucleotide polymorphisms (SNP, rs2297480) in farnesyl diphosphate synthase (FDPS) and the adverse event of acute phase reactions in patients with early stage breast cancer who have been randomly assigned to one of three adjuvant bisphosphonates on clinical trial **S0307**.

Secondary study objectives:

- To investigate whether the association between inherited germ-line single nucleotide polymorphisms (SNPs) in farnesyl diphosphate synthase (FDPS) and the adverse event of acute phase reactions in patients with early stage breast cancer is specific to one of the three bisphosphonates under study in **S0307**, or is generic to the entire class of drugs or only to the nitrogen containing bisphosphonates.
- To investigate whether there is an association between inherited germ-line single nucleotide polymorphisms in target SNPs and toxicities other than acute phase reactions as defined and collected in patients with early stage breast cancer within study in **S0307**.
- To establish a well-annotated data base and germ line DNA specimen collection in patients with early stage breast cancer who have been randomly assigned to one of three adjuvant bisphosphonates on clinical trial **S0307** for pharmacogenomic investigations, either by a candidate gene approach or by genome-wide association studies (GWAS), of genes affecting bone metabolism, effects of bisphosphonate therapy and/or outcomes of cancer and its therapies.

Brief justification:

Pharmacogenomics. Pharmacogenomics investigates the inherited variation in genes that dictate drug response and explores ways that these variations can be used to predict whether a patient will have a good response to a drug, a bad response to a drug, or perhaps, no response at all. In the practice of medical oncology, it is common to treat many patients, when only a few actually derive distinct benefit from a specific drug therapy. The admixing of pharmacology, genetics and oncology offers the opportunity to practice individualized medicine.

The Consortium on Breast Cancer Pharmacogenomics (COBRA) was established in 2001 to study pharmacogenomics of breast cancer therapies. COBRA, which is a funded consortium within the NIH Pharmacogenomic Research Network (PGRN), is led by Dr. David Flockhart at Indiana University, in collaboration with co-PI's, Dr. Daniel F. Hayes at University of Michigan and Dr. Vered Stearns at the Sidney Kimmel Cancer Center at Johns Hopkins. Recently, under the direction of Dr. Eric Winer, the Dana Farber Cancer Institute has also become a full member of COBRA. In addition, COBRA actively collaborates with other consortia within PGRN, specifically with the Mayo Clinic group. Thus, several cooperative groups (SWOG: University of Michigan; ECOG: Indiana, Johns Hopkins; CALGB: DFCI; NCCTG: Mayo) are represented within COBRA and are collaborators within PGRN. Dr. Van Poznak, the study chair of this proposed amendment to **S0307**, is a member of COBRA through U. Michigan, and she is a chair for a study investigating bisphosphonate related genes within the consortium.

COBRA and other investigators have demonstrated that inherited variations in candidate genes responsible for metabolism, distribution, and activity of tamoxifen may affect pharmacokinetics, non-tumor effects, and even cancer outcomes (Dezentje, 2009) COBRA is now prospectively addressing pharmacogenomics of the aromatase inhibitors (AI) and the anti-angiogenic agent, bevacizumab. In addition to the candidate gene approach, recent studies have demonstrated the ability to interrogate the entire genome for SNPs through genome wide analysis studies (GWAS). The technology to conduct these sorts of studies is advancing rapidly. Indeed, these technologies were reviewed in a recent summit convened by TBCI and PGRN in Bethesda in March, 2008 (http://ctep.cancer.gov/resources/tbci/nci_summit_2008.html) to stimulate collaborations between the two groups, such as is proposed in this amendment.

Bisphosphonates in Breast Cancer. Bisphosphonates are firmly established treatment for patients with breast cancer metastases to bone, and several studies have suggested that these agents not only prevent AI-induced osteoporosis but that they may prevent bone metastases and even non-bone metastases and effect mortality. The impact of adjuvant bisphosphonate therapy on the risk of breast cancer recurrence is central to the objectives of **S0307**. However, not all patients who receive bisphosphonates are likely to obtain clinical benefit, and these agents are associated with modestly common, bothersome side effects (such as acute phase reactions) and occasional serious toxicity, such as osteonecrosis of the jaw and renal dysfunction.

SWOG Protocol **S0307**. **S0307** is the ideal clinical trial to investigate genes that impact on the response to bisphosphonate therapy and breast cancer outcome. In **S0307**, patients with early stage breast cancer are randomized to receive one of three bisphosphontes as adjuvant therapy in an attempt to decrease the risk of breast cancer recurrence. The three bisphosphonates in **S0307** are clodronate (non-nitrogen containing), ibandronate (nitrogen containing) and zoledronic acid (nitrogen containing and the highest potency bisphosphonate). **S0307** provides opportunity to examine genes affected by both nitrogen and non-nitrogen containing bisphosphonates.

The objectives of **S0307** include comparing disease free survival and overall survival between the study arms. **S0307** compares the site of first recurrence between study treatments and assesses adverse events, markers of bone resorption (N-telopeptide) and parathyroid hormone related protein. In addition, serum and tumor tissue specimens are being collected in **S0307** for future translational studies. The well annotated data base generated in **S0307** with clinical outcomes, adverse events and bone specific out come data provides the best environment to investigate genes (with a focus on genetic variability through SNPs analysis) associate with bone metabolism and the effects of bisphosphonate therapy. The multiple specimen types (serum, germline DNA, and tumor tissues) collected for this study will permit in depth translational investigations.

