

December 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD
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swog.org

FROM: Sandi Jo Hita, Lead Protocol Coordinator (sjhita@swog.org)

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott

MEMORANDUM

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 801/213-6159
E-mail: lynn.henry@hci.utah.edu

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The purpose of this memorandum is to inform sites that patients' unblinded treatment assignments are now available for the above-referenced study.

A report for each follow-up investigator listing the patients for whom you are responsible and each patient's unblinded treatment assignment is available on the CRA Workbench of the SWOG website (www.swog.org). A patient-specific report providing the patient's treatment assignment, which you may give to the patient, is also available on the CRA Workbench.

Notifying patients of their blinded intervention assignment may proceed without a protocol revision or IRB approval. Sites may contact their patients to inform them of their treatment assignment upon request or per institutional guidelines.

The results of the **S1202** trial are available in Henry et al., *Journal of Clinical Oncology*, which was published online on November 14, 2017.

cc: PROTOCOL & INFORMATION OFFICE
Destin Carlisle – Alliance
Elliott Lee, Biologics, Inc.
Becky Fillingham – ECOG-ACRIN
Mary Bonds – ECOG-ACRIN

November 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS
FROM: SWOG Operations Offices
RE: Holiday Closure

GROUP CHAIR'S OFFICE

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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

Biologics, Inc. Clinical Trials Services will be closed Thursday, November 26, 2015 and Friday November 27, 2015 (in observance of Thanksgiving), Thursday December 24, 2015 and Friday December 25, 2015 (in observance of Christmas), and Friday January 1, 2016 (in celebration of the New Year).

Biologics, Inc. Clinical Trials Services will be open on New Year's Eve (Thursday December 31, 2015).

Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern. Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

This Holiday Closure pertains to the following studies:

<u>S0635</u> Lung	<u>S1304</u> Myeloma
<u>S1014</u> Genitourinary	<u>S1313</u> Gastrointestinal
<u>S1202</u> Cancer Control	<u>S1403</u> Lung
<u>S1216</u> Genitourinary	<u>S1406</u> Gastrointestinal
<u>S1300</u> Lung	

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

cc: PROTOCOL & INFORMATION OFFICE

Laura Kingsbury, M.R.T.
Amy Johnson
Brian Zeller
Christine McLeod
Jean Barce
Jeri Jardine
Larry Kaye

Monica Yee
Stephanie Edwards
Vicki Green
Destin Carlisle – Alliance
Elliott Lee, Biologics, Inc.
Becky Fillingham – ECOG-ACRIN
Mary Bonds – ECOG-ACRIN

September 15, 2015

GROUP CHAIR'S OFFICE

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

MEMORANDUM

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.edu

IRB Review Requirements

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 - () Study closure due to new risk information
- () Expedited review allowed
- (✓) No review required

MEMORANDUM

The funding memorandum for the above-referenced study has been updated and is located on the protocol abstract page of the SWOG website (www.swog.org).

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

cc: PROTOCOL & INFORMATION OFFICE
Joseph Unger, Ph.D.
Danika Lew, M.A.
Monica Yee
Paul Lawson - Lilly
Elliott Lee – Biologics, Inc.

swog.org

September 15, 2015

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

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD
CHAIR

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RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

STATUS NOTICE

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.edu

IRB Review Requirements

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cc: **PROTOCOL & INFORMATION OFFICE**
Joseph Unger, Ph.D.
Danika Lew, M.A.
Monica Yee
Paul Lawson - Lilly
Elliott Lee – Biologics, Inc.

PERMANENT CLOSURE

The above-referenced study has met its accrual goal and will permanently close to accrual **effective October 1, 2015 at 11:59 p.m. Pacific.**

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

August 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: Updated Drug Order Form and Holiday Closure

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MEMORANDUM

IRB Review Requirements

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- (☒) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. has developed a new form for sites to designate non-prescribers to order investigational agent. Please note this is an optional form and submission of the form will apply to all studies the treating investigator has registered patients on that utilize Biologics Inc. as a distributor. This form is available on the protocol abstract page on the SWOG website (www.swog.org). The drug order forms for the studies listed below have been updated to include this option.

The Primary Shipping Address and Designee Form pertains to the following studies:

<u>S0635</u> Lung	<u>S1304</u> Myeloma
<u>S1014</u> Genitourinary	<u>S1313</u> Gastrointestinal
<u>S1216</u> Genitourinary	<u>S1403</u> Lung
<u>S1300</u> Lung	<u>S1406</u> Gastrointestinal

Please also note that Biologics, Inc. Clinical Trials Services will be closed Monday, September 7, 2015 in observance of Labor Day.

Regular business hours will resume on Tuesday, September 8, 2015. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

This Holiday Closure pertains to the following studies:

<u>S0635</u> Lung	<u>S1304</u> Myeloma
<u>S1014</u> Genitourinary	<u>S1313</u> Gastrointestinal
<u>S1202</u> Cancer Control	<u>S1403</u> Lung
<u>S1216</u> Genitourinary	<u>S1406</u> Gastrointestinal
<u>S1300</u> Lung	

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

cc: PROTOCOL & INFORMATION OFFICE
Laura Kingsbury, M.R.T.
Amy Johnson
Brian Zeller
Christine McLeod
Jean Barce
Jeri Jardine
Larry Kaye
Monica Yee
Stephanie Edwards
Vicki Green
Destin Carlisle – Alliance
Elliott Lee, Biologics, Inc.
Becky Fillingham – ECOG-ACRIN
Mary Bonds – ECOG-ACRIN

CLOSED EFFECTIVE 10/01/2015

July 1, 2015

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: Updated Drug Order Form and Holiday Closure

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 purpose of this memorandum is to inform sites that Biologics, Inc has updated all SWOG Drug Order Forms to clarify that the prescriber's signature is required.

The updated Drug Order Form pertains to the following studies:

S1313 (Gastrointestinal)
S1406 (Gastrointestinal)
S1014 (Genitourinary)
S1216 (Genitourinary)

S0635 (Lung)
S1300 (Lung)
S1403 (Lung)
S1304 (Myeloma)

Please also note that Biologics, Inc will be closed Friday, July 3, 2015 in observance of Independence Day. Biologics, Inc. will resume regular business hours (M-F, 9-6 ET) on Monday July 6, 2015.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

This Holiday Closure pertains to the following studies:

<u>S1202</u> (Cancer Control – Symptomatic)	<u>S0635</u> (Lung)
<u>S1313</u> (Gastrointestinal)	<u>S0709</u> (Lung)
<u>S1406</u> (Gastrointestinal)	<u>S1300</u> (Lung)
<u>S1014</u> (Genitourinary)	<u>S1403</u> (Lung)
<u>S1216</u> (Genitourinary)	<u>S1304</u> (Myeloma)
<u>S0535</u> (Leukemia)	

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

cc: PROTOCOL & INFORMATION OFFICE Mary Alice Norrison - Boehringer Ingelheim
Laura Kingsbury, M.R.T. Linda Fischer - Bristol-Myers Squibb
Tracy Maher, C.C.R.P. Becky Fillingham – ECOG-ACRIN
Amy Johnson Laura Gagnon – ECOG-ACRIN
Austin Hamm. Mary Bonds – ECOG-ACRIN
Brian Zeller April Noska – Genentech
Christine McLeod NCI Coop Coverage - Genentech
Jean Barce Leta Truett, Ph.D., M.N. – Janssen Services, LLC
Jeri Jardine Mohan Chelladurai, Ph.D. M.S.A. –
Larry Kaye Janssen Services, LLC
Louise Highleyman Royce-Ann Adkins, Janssen Services, LLC
Monica Yee William Heckman - Lilly
Stephanie Edwards Theresa Bucher, R.N., Millennium
Vicki Green Mark Showers – Onyx
Guadalupe Aquino – Alliance Kellis Snodgrass – Pfizer
Samantha Sublett – Alliance Afrouz Bazmi – Quintiles, Inc.
Elliott Lee, Biologics, Inc. Steve Shuey – Halozyyme Therapeutics

Distribution Date: June 1, 2015
E-Mailed Date: May 19, 2015

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS
FROM: SWOG Operations Office
RE: Holiday Closure for Monday, May 25, 2015 in Observance of Memorial Day

MEMORANDUM

IRB Review Requirements

- () Full board review required. Reason:
 - () Initial activation (should your institution choose to participate)
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 - () Study closure due to new risk information
- () Expedited review allowed
- (✓) No review required

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MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Monday, May 25, 2015 in observance of Memorial Day.