Diagnostic utility of genetic biomarkers to direct bisphosphonates use in the adjuvant setting

This study investigates potential genetic biomarkers to aid in predicting which patients may be at increased risk for acute phase reactions. In addition, the amendment to **S0307** will create a DNA resource for future study of questions as they pertain to breast cancer and its therapies. The impact that this amendment will have on patient care hinges on the outcome of the 2 completed, but not yet reported, adjuvant bisphosphonate studies (NSABP B-34 & AZURE) and the results of **S0307**. Although the clinically relevant anticancer affects of bisphosphonates have not yet been defined, it is known that zoledronic acid carries a 10-20% risk of a patient having a toxicity of moderate intensity, such as a fever and myalgias and arthralgias that may last for 1-7 days.

The FDA alert of 1/7/2008 warned of a pain syndrome with bisphosphonate therapy. The FDA highlighted the *"possibility of severe and sometimes incapacitating bone, joint, and/or muscle (musculoskeletal) pain in patients taking bisphosphonates. Although severe musculoskeletal pain is included in the prescribing information for all bisphosphonates, the association between bisphosphonates and severe musculoskeletal pain may be overlooked by healthcare professionals, delaying diagnosis, prolonging pain and/or impairment, and necessitating the use of analgesics."*

The bisphosphonates, particularly the intravenous nitrogen containing bisphosphonates, are associated with acute phase reactions which are characterized by fever, chills, bone pain, myalgias and arthralgias. Acute phase reactions are unpleasant and can affect a patient's therapeutic decisions.

If the results of **S0307** demonstrate efficacy for the adjuvant use of bisphosphonates, then the medical community may be administering drugs such as zoledronic acid to approximately 100-150,000 woman annually (over 200,000 women are diagnosed with breast cancer in the USA yearly, but probably not all will be candidates for adjuvant bisphosphonate therapy) and roughly 10,000-30,000 women (10-20% of those treated with bisphosphonate therapy) could be at risk for an acute phase reactions annually. The proposed amendment to **S0307** seeks identify which individuals are at risk of acute phase reactions. This information could be used to improve counseling the patient on the associated, personalized, risks of bisphosphonate therapy, and/or to direct timing of bisphosphonate therapy to avoid treating at a time that could interfere with life events (work, social, etc) and, possibly, if the efficacy of the 3 bisphosphonates examined in **S0307** are equal, the genetic data could be used to select one drug over another (nitrogen versus non-nitrogen containing bisphosphonate) based on predicted toxicity profiles. If such an acute phase reaction were predictable on an individualized basis, and if alternative therapies were available, then personalized medicine could be practiced.

Genetic evaluation is commonly done in assessing oncology patients prior to exposure to irinotecan for toxicity, or for KRAS for efficacy. The resource developed within a **S0307** DNA bank could be used for future pharmacogenomic investigations that may include study of site specific relapse (bone versus viscera, versus both) or other cancer related outcomes. Simple genotyping could potentially aid in predicting response to therapy.

The FDA Guidance for Industry has encouraged the submission of pharmacogenomic data with new drug applications, likely increasing the demand for both more efficient genotyping/phenotyping technologies and for clinical study sites with the technology, expertise, and experience to carry out such studies. The field of pharmacogenomics can be viewed as having multiple layers of complexity including, determining the role of genetics in drug response, screening and identifying genetic markers, validating genetic markers, clinical utility assessment and pharmacoeconomic impact (Huang 2009).

In addition to study of bisphosphonate efficacy and toxicity, the DNA bank generated through the proposed amendment to S0307 could be used for future studies including the identification of genes that associate with risk of relapse and/or site specific risk of relapse (such as bone). An example for identifying genes associated with site specific relapse: Preclinical work has suggested that genes associated with metastases to bone include CXCR4, MMP1, CTGF, FGF5, IL-11, OPN (Kang 2003). It is possible that a specific SNP in such a gene may predispose (or protect) bone metastases at a greater frequency. Data indicating that an individual is an increased risk for bone metastases may direct adjuvant drug selection to impact on that risk.

Bisphosphonate Pharmacogenomics. All bisphosphonates are "hard drugs," meaning that they are metabolically inert; bisphosphonates are excreted unchanged by the kidneys. Therefore, there is no role for pharmacogenomic studies of candidate genes of metabolism; however, there are targets that may have genetic variability in the pathways affected by the bisphosphonates.

The nitrogen containing bisphosphonates (alendronate, ibandronate, risedronate and zoledronic acid) bind their target enzyme, farnesyl diphosphate synthase (FDPS) and inhibit protein prenylation, thereby preventing the prenylation of small GTPases, which are essential for osteoclast function. Hence, FDPS is an enzyme of importance to investigate as a mediator of nitrogen containing bisphosphonate activity.

The gene encoding for FDPS is polymorphic and therefore this gene stands as a reasonable candidate for pharmacogenomic associations of activity of the nitrogen containing bisphosphonates. Clodronate, a non-nitrogen containing bisphosphonate, inhibits osteoclast activity by interfering with ATP metabolism. Therefore, one would not hypothesize that polymorphisms in FDPS gene would be associated with activity or toxicity of clodronate. The non-nitrogen containing bisphosphonates (such as clodronate and etidronate) are incorporated into non-hydrolyzable analogs of adenosine triphosphate (ATP) and are resistant to hydrolysis by the ATP dependant enzymes, These nonhyrolyable ATP analogs and their intracellular accumulation inhibit numerous intracellular metabolic enzymes thereby having a detrimental effect on cell function and lead to apoptosis. Thus, the contrast between and among the bisphosphonates is of interest in **S0307**, in which patients are randomly assigned to clodronate, ibandronate or zoledronic acid.