Regular business hours will resume on Tuesday, May 26, 2015. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

This Holiday Closure pertains to the following studies:

S1202 (Cancer Control – Symptomatic)	S0635 (Lung)
S1313 (Gastrointestinal)	S0709 (Lung)
S1406 (Gastrointestinal)	S1300 (Lung)
S1014 (Genitourinary)	S1403 (Lung)
S1216 (Genitourinary)	S1304 (Myeloma - Active)
S0535 (Leukemia)	

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

cc: PROTOCOL & INFORMATION OFFICE Mary Alice Norrison - Boehringer Ingelheim
Laura Kingsbury, M.R.T. Linda Fischer - Bristol-Myers Squibb
Tracy Maher, C.C.R.P. Becky Fillingham – ECOG-ACRIN
Amy Johnson Laura Gagnon – ECOG-ACRIN
Austin Hamm. Mary Bonds – ECOG-ACRIN
Brian Zeller April Noska – Genentech
Christine McLeod NCI Coop Coverage - Genentech
Jean Barce Leta Truett, Ph.D., M.N. – Janssen Services, LLC
Jeri Jardine Mohan Chelladurai, Ph.D. M.S.A. – Janssen Services, LLC
Larry Kaye Royce-Ann Adkins, Janssen Services, LLC
Louise Highleyman William Heckman - Lilly
Monica Yee Theresa Bucher, R.N., Millennium
Stephanie Edwards Mark Showers – Onyx
Vicki Green Kellis Snodgrass – Pfizer
Guadalupe Aquino – Alliance Afrouz Bazmi – Quintiles, Inc.
Samantha Sublett – Alliance Steve Shuey – Halozyme Therapeutics
Elliott Lee, Biologics, Inc.

CLOSED EFFECTIVE 10/10/2015

February 1, 2015

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

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD
CHAIR

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RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

MEMORANDUM

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.edu

IRB Review Requirements

- () Full board review required. Reason:
 - () Initial activation (should your institution choose to participate)
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 - () Study closure due to new risk information
- () Expedited review allowed
- (√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites of changes to the Master Forms Set for the above-noted study.

- Validated Spanish versions of the following patient completed questionnaires have been added:
 - **S1202** Brief Pain Inventory Short Form (BPI-SF) [Cuestionario Breve Para La Evaluacion Del Dolor (Edicion Corta)]
 - **S1202** FACT – ES Trial Outcome Index (Version 4) [S1202 FACT – ES (4 Version)]
 - **S1202** Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index (Version 3.1) [WOMAC VA3.1 Cuestionario]
 - **S1202** Modified-Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH) [Puntuacion-Modificada Para la Evaluacion Y Cuantificacion De Afecciones Reumatoides Cronicas De Las Manos]
 - **S1202** Global Ratings of Change in Joint Pain and Stiffness [Valoraciones Globales De Cambio En Dolor Y Rigidez En Las Articulaciones]
 - **S1202** Patient Health Questionnaire-9 (PHQ-9) [Cuestionario Sobre La Salud Del Paciente-9 (PHQ-9)]

- **S1202** Patient Treatment Satisfaction Form [Formulario De Satisfaccion Con El Tratamiento Del Paciente]
- **S1202** Cover Sheet for Patient-Completed Questionnaires: "Language questionnaire(s) completed in [] English [] Spanish has been added."

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

cc: PROTOCOL & INFORMATION OFFICE
Danika Lew, M.A.
Monica Yee
William Heckman - Lilly
Elliott Lee – Biologics, Inc.

CLOSED EFFECTIVE 10/01/2015

Distribution Date: February 1, 2015
DCP Submission Date: January 19, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS
FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD
CHAIR

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RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

REVISION #5

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.edu

IRB Review Requirements

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REVISION #5

The above-referenced study has been updated as follows:

1. Title Page, Page 1: The Version Date of the protocol and Model Consent Form have been updated. Lisa Hansen has been removed as the Nurse Coordinator. NCIC CTG has been removed from the Participants table.
 2. Table of Contents, Page 3: The Table of Contents have been updated.
 3. Section 3.1f.4, Page 16: The first sentence has been revised from "...drugs received using the SWOG Blinded Drug Accountability Record available on the **S1202** abstract page on the SWOG website (<http://www.swog.org>)."
- to "...drugs received using the Investigational Agent Accountability Record for Oral Agents (Oral DARF). The Oral DARF can be found on the NCI home page (<http://ctep.cancer.gov>)."
- The Pharmaceutical Management Branch has created an NCI Investigational Agent Accountability Record for Oral Agents (Oral DARF). Use of the Oral DARF became mandatory effective March 1, 2014. Effective immediately, all **new** shipments of oral agents on SWOG and CTSU studies must be recorded on this Oral DARF which is available on the NCI home page (<http://ctep.cancer.gov>). Any current inventory of oral agents must also be transferred to the new form. An audit deficiency for failure to implement the new Oral DARF will not be given prior to the date of this notification.

4. Section 5.2a.4, Page 19: This criterion has been added to include patients on LHRH agonist therapy with estradiol levels consistent with institutional normal values for post-menopausal status.
5. Section 5.2h, Page 20: "...or while on protocol treatment" has been added to the end of the second sentence for clarification. "Aspirin is permitted (see Section 8.2)." has been added for clarification.
6. Section 5.2k, Page 20: "was not taken concurrently with AI therapy and" was removed from the last sentence as it is a barrier to accrual. Most patients take venlafaxine for treatment of depression or hot flashes and not for pain. There have been several patients who were taking venlafaxine for hot flashes while they were taking an AI, but stopped venlafaxine because the hot flashes improved. These patients are now experiencing pain while taking the AI and would like to enroll in the trial, but are unable to due to this criterion.
7. Section 5.2m, Page 21: "or Spanish" has been added as validated Spanish questionnaires are now available.
8. Section 7.2a, Page 22: The following sentence has been added to the 4th paragraph for clarification: "Bottle #1 and #2 are dispensed at this visit."
9. Section 7.2b, Page 23: The following sentence has been added as the last sentence in the 9th paragraph for clarification: "She is permitted to start this at any time following completion of the taper of the study drug (Day 92)."
10. Section 9.0, Page 28: The header, including required studies and timepoints in weeks and days, has been added to the top of this page.
11. Section 15.1a, Page 40: The following note was added to this section for clarification: "*** With patient consent, leftover specimens will be banked for future unknown use."
12. Section 15.2c.4, Page 41: Dr. Carol Moynour and Lisa Hansen have been replaced with Dr. Henry and the SWOG Data Operations Office.
13. Section 16.1f, Page 44: The section regarding the reporting of pregnancy, fetal death, and death neonatal has been removed as it is not applicable for this patient population of post-menopausal women. The pre-existing Page 44 has been removed and subsequent pages have been repaginated.

Institutions **must** update their local consent forms to include the change to the Model Consent Form. SWOG considers that the Model Consent Form change **does not** represent an alteration in risk/benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of this change. Patients need not be informed of the following changes unless required by the local IRB.
14. Model Consent Form, Page 9: Under "Will my medical information...", Alliance, ECOG-ACRIN, and NRG have been added to the bulleted list.
15. Model Consent Form, Page 10: Under "What are the costs...", the link to the insurance coverage website has been updated in the 6th paragraph.
16. Model Consent Form, Page 14: Under the Participant signature line: "(or legally authorized representative)" has been removed.

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

cc: PROTOCOL & INFORMATION OFFICE
Joseph Unger, Ph.D.
Danika Lew, M.A.
Monica Yee
William Heckman - Lilly
Elliott Lee – Biologics, Inc.

CLOSED EFFECTIVE 10/01/2015

December 15, 2014

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD
CHAIR

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swog.org

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

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

MEMORANDUM

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.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 purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Wednesday, December 24, 2014, Thursday, December 25, 2014, and Thursday, January 1, 2015, in observance of the seasonal holidays.

Regular business hours will continue on December 26 and January 2 from 9:00 a.m. – 6:00 p.m. Eastern.

If you have questions or need to coordinate shipments in advance, please contact your Clinical Research Services team at 800/693-4906 or via e-mail at clinicaltrials@biologicsinc.com.

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

cc: PROTOCOL & INFORMATION OFFICE Monica Yee
Joseph Unger, Ph.D. Paul Lawson - Lilly
Danika Lew, M.A. Elliott Lee – Biologics, Inc.

November 1, 2014

TO: ALL SWOG MEMBERS, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS
AND PATHOLOGISTS

GROUP CHAIR'S OFFICE

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swog.org

FROM: Kimberly F. Kaberle, Protocol Coordinator (kkaberle@swog.org)

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

MEMORANDUM

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.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 purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Thursday, November 27 and Friday, November 28, 2014 in observance of the Thanksgiving holiday.

Regular business hours will resume on Monday, December 1, 2014. Regular business hours are Monday through Friday, 9:00 a.m. – 6:00 p.m. Eastern.

For additional information, please access Biologics' website at www.biologicsinc.com.

If you have questions or need to coordinate shipments in advance, please contact your Clinical Trial Project Manager at 800/693-4906 or via email at clinicaltrials@biologicsinc.com.

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

cc: PROTOCOL & INFORMATION OFFICE
Joseph Unger, Ph.D.
Danika Lew, M.A.
Monica Yee

August 15, 2014

GROUP CHAIR'S OFFICE

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swog.org

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

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

MEMORANDUM

Study Chair: Norah Lynn Henry, M.D., Ph.D.

Phone number: 734/936-4991

E-mail: norahh@med.umich.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 purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Monday, September 1, 2014, in observance of Labor Day.

Regular business hours will resume on Tuesday, September 2, 2014. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

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

cc: PROTOCOL & INFORMATION OFFICE
Joseph Unger, Ph.D.
Danika Lew, M.A.
Monica Yee

Jo Ann Hartline, M.P.H., M.S.W.
William Heckman - Lilly
Elliott Lee – Biologics, Inc.