Other candidate genes may be associated with activity of the bisphosphonates as a class, or with specific agents. Emerging evidence from in vitro and in vivo preclinical studies in several tumor types suggests that nitrogen containing and non-nitrogen containing bisphosphonates can reduce tumor burden in bone and soft tissue, inhibit angiogenesis, prevent tumor cell invasion and adhesion in bone, and induce tumor cell apoptosis (Guise, Cancer Treatment Reviews 2008). The anti-angiogenic effect of bisphosphonates suggests that the VEGF pathway is another target to explore for SNPs in associate with the efficacy of adjuvant bisphosphonate therapy. As noted, COBRA investigators have recently reported that SNPs within the VEGF pathway has demonstrated a relationship to outcomes and toxicity of bevacizumab treatment and similar investigations will be applied in queries to be performed in S0307.

The primary objective of this proposal is to investigate whether there is an association between FDPS SNP rs2297480 and the adverse event of acute phase reactions in patients with early stage breast cancer who have been randomly assigned to one of three adjuvant bisphosphonates on clinical trial SWOG 0307. The secondary objectives of this study will investigate additional SNPs within FDPS, CYP2C8, and the VEGF pathway as they associate with the efficacy and toxicity of the 3 adjuvant bisphosphonate therapies administered in **S0307**.

Primary Objective and SNP rs2297480 The literature indicates that the FDPS SNP rs2297480 is biologically relevant; hence this SNP serves as the primary gene of interest.

The Adenosine (A)/Cytosine (C) polymorphisms in FDPS SNP rs2297480 was investigated for modulation of response to nitrogen containing bisphosphonate treatment (alendronate or ibandronate) in postmenopausal Danish women with osteoporosis (Marini Curr Med Res Opin 2008). In this study, baseline bone mineral density in the spine and femur did not show any relationship with FDPS polymorphisms. At 2 years of treatment with nitrogen containing bisphosphonate there were similar findings in the AA and AC genotypes; while the CC genotype demonstrated a lower BMD response (p=0.60 at the spine and p=0.59 at the femur). At 2 years of nitrogen containing bisphosphonate

therapy there was a statistically significant difference ($p<0.05$) in the urinary markers of bone metabolism in the CC genotype which showed decreased response of bone of bone turnover markers to nitrogen containing bisphosphonate therapy. This data suggests that FDPS, the target enzyme of the nitrogen containing bisphosphonates, may contain SNPs that affect response to nitrogen containing bisphosphonate therapy.

In a separate study investigating SNPs in FDPS in community dwelling Caucasian women age 65 or older, the same SNP, rs2297480, was found to show that CC or CA genotypes were associated with a lower bone mineral density (Levy Maturitas 2007). Interestingly, the "parent" study (Greenspan JAMA 2003) from which the patients were genotyped, included randomization to hormonal replacement therapy with or without alendronate (a nitrogen containing bisphosphonate), yet the SNP paper (Levy Maturitas 2007) does not identify whether or not study genotyped patients had been exposed to nitrogen containing bisphosphonate therapy. Therefore, this report does not permit direct comparisons to that of the Marini et al, although both studies suggest that the CC allele confers a diminished response to nitrogen containing bisphosphonates.

The proposal submitted here to investigate rs2297480 within **S0307** will build upon these findings and will investigate additional SNPs and pathways that may be predictive of response (efficacy and/or toxicity) to bisphosphonate therapy. This data may be applicable to patients receiving bisphosphonate therapy for breast cancer risk reduction but may also lend itself to the broader public health concern of osteoporosis and its therapies.

Primary Outcome to be assessed: Acute Phase Reactions: The nitrogen containing bisphosphonates are associated with acute phase reactions with the associated fever, chills, bone pain, myalgias and arthralgias and may occur with oral or intravenous bisphosphonate therapy. Fever has been reported in 9–44% of patients receiving intravenous nitrogen containing bisphosphonates. Typically occurring within 48 hours of infusion, fever is usually low-grade, though occasionally associated with rigors. Accompanying bone pain has also been reported in over half of the patients and the reactions typically are self-limited and resolve completely within 24-48 hours although patients may experience significant discomfort during this time. Most often the acute phase reaction occurs with the initial dosing of the intravenous nitrogen containing bisphosphonates and typically does not occur or is less severe with subsequent doses. Presently there is no mechanism to predict which patients may experience this toxicity.

In a clinical trial investigating bone health in postmenopausal women comparing orally administered nitrogen containing bisphosphonates (alendronate and ibandronate), the acute phase reaction symptoms were higher with ibandronate (6.8%) that with alendronate (3.0%) (Miller, Curr Med Res Op 2008). Of note, this study of postmenopausal women with osteoporosis used a lower dose of ibandronate (150 mg orally monthly) then S0307 uses (50mg orally daily). The frequency of acute phase reactions may vary with the different dosing regimens and the disease process being treated. Data investigating the ibandronate dosed at 50mg daily for metastatic bone disease suggests that the acute phase reaction occurs in 2% of patients while zoledronic acid dosed at 4mg intravenously is associated with 26-27% of patients experiencing an acute phase reaction (Devitt Ther Clin Risk Mang 2008). The differences between rates of acute phase reactions may be attributed to the different biochemical structure of each of the bisphosphonates. Of note, not all patients experience the acute phase reaction, suggesting the possibility that this outcome may related to a genetic variable such as variability within the binding pocket of FDPS.

Acute-Phase Reactions Reported Within 14 Days of the First and Second Infusion in Patients with Breast Cancer or Multiple Myeloma

Infusion	Zoledronic acid 4 mg	
	First	Second
Patients treated, n	563	542
Arthralgia, n (%)	18 (3.2)	10 (1.8)
Bone pain, n (%)	85 (15.1)	55 (10.1)
Fever, n (%)	65 (11.5)	24 (4.4)
Myalgia, n (%)	16 (2.8)	20 (3.7)

http://www.medscape.com/content/2003/00/46/23/462348/462348_tab.html

S0307 captures the adverse events (symptoms and grading of symptoms) associated with each of the three bisphosphonates, clodronate, ibandronate and zoledronic acid and provides the ideal study design to test the hypothesis that SNPS within FDPS correlate with toxicity.

Patients with significant toxicities are of interest to this pharmacogenomic study. However, it is possible that patients who had enrolled on S0307 earlier and experienced a significant acute phase reaction (or other adverse event or outcome) may not be available now to donate circulating leukocytes for DNA studies. To address this, consideration will be given to assessing paraffin embedded tissues from these individuals for analysis, should appropriate consents be in place and tissue be available from that individual. **S0307** includes collection of paraffin embedded tumor tissue and there is an evolving body of data demonstrating that many SNPs are concordant between germline DNA of leukocytes and that of somatic tumor tissue. A study ongoing at the University of Michigan (PI: C. Van Poznak) is investigating concordance of FDPS, VEGF and other bisphosphonate related genes within circulating leukocytes and paraffin embedded tissues. Since cancers contain a variety of mutations, circulating leukocytes remain a standard tissue for germline assessments, unless study SNP concordance has been shown with somatic tissue.

The adverse events to be used within this proposed analysis include: fever, flu like syndrome, musculoskeletal pain (back, bone, joint, limb, muscle) and pain (other). These will be pooled as a conglomerate “acute phase reaction” and patient may have multiple symptoms such as fever and bone pain.

Reporting of these adverse events in **S0307**, as of August 28, 2008, has demonstrated the following findings (collapsed over treatment assignment):

	Grade of adverse event				
Adverse Event	**≤ 1**	**2**	**3**	**4**	**5**
Fever	881	1	1	0	0
Flu like syndrome	881	2	0	0	0
Musculo Pain: Back	877	5	1	0	0
Musculo Pain: bone	846	20	17	0	0
Musculo Pain: joint	833	37	13	0	0
Musculo Pain: limb	877	5	1	0	0
Musculo Pain: muscle	871	6	6	0	0
Pain Other	880	2	1	0	0

Since a patient can have multiple toxicities we computed the percentage having any of these toxicities. Twelve percent had a toxicity of Grade 2 or higher and 3% had a Grade 3 toxicity. These are limited to toxicities possibly, probably, or definitely related to bisphosphonate treatment.

Study Target Genes: The study genes (and SNPs) have been identified from the literature and through Cancer Genome Anatomy Project, HapMap and National Center for Biotechnology Information. The lead study SNP FDPS rs2297480 and the lead outcome measures are outlined here.

The Primary Study Objective is to assess SNP FDPS rs 2297480 for association with acute phase reactions. The Secondary Objectives include assessing additional SNPs in SNP FDPS as well as other pathways, including VEGF, that may be critical to the efficacy, or toxicity, of bisphosphonate therapy.

Based on the present literature, additional genes of interest include those outlined in the below table and illustrating the frequency of SNP identification in the northern and western European population identified by HAPMAP. Allelic frequencies in other populations are not illustrated here to conserve space, but are available through the National Center for Biotechnology Information http://www.ncbi.nlm.nih.gov. When the frequency is low or unknown, the analysis will be exploratory.

Genes	SNP rs number	Allele Frequency In European populations identified by HAPMAP
FDPS -1 (SNP of Primary Objective)	rs2297480	A:0.692; C: 0.308
FDPS - 2	rs11264359	A: 0.683; G: 0.317
FDPS -3	rs11264361	T: 0.692; G: 0.308
CYP2C8 - 1	rs1934951	A: 0.192; G 0.808
CYP2C8 - 2	rs1934980	C: 0.208; T:0.792
CYP2C8 - 3	rs1341162	A: 0.195 G:0.805
CYP2C8 – 4	rs17110453	A: 0.891; C: 0.119
VEGF – 1: 1498	rs 833061	C: 0.420; T: 0.580
VEGF -2: 1154	rs 1570360	G > A: unknown
VEGF -3: 2578	rs 699947	A: 0.408; C: 0.592
VEGF - 4: 634	rs 2010963	G: 0.800; C:0.200
VEGF -5: 936	rs 3025039	C: 0.886; T: 0.114

The well annotated DNA specimen resource generated will provide materials investigation of additional genes and outcomes as well as serve as a resource for Genome-Wide Association Studies (GWAS). The use of GWAS may permit study of genetic variation across the entire human genome to identify genetic associations with observable traits or the presence or absence of a disease or condition. Whole genome information, when combined with clinical and other phenotype data, offers the potential for increased understanding of basic biological processes affecting human health, improvement in the prediction of disease and patient care, and ultimately the realization of the promise of personalized medicine. Details GWAS investigations within this resource will be proposed under separate cover at a future date.