June 15, 2014

GROUP CHAIR'S OFFICE

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swog.org

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

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

MEMORANDUM

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.edu

IRB Review Requirements

- () Full board review required. Reason:
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 - () Study closure due to new risk information
- () Expedited review allowed
- (☒) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Friday, July 4, 2014 in observance of Independence Day.

Regular business hours will resume on Monday, July 7, 2014. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

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

cc: PROTOCOL & INFORMATION OFFICE Monica Yee
William Barlow, Ph.D. Jo Ann Hartline, M.P.H., M.S.W.
Joseph Unger, Ph.D. William Heckman - Lilly
Danika Lew, M.A. Elliott Lee – Biologics, Inc.

May 15, 2014

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD

CHAIR

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swog.org

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

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

MEMORANDUM

Study Chair: Norah Lynn Henry, M.D., Ph.D.

Phone number: 734/936-4991

E-mail: norahh@med.umich.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 purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Monday, May 26, 2014 in observance of Memorial Day.

Regular business hours will resume on Tuesday, May 27, 2014. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

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

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Joseph Unger, Ph.D.
Danika Lew, M.A.
Monica Yee
Jo Ann Hartline, M.P.H., M.S.W.
William Heckman - Lilly
Elliott Lee – Biologics, Inc.

Distribution Date: May 15, 2014
DCP Submission Date: April 29, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

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swog.org

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

REVISION #4

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.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 #4

The above-referenced study has been updated as follows:

1. The Version Date of the protocol and Model Consent Form have been updated.
2. Title Page, Page 1: The participants list has been revised to the new NCI approved format. Joseph Unger's degree has been updated from "M.S." to "Ph.D."
3. Table of Contents, Pages 2-3: The Table of Contents has been updated.
4. Section 5.2h, Page 20: The following eligibility criterion has been revised from "Patients must not be taking any contraindicated medications listed on the duloxetine package insert including the following: treatment with phenothiazines, propafenone, flecainide, or linezolid; treatment with MAO-Inhibitor within 14 days prior to registration; current use of anticoagulation medication (e.g., heparin, warfarin)." to "Patients must not take MAO-Inhibitors for 14 days before registration or any time during study treatment. Concomitant therapy with heparin and warfarin is also not permitted at registration." for clarification purposes.

5. Section 5.2n, Page 21: "Patients with osteoarthritis are eligible." was added to the end of this eligibility criterion for clarification.
6. Section 5.4a, Page 21: "or their legally authorized representative" was added after "All patients" per new SWOG standard language.
7. Section 8.2, Page 25: The third paragraph was added to provide clarification to treating investigators that caution should be taken if patients take aspirin or non-steroidal anti-inflammatory drugs while on study. The following was added to the fourth paragraph to include additional specific drugs that increase risk of serotonin syndrome with duloxetine: "tramadol, linezolid, or other serotonergic medications". "Triptans" was replaced with "these medications". A note regarding concomitant use of heparin and warfarin was added at the end of this section. Information from Page 25 has been displaced to Page 26.
8. Section 8.5, Page 26: The reference to "AdEERS" has been changed to "CTEP-AERS".
9. Section 9.0, Page 28: An X has been added on the "Dispense blinded study drug" during Week 12 for clarification that sites should dispense bottle #3 during this visit.
10. Section 16.1b, Pages 42-43: The reference to the "NCI's Adverse Event Expedited Reporting System (AdEERS)" has been changed to "CTEP Adverse Event Reporting System (CTEP-AERS)" in this section. The link for NCI guidelines for CTEP-AERS has been updated. The sentence regarding paper forms being removed from the website and no longer accepted has been removed.
11. Section 16.1e, Page 43: References to "AdEERS" have been changed to "CTEP-AERS" throughout this section.
12. Section 16.1f, Page 44: This section regarding reporting pregnancy, fetal death, and death neonatal has been added as it is a new SWOG standard section. Subsequent pages have been renumbered accordingly.

Institutions **must** update their local consent forms to include the changes to the Model Consent Form within 90 days of distribution of this notice. 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 duloxetine/placebo and patients who sign a consent form prior to local implementation of the consent form changes **must** be informed of the following changes. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart.

13. Model Consent Form, Page 8: A new paragraph regarding not using MAO-Inhibitors, heparin and warfarin was added for patient's information. Additional information regarding a possible increase in bleeding risk was included in this paragraph for patients who take aspirin and NSAIDs while on study.
14. Model Consent Form, Page 11: An italicized paragraph beginning with "NOTE: Use the following types of format..." has been deleted as it was inadvertently left in the consent form.
15. Model Consent Form, Page 14: "(or legally authorized representative)" was added beneath the participant signature line as it is now a SWOG standard item.

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

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Joseph Unger, Ph.D.
Danika Lew, M.A.
Monica Yee
Jo Ann Hartline, M.P.H., M.S.W.
William Heckman - Lilly
Elliott Lee – Biologics, Inc.

CLOSED EFFECTIVE 10/01/2015

March 1, 2014

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swog.org

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

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

MEMORANDUM

Study Chair: Norah Lynn Henry, M.D., Ph.D.

Phone number: 734/936-4991

E-mail: norahh@med.umich.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 (if your site decides to distribute materials)

(√) No review required (if your site does not decide to distribute materials)

MEMORANDUM

A sample brochure and flier for recruitment to **S1202** have been posted to the study guidelines page on the SWOG website (www.swog.org).

If your institution would like to use these materials, you may add your contact information on the documents and must submit the materials to your local Institutional Review Board (IRB) for approval prior to distribution.

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

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Joseph Unger, M.S.
Danika Lew, M.A.
Monica Yee

Jo Ann Hartline, M.P.H., M.S.W.
William Heckaman-Lilly Pharmaceuticals
Elliott Lee - Biologics inc.
Emily Demske - CTSU

Distribution Date: February 1, 2014
DCP Submission Date: January 23, 2014

GROUP CHAIR'S OFFICE

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swog.org

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

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

REVISION #3

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.edu

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

REVISION #3

The above-referenced study has been updated as follows:

1. Title page, Page 1: The version date has been updated. The NCT number has been added below the title.
2. Section 3.1f.3, Pages 14-16: The first paragraph has been divided into three sections. "SWOG Institutions" has been added as the first section. "Non-SWOG Institutions" has been added as the second section with instructions for sending institution contact information to the distributor. "All Institutions" has been added as the third section. These changes have been made to clarify the drug ordering process for SWOG institutions and non-SWOG institutions.

3. Section 5.2k, Page 20: The following sentence has been bolded in order to reduce ineligibility: "Patients must not have previously taken the serotonin norepinephrine reuptake inhibitors (SNRI) duloxetine or milnacipran." The spelling of norepinephrine has been corrected.

Institutions **must** update their local consent forms to include the changes to the Model Consent Form within 90 days of distribution of this notice. 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 need not be informed of the following changes unless required by the local IRB.

4. Model Consent Form, Page 7: Under "Likely", vomiting, constipation, diarrhea, dizziness, decreased appetite, and increased sweating have been moved under "Less Likely" to be consistent with the adverse events listed in Section 3.1c. The heading of "likely" has been corrected from "...more than 5% of patients" to "...more than 10% of patients". "(Occurring in 1-10% of patients)" was added to the "Less Likely" heading.
5. Model Consent Form, Page 8: "(Occurring in less than 1% of patients)" was added to the Rare but serious heading in order to be consistent with the adverse events listed in Section 3.1c.

Please attach this memorandum to your copy of the protocol. Replacement pages are attached for the revised pages referenced above.

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

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Joseph Unger, M.S.
Danika Lew, M.A.
Monica Yee
Jo Ann Hartline, M.P.H., M.S.W.

December 15, 2013

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

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for
Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in
Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and
A.F. Schott.

GROUP CHAIR'S OFFICE

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swog.org

MEMORANDUM

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.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 purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Tuesday, December 24, 2013, Wednesday, December 25, 2013, and Wednesday, January 1, 2014, in observance of the seasonal holidays.

Regular business hours will continue December 26-27 and December 30-31 from 9:00 a.m. – 6:00 p.m. Eastern.

If you have questions or need to coordinate shipments in advance, please contact your Clinical Research Services team at 800/693-4906 or via e-mail at clinicaltrials@biologicsinc.com.

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

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Joseph Unger, M.S.
Danika Lew, M.A.
Monica Yee
Jo Ann Hartline, M.P.H., M.S.W.

Distribution Date: December 15, 2013
DCP Submission Date: November 22, 2013

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

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD

CHAIR

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FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

REVISION #2

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.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 #2

The above-referenced study has been updated as follows:

1. Title Page, Page 1: The version date has been updated. Study Coordinator has been updated to Study Chair. This change has also been made in Sections 3.1c.4 (Page 14) and 8.5 (Page 26).
2. Section 5.2a.3, Page 19: "unless ≥ 60 years of age" has been added in order to not require a non-standard of care blood draw and FSH lab test in women 60 years old and older.
3. Section 5.2b, Page 19: Initial start of AI therapy has been changed from "no more than 12 months prior to registration" to "no more than 36 months prior to registration" in order to allow more patients to be eligible for this study. The limit of 12 months since AI treatment initiation has shown to be too restrictive for patients who have tried multiple aromatase inhibitor medications before considering enrollment in this trial.

4. Section 9.0, Pages 27 and 29: The “~” footnote has been added in the boxes for pre-study history and pre-study physical exam on Page 27. On Page 29, the “~” has been added and defined as “Must be performed within 28 days prior to registration.”
5. Section 14.4b, Page 37: “Institutional surgical pathology report to confirm diagnosis of ER/PgR status” has been added as it was inadvertently missing previously.
6. Section 16.0, Pages 42-43: SWOG’s standard confidentiality statement has been added above Section 16.1. The second paragraph in Section 16.1b has been displaced to the next page.

No changes have been made to the Model Consent Form; its Version Date remains 9/18/13.

Please attach this memorandum to your copy of the protocol. Replacement pages are attached for the revised pages referenced above.

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

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Joseph Unger, M.S.
Danika Lew, M.A.
Monica Yee
Jo Ann Hartline, M.P.H., M.S.W.

November 1, 2013

TO: ALL SWOG MEMBERS, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS
AND PATHOLOGISTS

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

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

MEMORANDUM

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.edu

OPERATIONS OFFICE

4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

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

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PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

MEMORANDUM

The purpose of this memorandum is to inform sites of a holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trials Services is closed Thursday, November 28 and Friday, November 29, 2013 in observance of the Thanksgiving holiday.

Regular business hours will resume on Monday, December 2, 2013. Regular business hours are Monday through Friday, 9:00 a.m. – 6:00 p.m. Eastern.

For additional information, please access Biologics' website at www.biologicsinc.com.

If you have questions or need to coordinate shipments in advance, please contact your Clinical Trial Project Manager at 800/693-4906.

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

swog.org

cc: PROTOCOL & INFORMATION OFFICE Danika Lew, M.A.
William Barlow, Ph.D. Monica Yee
Joseph Unger, M.S. Jo Ann Hartline, M.P.H., M.S.W.

Distribution Date: November 1, 2013
DCP Submission Date: September 18, 2013

GROUP CHAIR'S OFFICE

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CHAIR

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

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for
Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in
Women with Early Stage Breast Cancer." Study Coordinators: Drs. N.L.
Henry and A.F. Schott.

REVISION #1

Study Coordinator: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.edu

IRB Review Requirements

- ☐ Full board review required. Reason:
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REVISION #1

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 on treatment need not be informed of these changes unless required by the local Institutional Review Board (IRB).

The above-referenced study has been updated as follows:

1. Title Pages, Pages 1-3: The title pages have been reformatted to the new SWOG standard. CTSU has been added to the Participant's list. The version date has been updated.
2. CTSU Information, Page 4: This page has been added to include CTSU information. Subsequent pages have been renumbered accordingly.
3. Section 3.1e, Page 14: The temperature storage instructions have been revised from "25°C (77°F), excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]" to "(15°C to 25°C). Do not refrigerate or freeze." in order to be consistent with Section 3.2c.
4. Section 5.1a, Page 19: "(Stage I-III)" has been added to clarify which stage patients are eligible.
5. Section 5.2b, Page 19: In the first sentence "but no longer than 12 months" has been removed. The following sentence has been added for additional clarification regarding prior and current AI therapy: "Patients may have received any number of prior AI therapies, but the first AI therapy must have started no more than 12 months prior to registration."
6. Section 7.7, Page 24: This section has been added to include information regarding non-emergency unblinding once all patients have completed follow-up.
7. Section 9.0, Page 28: The **S1202** Patient Treatment Satisfaction Form has been added to the calendar under Week 12 as this form has been added to the protocol and Section 14.4e. The "X" on Day 43 for dispensing study drug has been removed as all drug is dispensed on Day 1.
8. Section 13.2, Pages 34-36: This section has been added to include CTSU registration information. Subsequent sections have been renumbered accordingly. An affected section reference was updated on Page 21, Section 5.4b.
9. Section 13.3e, Pages 34-35: This section has been added because Cooperative Group Credit must be assigned for CTSU registration. Subsequent sections have been renumbered accordingly.
10. Section 14.3c, Page 37: This section has been added to reference the CTSU Participation Table on Page 4 for more information.
11. Section 14.4e, Pages 38-39: This section has been added to include submission of the **S1202** Patient Treatment Satisfaction Form within 14 days of the Day 85 assessment. Subsequent sections have been renumbered accordingly. Affected section references were updated on Page 24, Section 7.4 and Page 39, Section 14.4.
12. Section 18.3, Page 53: Anne F. Schott, M.D. and her contact information have been replaced with those of Craig R. Nichols, M.D. as Dr. Schott is no longer the SWOG Executive Officer for this protocol.
13. Model Consent Form, Page 9: Under "Will my medical information be kept private?", the Cancer Trials Support Unit (CTSU) has been added to the list of organizations that may look at medical records.

In addition to the protocol revisions above, the form packet, located on the protocol abstract page on the SWOG website (www.swog.org), has been revised with the following changes:

- **S1202** Onstudy Form (Form #62636): Questions were updated about other treatment on the bottom of Page 1 to match eligibility requirements in Section 5.0 of the protocol.
- **S1202** Cover Sheet for Patient-Completed Questionnaires (Form #54672): The **S1202** Patient Treatment Satisfaction Form was added.
- **S1202** Patient Treatment Satisfaction Form (Form #37300): This form has been added to the forms packet as it was inadvertently missing previously.

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

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Joseph Unger, M.S.
Danika Lew, M.A.
Monica Yee
Jo Ann Hartline, M.P.H., M.S.W.

October 15, 2013

TO: ALL SWOG MEMBERS, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS
AND PATHOLOGISTS

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
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503-494-5586
503-346-8038 FAX

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for
Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in
Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry
and A.F. Schott.

MEMORANDUM

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.edu

OPERATIONS OFFICE

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San Antonio, TX 78229

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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

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MEMORANDUM

The purpose of this memorandum is to request that sites with registered currently patients and patients registered in the future submit the pre-registration pathology report to the SWOG Data Operations Center by uploading the report via Medidata Rave® on the Source Documentation page. Data submission procedures are located in Section 14.3 of the protocol. The pre-registration pathology report will be added to Section 14.4b in a future amendment.

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

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Joseph Unger, M.S.
Danika Lew, M.A.
Monica Yee
Jo Ann Hartline, M.P.H., M.S.W.

swog.org

August 15, 2013

TO: ALL SWOG MEMBERS, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS
AND PATHOLOGISTS

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

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

MEMORANDUM

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.edu

OPERATIONS OFFICE

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MEMORANDUM

The purpose of this memorandum is to inform sites of the Holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trial Services is **closed Monday, September 2, 2013** in observance of the Labor Day holiday.

Regular business hours are Monday through Friday, 9:00 a.m. – 6:00 p.m. Eastern.

For additional information, please access Biologics' new website at www.biologicsinc.com.

If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Joseph Unger, M.S.

Danika Lew, M.A.
Monica Yee
Jo Ann Hartline, M.P.H., M.S.W.

June 15, 2013

TO: ALL SWOG MEMBERS, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS
AND PATHOLOGISTS

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
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Portland, OR 97239

503-494-5586
503-346-8038 FAX

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Chairs: Drs. N.L. Henry and A.F. Schott.

MEMORANDUM

Study Chair: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.edu

IRB Review Requirements

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swog.org

MEMORANDUM

The purpose of this memorandum is to inform sites of the Holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trial Services is **closed Thursday, July 4, 2013** in observance of the Independence Day holiday.

Regular business hours are Monday through Friday, 9:00 a.m. – 6:00 p.m. Eastern.

For additional information, please access Biologics' new website at www.biologicsinc.com.

If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Joseph Unger, M.S.

Danika Lew, M.A.
Monica Yee
Jo Ann Hartline, M.P.H., M.S.W.

Distribution Date: June 1, 2013
E-mailed Date: May 21, 2013

TO: ALL SWOG MEMBERS, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS
AND PATHOLOGISTS

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD

CHAIR

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Seattle, WA 98109

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swog.org

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Coordinators: Drs. N.L. Henry and A.F. Schott.

MEMORANDUM

Study Coordinator: Norah Lynn Henry, M.D., Ph.D.
Phone number: 734/936-4991
E-mail: norahh@med.umich.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 purpose of this memorandum is to inform sites of the Holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trial Services is **closed Monday, May 27, 2013** in observance of the Memorial Day holiday.

Regular business hours are Monday through Friday, 9:00 a.m. – 6:00 p.m. Eastern.

For additional information, please access Biologics' new website at www.biologicsinc.com.

If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Joseph Unger, M.S.

Danika Lew, M.A.
Monica Yee
Jo Ann Hartline, M.P.H., M.S.W.

May 15, 2013

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD

CHAIR

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TO: ALL SWOG MEMBERS, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS

FROM: Kimberly F. Kaberle, Protocol Coordinator

RE: **S1202**, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer." Study Coordinators: Drs. N.L. Henry and A.F. Schott.

STATUS NOTICE

Study Coordinator: Norah Lynn Henry, M.D., Ph.D.

Phone number: 734/936-4991

E-mail: norahh@med.umich.edu

IRB Review Requirements

- (☒) Full board review required. Reason:
 - (☒) Initial activation (should your institution choose to participate)
 - () Increased risk to patient
 - () Complete study redesign
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 - () 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 SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Joseph Unger, M.S.
Danika Lew, M.A.
Monica Yee
Jo Ann Hartline, M.P.H., M.S.W.