Genotyping Analysis for specific SNP assessment: The DNA will be extracted from circulating leukocytes at the SWOG Solid Tumor Tissue Bank in Colorado. An aliquot of DNA will be sent to the Rae laboratory at the University of Michigan for genetic analysis as outlined here. The SNPs to be investigated will be detected using Taqman® Allelic Discrimination Assay (Foster City, CA). DNA samples will be assayed for SNPs in our candidate genes. Briefly, a 2ul DNA sample will be added to a 25ul reaction containing forward and reverse primers along with 2 allele specific labeled probes (one wild-type and one variant allele specific). The PCR and fluorescence measurements will be performed using the ABI Prism 7700 sequence detection system. Since the genotyping field is rapidly evolving, the best approach available will be employed, and this may change over time. If a polymorphisms cannot be reliably genotyped using the Taqman Allelic Discrimination, then an alternative method(s) such allele specific PCR and restriction fragment length polymorphisms PCR (RFLP-PCR will be used.

Circulating Leukocytes: As per published methods (Rae 2003) (Miller 1988) the buffy coat will be created from the whole blood collected and DNA will be extracted using Qiagen DNeasy Tissue kit and the QIAamp DNA Blood Midi kit (Quiagen Inc, Valencia CA) according to manufacturer's instructions. The DNA yield will be assessed by spectrophotometery (Beckman DU 640, Beckman Coulter, Fullerton CA).

Management of the specimens and study assays are to be performed by leaders in the pharmacogenomic translational science field.

The research team has experience with pharmacogenomics within Intergroups and COBRA. Data generated through SWOG and Gynocologic Oncology Group related pharmacogenomic research performed by Dr. Ambrosone (Kuptsova Blood 2007) (Krivak JCO 2008) and Dr. Hayes through the NIH Pharmacogenetic Research Network (PGRN) and the Consortium on Breast Cancer Pharmacogentics (COBRA) (Jin JCO 2008) has demonstrated the viability of patient directed therapies and of individualized medicine. The PI of this proposed amendment (Van Poznak) has experience investigating biomarkers in breast cancer and bone including study of correlation between breast tumor estrogen receptor status and bone mineral density (BMD), effect of breast cancer therapy on BMD and markers of bone metabolism, toxicities of bisphosphonates (renal and osteonecrosis of the jaw), genes associated with site specific metastases in preclinical studies, and biomarkers associated with taxane sensitivity. Dr. Van Poznak is presently conducting a clinical study investigating concordance of FDPS and VEFG genes across a variety of tissues. Drs Van Poznak and Gralow are lead investigators of SWOG **S0702**, "A Prospective Observational Multicenter Cohort Study to Assess the Incidence of Osteonecrosis of the Jaw (ONJ) in Cancer Patients with Bone Metastases Starting Zoledronic Acid Treatment." S0702 banks serum and DNA for study of the effects of bisphosphonate therapy on the risk of ONJ. It is likely that the pharmacogenomic generated within S0307 and S0702 will complement each other and permit genomic validation of biologically important pathways.

Statistical Plan:

This translational study seeks to collect circulating leukocytes from as many, if not all patients, enrolled on **S0307** to build a well annotated DNA bank for present and future investigations relating to bisphosphonate therapy and cancer outcomes, as well as other potential pharmacogenomic questions. As of May 1 there were 3,425 of the 4,500 patients accrued to **S0307**, with an accrual rate of approximately 293 patients within the last month. If 60-70% of enrolled patients donate DNA, then approximately 3000 patients will participate in this amendment, with an estimated 1000 patients per bisphosphonate arm (clodronate, ibandronate, zoledronic acid). There is some possibility that the accrual goal will be increased back to the original goal of 6,000 patients since the rapid accrual is shortening the overall follow-up period and therefore fewer events would be observed. That proposed amendment is currently under review by CTEP.

The power to investigate SNP FDPS rs2297480 and acute phase reactions within S0307 is outlined below. The specific sample size required for each SNP investigation is not presented here, as the study SNPs may evolve over time.

Primary Objective:
To investigate whether there is an association between inherited germ-line SNP FDPS rs2297480 and acute phase reactions in patients with early stage breast cancer who have been randomly assigned to one of three adjuvant bisphosphonates on clinical trial SWOG 0307.

FDPS SNP rs number	Allele Frequency
rs2297480	A:0.692; C: 0.308

We assume that the overall rate of an acute phase reaction Grade 2 or higher for the entire class of bisphosphonates is 12% based on the current data. We would like to detect a 5% absolute difference in acute phase reactions due to SNP effects. The 5% is large enough to be a clinically meaningful difference. To detect such a difference with 90% power (2-sided α = 0.05) we would need 2,272 samples. That is, the minor allele (C) would have a toxicity rate of 15.4% and the major allele (A) a rate of 10.4% (5% difference; 12% overall rate). If we are able to obtain the expected 3,000 patients, then the power increases to 96%. That sample size would allow us to detect a 4.4 % difference or larger between the minor and major alleles with 90% power. The analysis would use logistic regression on the outcome (acute phase reaction) by allele type stratified by treatment type. Additive, dominant, and recessive models will be considered for the three genotypes as well. The additive model uses (0,1,2) coding for AA, AC, and CC, respectively. The dominant model uses coding (0,1,1) and the recessive model (0,0,1).