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activated 5/15/13

SWOG

A RANDOMIZED PLACEBO-CONTROLLED PHASE III STUDY OF DULOXETINE FOR TREATMENT
OF AROMATASE INHIBITOR (AI)-ASSOCIATED MUSCULOSKELETAL SYMPTOMS IN WOMEN WITH
EARLY STAGE BREAST CANCER

NCT#01598298

STUDY CHAIRS:

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and Translational Medicine)
University of Michigan
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Ann Arbor, MI 48109
Phone: 734/936-4991
FAX: 734/936-4940
E-mail: norahh@med.umich.edu

AGENTS:

Duloxetine hydrochloride (NSC-744012)
(IND-exempt)

BIOSTATISTICIANS:

Anne F. Schott, M.D. (Medical Oncology)
University of Michigan
Comprehensive Cancer Center
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Joseph Unger, Ph.D. (Biostatistics)
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PARTICIPANTS

ALLIANCE/Alliance for Clinical Trials in Oncology
ECOG-ACRIN/ECOG-ACRIN Cancer Research Group
NRG/NRG Oncology
SWOG/SWOG

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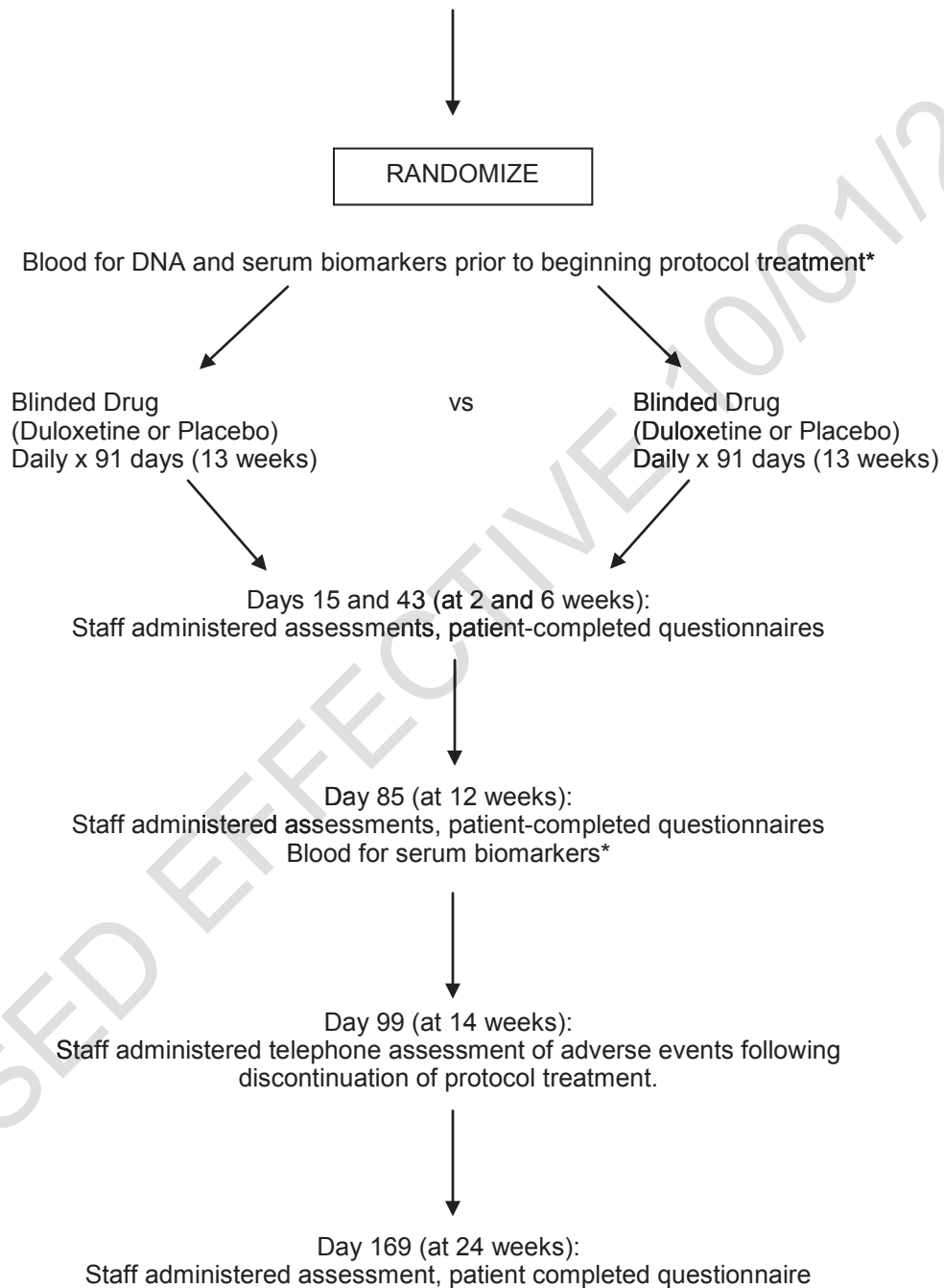
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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	For patient enrollments:	Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:
<p>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103</p> <p>Fax: 215-569-0206</p> <p>Email:</p> <p>CTSURegulatory@ctsu.coccg.org</p> <p>For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.</p>	<p>Please refer to the patient enrollment section for instructions on using the OPEN system.</p>	<p><u>Online Data Submission:</u> This protocol will use Medidata Rave® for electronic data submission. Access Rave® using your active CTEP-IAM userid and password at the following url:</p> <p>https://login.imedidata.com/selectlogin</p> <p><u>Other Tools and Reports:</u> Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url:</p> <p>https://crawb.crab.org/TXWB/ctsulogon.aspx</p>
<p>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://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol.</p> <p>CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.</p>		
<p><u>For patient eligibility questions</u> contact the SWOG Data Operations Center by phone or email:</p> <p>206-652-2267 cancercontrolquestion@crab.org</p> <p><u>For treatment or toxicity related questions</u> contact the Study PI of the Coordinating Group.</p>		
<p><u>For questions unrelated to patient eligibility, treatment, or data submission</u> contact the CTSU Help Desk by phone or e-mail:</p> <p>888-823-5923 ctsucontact@westat.com</p> <p>All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p><u>For detailed information on the regulatory and monitoring procedures for CTSU sites</u> please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website:</p> <p>https://www.ctsu.org</p>		
<p>The CTSU Web site is located at https://www.ctsu.org</p>		

SCHEMA

Women with hormone receptor-positive breast cancer who are receiving AIs and report average pain of at least 4 (out of 10) that has started or increased since initiation of AI treatment



* See [Section 15.1](#) for specimen submission instructions.

1.0 OBJECTIVES

1.1 Primary Objectives

- a. To assess whether daily duloxetine decreases average joint pain in women with aromatase inhibitor-associated musculoskeletal syndrome (AIMSS), as measured at 12 weeks by the modified Brief Pain Inventory Short Form (BPI-SF).

1.2 Secondary Objectives

- b. To assess whether daily duloxetine decreases worst joint pain in women with AIMSS, as measured at 12 weeks by the modified BPI-SF.
- c. To assess whether daily duloxetine decreases pain interference in women with AIMSS, as measured at 12 weeks by the modified BPI-SF.

1.3 Additional Exploratory Objectives

- d. To investigate whether daily duloxetine improves functioning, pain, and stiffness in the knees/hips according to the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) scale;
- e. To investigate whether daily duloxetine improves function, pain and stiffness in the hands according to the Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH);
- f. To investigate whether daily duloxetine improves functional quality of life as measured by the Functional Assessment of Cancer Therapy-Endocrine Scale (FACT-ES);
- g. To investigate whether daily duloxetine improves the proportion of patients reporting changes for the better versus worst as measured by the Global Rating of Change Scale;
- h. To investigate whether daily duloxetine improves/decreases analgesic use;
- i. To investigate whether daily duloxetine improves/increases adherence to, and reduces the discontinuation rate for, aromatase inhibitor (AI) therapy.
- j. To assess whether patients receiving duloxetine as compared to placebo have improved depression as measured by the Patient Health Questionnaire (PHQ-9) at Weeks 6 and 12 (for patients experiencing depression at baseline).
- k. To explore the relationship between inherited variants in genes responsible for duloxetine metabolism and activity (COMT, HTR3A, SLC6A2, SLC6A4, CYP1A2, CYP2D6) and aromatase (CYP19A1) and change in pain with 12 weeks of treatment.
- l. To explore the impact of treatment on serum inflammatory cytokine levels with 12 weeks of treatment at baseline and 12 weeks.
- m. To bank blood samples for future correlative analyses.

2.0 BACKGROUND

Almost 180,000 women are diagnosed with breast cancer each year in the United States. (1) The incidence of breast cancer increases with age; approximately 75% of patients are postmenopausal at the time of diagnosis. In addition, hormone receptors (HR) are over expressed on 80% of breast cancer tumors in postmenopausal women. Therefore, more than 100,000 postmenopausal women who are diagnosed with breast cancer each year in this country are potential candidates for anti-endocrine breast cancer therapy.

Two classes of anti-endocrine therapies are used for treatment of HR-positive breast cancer: tamoxifen and the aromatase inhibitors (AIs). AIs can only be used to treat postmenopausal women because they are ineffective in women with functional ovaries. Because of their superior efficacy, AIs are increasingly used for adjuvant treatment of postmenopausal women with HR-positive breast cancer. Based on currently available data, women are treated with either tamoxifen or AI therapy for 5 years, although studies are underway to determine if treatment should be continued for a longer period of time.

AI-associated Musculoskeletal Symptoms (AIMSS).

Initial studies suggested that AIs are fairly well tolerated medications. However, it has been increasingly recognized that arthralgias are a significant AI-associated toxicity, affecting as many as 50% of patients. (2,3) No factors associated with breast cancer treatment (such as chemotherapy) or co-morbid conditions (such as diabetes or body mass index) have been clearly shown to be predictive of the development of arthralgias. (3) The etiology of AI-associated musculoskeletal symptoms remains elusive. The hypotheses include direct effects of estrogen deprivation on bone, neurohormonal changes which result in change of pain sensitivity, and immune system changes resulting in alteration of circulating or local inflammatory cytokine concentrations.

A greater than 20% treatment discontinuation rate due to AI-associated arthralgias in a prospective trial of AI therapy was reported. (4,5) Based on the number of patients treated with aromatase inhibitor therapy and the incidence of musculoskeletal symptoms that occur with therapy, as many as 40,000 women are affected by this toxicity in the United States annually. More importantly, up to 20,000 women discontinue these potentially life-saving medications because of intolerable arthralgias and myalgias.

No effective pharmacologic therapy has yet been identified for management of these symptoms, as many patients do not experience relief of symptoms with analgesic therapy. The current treatment for AIMSS is limited to oral analgesics and exercise. Neither has optimal effect, and long term use of oral analgesics is problematic. Six weeks of acupuncture therapy has been shown to be beneficial compared to sham acupuncture, but long-term benefit of this treatment is unclear. (6)

Investigators at the University of Michigan recently conducted a Phase II open-label clinical trial of duloxetine in 35 postmenopausal women who had been treated with AI therapy for at least 2 weeks and who developed new or worsening pain after starting AI therapy (details below). This definitive multi-institutional randomized, placebo-controlled Phase III trial is founded upon the positive results of the pilot study.

Duloxetine.

Duloxetine is a selective serotonin- and norepinephrine-reuptake inhibitor (SNRI) which is FDA-approved for the treatment of major depressive disorder (MDD), diabetic peripheral neuropathic pain, generalized anxiety disorder, fibromyalgia, and chronic musculoskeletal pain, including osteoarthritis (OA) and low back pain. (7-14) Small uncontrolled studies have also demonstrated that it is potentially effective for treatment of menopausal symptoms and sleep disturbances. (17,18)

Multiple duloxetine doses and schedules have been studied in these various clinical scenarios. (10,11,13,22) In general, duloxetine 60 mg daily was effective and relatively well tolerated in the majority of trials. Some studies demonstrated improved tolerability with a dose-escalation rather than initiation of treatment at the effective dose. Improvement in pain control occurred rapidly in all studies, which typically demonstrated a partial response within 1 to 2 weeks and near maximal response within 6 weeks. In studies of patients with fibromyalgia, the improvement in BPI average pain score was independent of the presence of major depressive disorder.

A small study demonstrated a possible effect of duloxetine therapy on menopause-related symptoms in women with depression. (18) In the 14 postmenopausal patients with MDD who completed the study, improvement was noted in vasomotor, sleep, and anxiety symptoms. Overall pain and pain interference also improved significantly compared to baseline.

The mechanism of action of duloxetine is not completely understood. Descending noxious inhibitory control (DNIC) is one of several endogenous central nervous system mechanisms involved in the modulation of pain. Attenuated DNIC is believed to reflect altered descending inhibitory pain pathways, and has been consistently observed to be attenuated or absent in approximately two-thirds of patients with chronic pain disorders such as fibromyalgia, compared to approximately 20% of healthy controls. (23-26) In addition, attenuated DNIC is associated with decreased red nucleus activation on functional neuroimaging in fibromyalgia patients as compared to healthy controls. This decreased DNIC activity can lead to increased sensitivity to pain, which is believed to be mediated in part by an attenuated serotonin-norepinephrine system. (27) Therefore, treatment with duloxetine, which inhibits serotonin and norepinephrine reuptake, may augment and restore DNIC in patients with chronic pain, resulting in decreased pain.

Duloxetine for AIMSS.

A Phase II open-label clinical trial of duloxetine in 35 postmenopausal women who had been treated with AI therapy for at least 2 weeks and who developed new or worsening average pain after starting AI therapy that was rated at least 4 on a 10 point Visual Analog Scale was recently conducted at the University of Michigan. (16) Subjects were treated with duloxetine 30 mg daily for one week, and then 60 mg daily for 7 weeks, with the option of increasing the dose to 60 mg twice daily after 3 weeks depending on patient-perceived response to therapy. Benefit from therapy was defined as a 30% decrease in average pain score from baseline to 8 weeks as assessed using the Brief Pain Inventory (BPI).

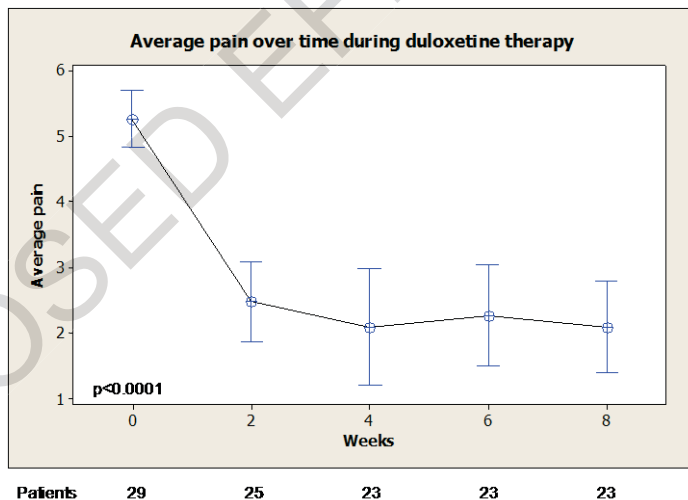


Figure 1. Average pain over time during duloxetine therapy in AI-treated patients. Number of evaluable patients at each timepoint is listed below the graph.

Of the 29 evaluable patients who initiated protocol-directed therapy, 21 (72.4%) experienced the protocol-specified primary endpoint of at least a 30% decrease in average pain score with 8 weeks of therapy, and 16 (55.2%) experienced at least a 50% decrease in average pain score.

The mean percent reduction in average pain from baseline to 8 weeks was 60.9% with a 95% CI of 48.6%-73.1% ([Figure 1](#), [Table 1](#)). Nineteen (65.5%) experienced at least a 30% decrease in worst pain with 8 weeks of therapy, and 17 (58.6%) experienced at least a 50% decrease in worst pain. The mean percent reduction in worst pain from baseline to 8 weeks was 59.9% (95% CI 47.0%-72.7%). Change in interference of pain with activities of daily living as measured using the BPI demonstrated that the mean percent reduction in pain interference with 8 weeks of duloxetine therapy was 78.9% (95% CI 68.1-89.8%). Only 1 subject chose to increase the dose of duloxetine to 60 mg twice daily after 4 weeks of therapy. Eighteen of the 23 patients (78.3%) who completed all 8 weeks of study treatment chose to remain on duloxetine therapy. After completion of study therapy, 3 patients discontinued treatment because of lack of improvement in pain symptoms, and 2 chose to stop therapy because of duloxetine-associated side effects.

Multiple patient-completed questionnaires were utilized to capture information related to changes in pain symptoms (Brief Pain Inventory [BPI] and pain visual analog scale [VAS]), functional status (Health Assessment Questionnaire), depressive symptoms (CES-D), vasomotor symptoms (Hot Flash Related Daily Interference Scale (HFRDIS), Menopause-Specific Quality of Life-Intervention Questionnaire (MENQOL-I)), and sleep quality (Pittsburgh Sleep Quality Index), during the 8 week study period. (28-32) Results suggest that duloxetine therapy leads to improvements in functional status and depression, and may lead to small improvements in hot flashes and sleep.

Safety was assessed in all 34 patients who received at least one dose of study medication. Adverse events and treatment discontinuation rates were similar to previously reported duloxetine studies ([10,11,19,20](#)) Seven patients (20.6%) discontinued therapy due to adverse events. The majority of subjects who discontinued therapy because of adverse events did so within a few days of starting treatment. Reasons for treatment discontinuation included Grade 1 and/or 2 drowsiness, headache, and nausea. The majority of reported adverse events were Grade 1 and/or 2 fatigue and drowsiness, nausea, xerostomia, constipation, and headache, consistent with prior studies of duloxetine, and 76.5% of patients reported at least one adverse event. The only Grade 3 or 4 adverse event reported was tachycardia, thought by the treating physician to be unlikely related to treatment. Since AI therapy acts by suppressing estradiol production, the impact of duloxetine therapy on serum estradiol concentration was assessed. Duloxetine therapy did not affect serum estradiol concentrations in the 23 subjects who completed 8 weeks of treatment.