Secondary Objectives:
The proposed amendment will investigate whether the study SNP FPDS rs2297480 and acute phase reactions associate together specifically in the setting of one bisphosphonate or the nitrogen containing bisphosphonates or appears generic to the class of drugs.
If we wish to detect a difference in acute phase reactions within each drug (n=1000), then with 90% power using a 2-sided α = 0.05, we could detect a 7.8% difference (17.4% versus 9.6%) between the minor and major alleles. To demonstrate that the acute phase reaction rate depends on which drug, we would look for an interaction between treatment and allele type. Suppose that one treatment shows no effect of allele type (12% for both major and minor alleles), but that the other treatment shows a 10.2% difference (19.1% versus 8.9%), then we would have 90% power to detect that interaction. The analysis would use logistic regression on the outcome (acute phase reaction) by allele type, treatment type, and their interaction.
The proposed amendment will investigate the association of SNPs in FDPS with other toxicities and outcomes as collected within S0307. This sample size is determined by the sample size of the primary question, since the same DNA is being used. Power would increase with events higher than 12%, but would decrease with more rare toxicities. We are also interested in exploratory analysis of other Snip's shown below. For these we set a 2-sided α = 0.005 to guard against spurious findings due to multiple comparisons. The power to detect a 6% difference is given below as well as the detectable difference at 90% power keeping the overall event rate at 12% and accounting for the differences in allele frequencies is the following.

Genes	**SNP rs number**	**Allele Frequency** In European populations identified by HAPMAP	Power to Detect a 6% Change	Detectable Difference
FDPS - 2	rs11264359	A: 0.683; G: 0.317	96%	5.5%
FDPS -3	rs11264361	T: 0.692; G: 0.308	95%	5.5%
CYP2C8 - 1	rs1934951	A: 0.192; G 0.808	84%	6.8%
CYP2C8 - 2	rs1934980	C: 0.208; T:0.792	86%	6.6%
CYP2C8 - 3	rs1341162	A: 0.195 G:0.805	84%	6.8%
CYP2C8 – 4	rs17110453	A: 0.891; C: 0.119	58%	8.5%
VEGF – 1: 1498	rs 833061	C: 0.420; T: 0.580	98%	5.1%
VEGF -2: 1154	rs 1570360	G > A: unknown	Depends on frequencies	Depends on frequencies
VEGF -3: 2578	rs 699947	A: 0.408; C: 0.592	97%	5.1%
VEGF - 4: 634	rs 2010963	G: 0.800; C:0.200	85%	6.5%
VEGF -5: 936	rs 3025039	C: 0.886; T: 0.114	61%	8.3%

We will establish a well annotated data base and germline DNA specimen collection for future studies involving candidate gene investigation or GWAS for correlation with bone metabolism, effects of bisphosphonate therapy and/or cancer and its therapies.

19.4 **S0307** Statistical Analysis Plan

Overview
S0307 compares three bisphosphonate agents, none of which constitute standard of care at the current time. Clodronate is currently being tested against placebo in the NSABP B-34 trial, but no results are available. The other two agents, ibandronate and zoledronic acid, are higher potency bisphosphonates, but efficacy compared to clodronate is unknown. Consequently, we consider a comparison of all three agents with no one agent presumed to be inferior or superior *a priori*. Therefore, all statistical comparisons are 2-sided.

We will compare all three agents simultaneously to determine if there is a significant difference among the three agents (called the omnibus or global test). If the omnibus test shows a significant overall effect at level α, then we will proceed with three pairwise comparisons, each at level α (Liu and Dahlberg, 1995). This conditional sequence is more powerful than using a Bonferroni procedure testing each pairwise comparison at α/3 without the preliminary overall test. Alpha is determined by the timing of the analysis (e.g. interim analysis or final).

Endpoints
The primary endpoint is invasive disease-free survival (DFS). This is the time from registration (randomization) to death by any cause, local, regional or distant recurrence, or a new breast primary whichever comes first. In situ disease is not counted as a recurrence. Patients not having an event are censored at the last follow-up visit. The primary secondary outcomes are overall survival and toxicity. Overall survival is time from registration to death by any cause. Site of first metastases is a secondary endpoint of interest since bisphosphonates should prevent metastases to bone.

Stratification
Due to the large sample size, randomization was not stratified by any prognostic factors. Time of randomization will be a stratifying variable in the analysis as described below.

Interim analysis
Interim analysis begins when approximately 31% of the expected failures are recorded. This should occur early in 2011. Annual interim analyses are performed thereafter. Decision making following a significant interim analysis is described in the protocol.

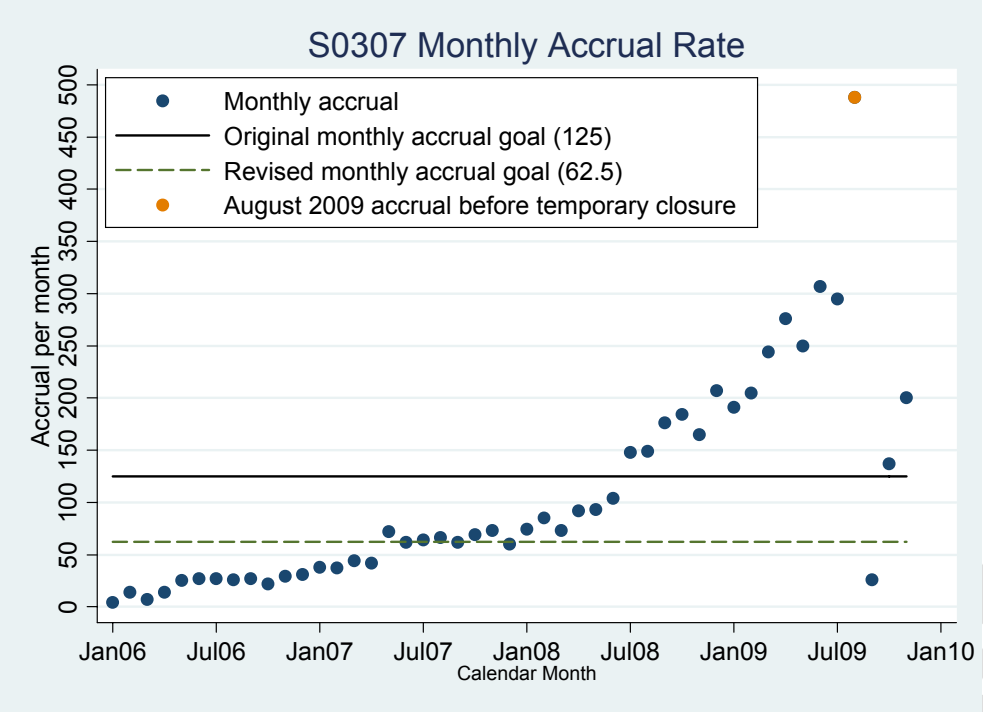
Year	Analysis	Percent of Events	Alpha Level for Test	Cumulative probability
4	Interim 1	31%	0.0010	0.0010
5	Interim 2	46%	0.0012	0.0022
6	Interim 3	60%	0.0068	0.0077
7	Interim 4	74%	.0158	0.0158
8	Interim 5	87%	.0265	0.0265
9	Final	100%	.0391	0.0500

Accrual goal
This trial has a complex history with regard to the accrual goal. The trial was designed to include 6,000 patients with 2,000 per arm. Accrual was expected to be 125 per month. After the trial was activated, accrual was very slow. This was possibly due to reports of osteonecrosis associated with bisphosphonates, particularly zoledronic acid. After one year, NCI clinical trial guidelines require amendment of the sample size goals such that projected monthly accrual is consistent with actual accrual. The trial was amended to accrue 62.5 patients per month, consistent with the observed accrual at that time. The

sample size goal was lowered to 4,500 based on the slower accrual and hence longer median follow-up time. The same effect sizes were used so only accrual and follow-up time considerations were changed. After the change in sample size goals, the pharmaceutical manufacturer of ibandronate revised the contract to provide support for a total of 1,500 patients instead of 2,000. The other two contracts remained at 2,000 patients.

Immediately after the amendment to change the accrual goal, accrual picked up dramatically. It was further accelerated by a report at ASCO in June 2008 of the benefit of zoledronic acid found in another trial (ABCSG-12). By early 2009 accrual had reached 300 patients per month. It became clear that the accrual goal of 4,500 patients would be met two years early and thus median follow-up time would be too short. We submitted a new amendment to increase the total accrual goal to 5,400 patients. This would restore the accrual goal to 2,000 per arm for zoledronic acid and clodronate, but limit accrual to only 1,400 patients for ibandronate. Ibandronate was no longer going to be marketed in the U.S. market for this indication and the manufacturer did not want to increase its level of support. The amendment was approved July 23, 2009.

At the end of July 2009, SWOG announced that the trial would close temporarily on August 24, 2009 due to a change in design. The change in accrual would require a change in the random allocation to treatment since the informed consent specified equal allocation to the three arms and thus any change in random allocation would require a revised informed consent. It was necessary to close the trial so that sites could update their IRB approval before they would be allowed to open the trial again. The pending closure sparked increased demand such that 488 patients were registered in a 3-week period corresponding to a rate of 600/month. By the time the trial closed temporarily on 8/24/09 there were 4,747 patients with 1,567 allocated to ibandronate. This exceeded the goal in this arm by 167 patients. The trial was designated to re-open on September 1, 2009 with only two arms since the ibandronate arm was complete. All institutions had to renew IRB approval before being allowed to register patients again. Accrual has started to reach its former levels, reaching 256 patients in December 2009. In order to obtain 2,000 patients in the two remaining arms, the total accrual will be approximately 5,600 since the ibandronate arm was overaccrued. At the current rate this should occur very early in 2010. Accrual to the trial will close on February 1, 2010. The change in the randomization allocation has an impact on the analysis plan as described below.



Power

While the accrual rates and total accrual goals have changed, the underlying expected effect sizes have been held constant for the duration of the trial. It was assumed that all pairwise comparisons were of equal interest and would be 2-sided. For the purpose of power calculations, clodronate was assumed to have the lowest expected DFS of 80% at five years. The best treatment was expected to have a 5-year DFS of approximately 83.4% or a hazard ratio of 1.25 for clodronate versus the best treatment. The intermediate treatment would have a HR between 1.25 to 1.00 when clodronate is compared to it. Power is a function of the actual location of this intermediate treatment and ranges from 78% to 93% for the omnibus test for the 5,400 sample size. Power is the lowest if the intermediate treatment is exactly in the middle of the two extremes and highest when the intermediate treatment is closer to one of the extremes. Power for the pairwise comparison of clodronate versus zoledronic acid ranges from 85% to 89% if HR=1.25. Power for ibandronate versus the other two agents individually is 77-85% for a HR=1.25 due to the smaller sample size. Power for the pairwise comparisons includes conditioning on a significant overall omnibus test. Power calculations were also computed for the Bonferroni approach which showed lower power than the chosen approach.

When the accrual goals and rates were changed officially, power in the range 80%-90% was maintained in most likely scenarios by changing the accrual goal to fit the actual expected accrual rate. In the last revision of the accrual goal, the change in accrual by month was incorporated into the power calculations (i.e. uniform accrual was not assumed). Actual outcome rates in the trial were never used to make changes in the accrual goals. Power was always based on the same effect treatment effects as used in the initial trial design.