Table 1. Change in outcome measures with duloxetine therapy (n=29).						
Outcome measure	Baseline	2 weeks	4 weeks	6 weeks	8 weeks	P value ²
Average pain (0-10)	5.5 (1.1) ¹	2.5 (1.5)	2.1 (2.0)	2.3 (1.8)	2.1 (1.6)	<0.0001
Worst pain (0-10)	7.2 (1.4)	3.4 (2.4)	3.1 (2.6)	3.3 (2.0)	2.9 (2.3)	<0.0001
Pain interference (0-10)	4.3 (2.0)	1.6 (1.7)	1.3 (1.7)	1.1 (1.0)	1.0 (1.3)	<0.0001
HAQ (0-3)	0.48 (0.31)	0.20 (0.26)	0.25 (0.33)	0.21 (0.29)	0.23 (0.28)	0.001
Hot flash interference (0-100; HFRDIS)	17.1 (21.9)		10.1 (14.5)		7.0 (12.5)	0.02
Hot flash interference (1-8; MENQOL vasomotor subscale)	2.9 (2.0)		2.2 (1.4)		2.6 (1.7)	0.31
Depression (CESD)	10.1 (8.8)		5.8 (4.7)		3.5 (3.2)	0.004
Sleep (0-21)	8.0 (3.3)		7.8 (4.1)		6.9 (4.0)	0.03
¹ Baseline to 8 weeks columns show mean score (SD)						
² Comparison between baseline and 8 weeks						

Correlative studies.

Identification of patients who are more likely to respond to duloxetine therapy prior to treatment initiation could impact management of AIMSS and could yield additional information regarding the mechanism underlying development of AIMSS. Potential approaches for identifying predictive markers of response to therapy include evaluation of associations with inherited genetic variants in candidate genes and with baseline or change in circulating inflammatory markers.

Inherited genetic variants in genes associated with duloxetine metabolism or activity could potentially influence response to or toxicity from therapy. Alternatively, patients who harbor a specific genetic variant and subsequently develop AIMSS may be more likely to respond to duloxetine. For example, a genetic variant in the COMT gene has been associated with chronic pain, including osteoarthritis and temporomandibular joint disorder. (33) In a study of patients with radiographically-documented arthritis, patients with the high pain sensitivity haplotype of the COMT gene were more likely to develop pain compared to those without that haplotype. (34) Recently, a single nucleotide polymorphism (SNP) in COMT was found to be associated with increased post-surgical pain and fatigue in breast cancer survivors. (35,36) In addition, a different SNP in COMT has also been associated with response to duloxetine and to the related SNRI milnacipran in MDD. (37,38) SNPs in serotonin and norepinephrine transporters have been associated with duloxetine-associated toxicities. (Lilly Pharmaceuticals, unpublished observation) In addition, it has previously been demonstrated that inherited genetic variants in multiple genes, including aromatase and the inflammatory cytokine interleukin-6 (IL-6), may predispose patients to development of AIMSS. (39,40) Finally, in a prospective clinical trial of AI therapy we demonstrated potential associations between SNPs in estrogen receptor alpha and aromatase and the estrogen receptor and discontinuation of AI therapy due to toxicity. (Henry et al, submitted) Therefore, there are a number of genetic variants in candidate genes that may be associated with response to duloxetine therapy in women with AIMSS.

Treatment-associated changes in serum concentrations of inflammatory cytokines have been demonstrated in patients with chronic pain. In addition, a recent study of patients with major depression treated with duloxetine found that serum IL-6 concentrations increased in those patients who responded to therapy. (41) Although there are minimal data to suggest that women with AIMSS have altered levels of circulating inflammatory markers prior to therapy, it is possible that treatment with a medication such as duloxetine could impact serum concentrations of pro- or anti-inflammatory factors, or that subsets of women who have altered levels prior to treatment initiation could be more likely to benefit. Given the paucity of data, however, these investigations would be purely exploratory.

Summary. This is a Phase III randomized, placebo-controlled clinical trial of duloxetine 60 mg daily versus placebo that aims to evaluate the benefit of duloxetine for management of AIMSS and other related symptoms that can impact quality of life, such as depression, anxiety, hot flashes, and sleep quality. We will perform exploratory correlative studies for hypothesis generation. Improvement in treatment-related symptoms may improve persistence with AI therapy, and thereby lead to improved breast cancer outcomes.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below. Aromatase inhibitors are not used in men with breast cancer, so men will not be included in this study.

Ethnic Category			
	Females	Males	Total
Hispanic or Latino	12	0	12
Not Hispanic or Latino	282	0	282
Total Ethnic	294	0	294
Racial Category			
	Females	Males	Total
American Indian or Alaskan Native	6	0	6
Asian	6	0	6
Black or African American	26	0	26
Native Hawaiian or other Pacific Islander	6	0	6
White	250	0	250
Racial Category: Total of all Subjects	294	0	294

3.0 DRUG INFORMATION

3.1 Duloxetine hydrochloride (Cymbalta®) (NSC-744012)

a. PHARMACOLOGY

Mechanism of Action: Duloxetine, a SNRI, is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and a less potent inhibitor of dopamine reuptake.

b. PHARMACOKINETICS

1. Absorption: Orally administered duloxetine is well absorbed. There is a median 2 hour lag until absorption begins (T_{lag}), with maximal plasma concentrations (C_{max}) of duloxetine occurring 6 hours post dose. Food does not affect the C_{max} of duloxetine, but delays the time to reach peak concentration from 6 to 10 hours and it marginally decreases the extent of absorption (AUC) by about 10%. There is a 3 hour delay in absorption and a one-third increase in apparent clearance of duloxetine after an evening dose as compared to a morning dose.
2. Distribution: The apparent volume of distribution averages about 1640 L. Duloxetine is highly bound (>90%) to proteins in human plasma, binding primarily to albumin and α_1 -acid glycoprotein. The interaction between duloxetine and other highly protein bound drugs has not been fully evaluated. Plasma protein binding of duloxetine is not affected by renal or hepatic impairment.
3. Metabolism: Duloxetine undergoes extensive metabolism to numerous metabolites, however the major circulating metabolites have not been shown to contribute significantly to the pharmacologic activity. The major biotransformation pathways for duloxetine involve oxidation of the naphthyl ring by CYP1A2 and CYP2D6 followed by conjugation and further oxidation. Metabolites found in plasma include 4-hydroxy duloxetine glucuronide and 5-hydroxy, 6-methoxy duloxetine sulfate. Many additional metabolites have been identified in urine, some representing only minor pathways of elimination. Only trace (<1% of the dose) amounts of unchanged duloxetine are present in the urine. Most (about 70%) of the duloxetine dose appears in the urine as metabolites of duloxetine; about 20% is excreted in the feces.
4. Elimination: Duloxetine has an elimination half-life of about 12 hours (range 8 to 17 hours) and its pharmacokinetics are dose proportional over the therapeutic range. Steady-state plasma concentrations are typically achieved after 3 days of dosing.

c. ADVERSE EFFECTS

1. Refer to the package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Reactions	> 10%	1% - 10%
Cardiovascular		Palpitation
Central nervous system	Headache Somnolence Fatigue	Insomnia Agitation Anxiety Abnormal dreams Yawning Hypoesthesia Lethargy Vertigo Chills

Dermatologic		Hyperhidrosis
Endocrine & metabolic		Decreased libido Hot flashes Sexual dysfunction
Gastrointestinal	Nausea Xerostomia	Constipation Diarrhea Decreased appetite Abdominal pain Vomiting Dyspepsia Weight loss Flatulence Abnormal taste Weight gain
Genitourinary		Erectile dysfunction Delayed ejaculation Ejaculatory dysfunction
Hepatic		ALT > 3x ULN
Neuromuscular & skeletal		Muscle spasms Tremor Musculoskeletal pain Paresthesia Rigors
Ocular		Blurred vision
Respiratory		Nasopharyngitis Cough
Miscellaneous		Influenza

The following serious or life-threatening adverse reactions occurred in less than 1% of patients: Alkaline phosphatase increased, anaphylactic reaction, angioneurotic edema, apathy, bruxism, contact dermatitis, dehydration, dermatitis, diastolic blood pressure increased, diplopia, disorientation, dysarthria, dyskinesia, dysuria, eructation, erythema, erythema multiforme, EPS, gastritis, gastroenteritis, glaucoma, gynecological bleeding, hallucinations, Hb A_{1c} increased, hepatic failure, hepatitis, hepatomegaly, hyperbilirubinemia, hypercholesterolemia, hyperglycemia, hyperlipidemia, hypersensitivity, hypertensive crisis, hyponatremia, hypothyroidism, jaundice, malaise, mania, MI, micturition urgency, mood swings, muscle spasm, muscle tightness, muscle twitching, night sweats, nocturia, orthostatic hypotension, peripheral coldness, photosensitivity, polyuria, rash, restless leg syndrome, seizure, serotonin syndrome, SIADH, Stevens-Johnson syndrome, stomatitis, supraventricular arrhythmia, syncope, systolic blood pressure increased, tachycardia, thirst, throat tightness, transaminases increased, trismus, urinary retention, urticaria

2. Contraindications: Uncontrolled narrow-angle glaucoma. Estimated creatinine clearance < 30 ml/min.
3. Pregnancy and Lactation: Pregnancy Category C. Duloxetine is excreted into the milk of lactating women. Nursing while on duloxetine is not recommended.