Analysis
The primary analysis of DFS is a comparison of all three groups using a log-rank test performed at level α. If significant, this would be followed by three pairwise comparisons also performed at level α. The change in randomization probabilities must be considered as well since it could affect the results if not accommodated in the analysis. Suppose that over the course of the trial that overall DFS actually increased due to better adjuvant treatment, but that the hazard ratios linking the three groups were fixed over the duration of the study. Assuming that the treatment hazard ratios are constant over the study duration is the usual assumption in any randomized trial. However, there could still be "temporal drift" in absolute survival over time that affects all three groups equally. This drift poses no problem for the analysis if the randomization allocation does not change over time since all three groups are affected in the same way. However, in this case the allocation probabilities were changed since the ibandronate group was closed in August 2009. This change needs to be accommodated in the analysis. Even if the ibandronate group was not closed, but had a highly reduced allocation probability (e.g. from 33.3% to 1%) that change must be considered in the analysis as shown below.

Let s=1, 2 where s=1 is the period of equal randomization to three groups (up to 8/09) and s=2 is the period of changed allocation. In this study it is randomization to the two groups in equal allocation from 9/09 on. However, it could be any dramatic change in randomization (e.g. metering ibandronate to 1% so that there is still randomization to three groups over the course of the trial). Our underlying model for the hazard rate is the following:

$$\lambda_s(t;trt) = \lambda_{0s}(t)\, e^{\beta_1\, zoledronic + \beta_2\, ibandronate} \qquad (1)$$

where $\lambda_{0s}(t)$ is the baseline hazard rate for clodronate in randomization period 1 or 2. The baseline hazard rates for the two periods need not be the same since temporal drift may have occurred. Because of the stratification, patients are compared only within their own stratum, i.e. during the same contemporaneous randomization period. In stratum 2, there are no patients randomized to ibandronate so there is no contribution to the estimate of β_2 in that period. We do assume that the hazard ratio of zoledronic acid to clodronate is the same in both periods. This can be seen in the more general model:

$$\lambda_s(t;trt) = \lambda_{0s}(t)\, e^{\beta_1\, zoledronic + \beta_2\, ibandronate\, +\, \beta_3\,(s-1)^*\, zoledronic} \qquad (2)$$

where β_3 would represent a change in the HR between zoledronic acid and clodronate from the first randomization period to the next. In fact, the estimates β_1 and β_2 in model (2) exactly correspond mathematically to what would be obtained by excluding all patients randomized after the change in randomization to two arms. Therefore, model (2) is very inefficient since it assumes a change in HR. Model (1) represents the usual assumptions in randomized trials about constant treatment hazard ratios during the conduct of the trial, but allows the baseline hazard to change by randomization period. Furthermore, contemporaneous randomization is retained since patients are compared only within their own stratum.

The omnibus test corresponds to a joint test of $\beta_1 = \beta_2 = 0$ from Model (1). The stratified log-rank test is the score test corresponding to the test of this hypothesis. If that test is significant, than we proceed with pairwise comparisons. For the pairwise comparisons, only the comparison of zoledronic acid to clodronate is based on both randomization periods. Essentially, it is the test of $\beta_1 = 0$ from Model (1). The pairwise comparisons of ibandronate to (1) clodronate and (2) zoledronic acid will be based only on period 1. These tests are mathematically equivalent to testing (1) $\beta_2 = 0$ and (2)

$\left(\beta_2 - \beta_1\right) = 0$ in Model (2). There is a slight loss of power in the pairwise comparisons involving ibandronate since only data from the first time period are used. Thus, all pairwise comparisons are performed in contemporaneous periods, while the omnibus test is based on the stratified model (1).

In the absence of temporal drift, stratification is not strictly necessary, but accounting for it causes little loss in power. If there is temporal drift, then failure to account for it could lead to bias when changing allocation probabilities. Simulation for extreme drift in DFS over time shows that alpha is inflated to 7% under the null hypothesis when stratification is not used. Even if the third group is "metered" (randomization for ibandronate continues at a low level), there is still inflation of alpha in the presence of temporal drift. This is due to imbalance in projected outcomes since patients have different projections over time. Thus, any change in randomization allocation must be addressed in the analysis. Our simulation shows that alpha is correctly maintained by stratification in the presence of temporal drift.

With regard to power, maximal power is obtained using stratified model (1) above for the omnibus test. Power is 85% to 92% depending on the distribution of the three groups. Pairwise comparisons range in power from 83% to 90% for the two extreme groups. These estimates are based on an expected final sample size of 5,600.

Therefore, the primary analysis will be based on Model (1) to obtain the significance of the overall comparison and the pairwise comparison of zoledronic acid to clodronate. The two remaining pairwise comparisons (ibandronate vs. clodronate and ibandronate vs. zoledronic acid) are based on the first time period only when there was randomization to ibandronate.

Secondary comparisons will include adjustment for prognostic factors such as HER2 status, AJCC stage, and hormone-receptor status. Subgroup analysis will include determination of the hazard ratios (compared to clodronate) separately by age group, race, Her2 status, hormone-receptor status, AJCC stage, and type of adjuvant treatment received. These will be presented in a forest plot so that apparent discrepancies from the overall results will be visually apparent. These latter analyses are exploratory as there are no expected interactions of treatment with these prognostic factors.

Reference

Liu PY, Dahlberg S. Design and analysis of multiarm clinical trials with survival endpoints. Controlled Clinical Trials. 1995; 16:119-130.