4. **Drug Interactions:** Duloxetine is metabolized by both CYP1A2 and CYP2D6. Refer to the Cytochrome P450 Drug Interaction Tables provided by the Pharmaceutical Management Branch (PMB) available at <http://ctep.cancer.gov/branches/pmb/>. All drugs co-administered with duloxetine should be evaluated for potential drug interactions. Questions should be addressed to the SWOG Study Chair.

CYP1A2 Inhibitors	Do not co-administer with duloxetine.
CYP2D6 Inhibitors	Results in higher concentrations of duloxetine (on average of 60%).
Drugs Metabolized by CYP2D6	Co-administration of duloxetine with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index should be approached with caution.
Warfarin	Carefully monitor when duloxetine is initiated or discontinued due to potential effect of serotonin on platelets.
Monoamine Oxidase Inhibitors (MAOIs)	Co-administration with duloxetine is CONTRAINDICATED . MAOI therapy must be stopped for 14 days before duloxetine is initiated. Treatment with MAOIs should not be initiated until 5 days after the discontinuation of duloxetine.

d. **DOSING & ADMINISTRATION**

1. Dosing – See Treatment Plan in [Section 7.1](#).
2. Administration: Duloxetine should be swallowed whole and should not be chewed or crushed, nor should the capsule be opened and its contents sprinkled on food or mixed with liquids. Duloxetine can be given without regard to meals.
3. Duloxetine should be administered with caution in patients with renal and hepatic impairment.

e. **STORAGE & STABILITY**

Store at room temperature (15°C to 25°C). Do not refrigerate or freeze.

f. **HOW SUPPLIED**

1. Duloxetine or placebo is available as delayed released 30 mg capsules packaged in bottles of 7 or 154 capsules for this study.
2. Duloxetine or placebo is supplied free of charge by Lilly for distribution by Biologics, Inc.
3. **SWOG Institutions:** Upon randomization to the study, SWOG will notify Biologics, Inc. via secure data transmission, including randomization information.

Non-SWOG Institutions: Prior to registering its first patient, the institution must provide Biologics, Inc. with its pharmacy information via e-mail to clinicalresearchservices@biologicsinc.com.

This communication must include the following information:

- Name of institution;
- NCI CODE of institution
- Head CRA name, telephone number and e-mail address;
- Names of all investigators at that institution who are participating in the protocol;
- Name, telephone number and e-mail address of pharmacy contact person;
- Shipping address (street, city, state, zip code/postal code) for pharmacy

These institutions must notify Biologics, Inc. promptly if there is any change in the above information. Once the information is on file at Biologics, Inc., requests for initial supplies of study drug will be automatically generated based on the participant's registration date.

All Institutions: Orders received before 2 p.m. EST Monday through Friday will be processed and shipped for next business day delivery. Orders received after 2 p.m. Monday through Friday will be processed and shipped the next business morning. All shipments will be sent via FedEx for Priority Overnight delivery. Biologics will be closed the following holidays: New Years Eve, New Years Day, Memorial Day, Independence Day, Labor Day, Thanksgiving, Thanksgiving Friday, Christmas Eve, and Christmas Day.

Upon receipt of patient registration and randomization notification, Biologics will:

- Place a call to the study site confirming the order was received, while providing the estimated day and time of arrival for the study drug.
- Prepare shipment of patient-specific drug. Shipments will include 3 bottles (Bottles 1 & 3 will have 7 tablets of 30 mg duloxetine or placebo; Bottle 2 will have 154 tablets of 30 mg duloxetine or placebo) of study drug to cover the 12 week treatment period accompanied by a patient-specific labeled resealable bag.
- Process and ship authorized and completed orders "same day" of order receipt if received before 2:00 p.m. E.T. Monday through Friday. Authorized and completed orders received after 2:00 p.m. E.T. Monday through Friday will be processed and shipped the next business day.
- Each shipment includes a patient label on the resealable bags with the following information:
 - Study Number
 - IND caution statement and/or local regulatory statements
 - Drug identification
 - Expiration date
 - Storage conditions
 - Detailed dosing instructions
 - Subject ID number, initials, and date dispensed

Packages are tracked until confirmed delivered and delivery exceptions are managed with the highest level of urgency to ensure therapy start date adherence. Packing slips with the shipment tracking number will be faxed to the designated site coordinator for all shipments.

- Once study drug is received at the clinical trial site: The designated site coordinator verifies and matches the information on each of the 3 bottles and labeled resealable bag to the packing slip, signs off on the packing slip, and faxes completed form to Biologics to validate shipment has been received and is accurate.
- The site investigators are responsible to fill in the "Date Dispensed" on the label of the resealable bag and each of the study drug bottles prior to dispensing the study drugs to the patient.
- The site investigator should provide instructions to subjects on drug administration, missed dose, adherence, and drug return.

4. Drug Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received using the Investigational Agent Accountability Record for Oral Agents (Oral DARF). The Oral DARF can be found on the NCI home page (<http://ctep.cancer.gov>). A separate Blinded Drug Accountability Record must be maintained for each patient ID number on this protocol. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the Oral DARF.

5. Drug Return and/or Disposition Instruction

- a. Drug Returns: All unused drug (unopened and unused vials remaining when a subject goes off treatment, and expired vials) should be destroyed on-site in accordance with institutional policy and documented accordingly on the DARF. Opened bottles with remaining tablets should be documented in the patient-specific accountability record (i.e., logged in as "# of capsules returned") and destroyed on-site in accordance with institutional policy.
- b. Drug Expiration: If packaging does not have expiration date, check with drug ordering designee and/or PI at site to confirm receipt of ongoing stability testing letter from Lilly when internal drug audits are performed.

6. Questions about drug orders, transfers, returns or accountability should be addressed to Elliott Lee at Biologics, Inc. (800/693-4906 or elee@biologicsinc.com).

3.2 Placebo Information

- a. Placebo pellets (Nu-Pareli sugar spheres) filled into size 1 blue/blue capsugel shells
- b. Stability: Expiration after 60 months.
- c. Storage: Store at room temperature (15°C to 25°C). Do not refrigerate or freeze.

4.0 STAGING CRITERIA

Breast Cancer Staging Criteria, AJCC 7th Edition, 2009

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 not associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted.
T1	Tumor 20 mm or less in greatest dimension
T1mic	Microinvasion 1 mm or less in greatest dimension
T1a	Tumor more than 1 mm but no more than 5 mm in greatest dimension
T1b	Tumor more than 5 mm but not more than 10 mm in greatest dimension
T1c	Tumor more than 10 mm but not more than 20 mm in greatest dimension
T2	Tumor more than 20 mm but not more than 50 mm in greatest dimension
T3	Tumor more than 50 mm in greatest dimension
T4	Tumor of any size with direct extension to chest wall and/or skin (ulceration or skin nodules)
T4a	Extension to chest wall, not including pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Regional Lymph Nodes (N)

Clinical

NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastasis in ipsilateral level I, II axillary lymph nodes fixed or matted, or in clinically detected* ipsilateral internal mammary nodes in the <i>absence</i> of clinically evident axillary lymph node metastasis
N2a	Metastasis in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastasis only in clinically detected* ipsilateral internal mammary nodes and in the <i>absence</i> of clinically evident level I, II axillary lymph node metastasis
N3	Metastasis in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement, or in clinically detected* ipsilateral internal mammary lymph node(s) and in the <i>presence</i> of clinically evident level I, II 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 detected* is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

Distant Metastasis (M)

M0	No clinical or radiographic evidence of distant metastasis
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STAGE GROUPING

Stage IA	T1*	N0	M0
	T0	N1mi	M0
Stage IB	T1*	N1mi	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

** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB

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 record this information on the Onstudy 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.

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 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14, 28, 30, 42 or 90 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 Disease Related Criteria

- _____ a. Patients must be women with histologically confirmed estrogen receptor (ER) and/or progesterone receptor (PgR) positive invasive carcinoma of the breast (Stage I-III) with no evidence of metastatic disease (M0).
- _____ b. Patients must have completed mastectomy or breast sparing surgery, and must have recovered from all side effects of the surgery. If patients were treated with chemotherapy and/or radiation therapy, these treatments must be completed at least 28 days prior to study registration. Patients should have recovered from all Grade 2 or higher side effects of chemotherapy and/or radiation therapy with the exception of alopecia and peripheral neuropathy. Concurrent bisphosphonate and trastuzumab therapies are allowed.

5.2 Clinical/Laboratory Criteria

- _____ a. Patients must be post-menopausal, as defined by at least one of the following:
 - 1. ≥ 12 months since the last menstrual period OR
 - 2. prior bilateral oophorectomy OR
 - 3. previous hysterectomy with one or both ovaries left in place (or previous hysterectomy in which documentation of bilateral oophorectomy is unavailable) AND (unless ≥ 60 years of age) FSH values consistent with the institutional normal values for the post menopausal state OR
 - 4. have been on LHRH agonist therapy for at least 3 months and estradiol levels drawn within 28 days prior to registration are consistent with the institutional normal values for post-menopausal state.
- _____ b. Patients must currently be taking one of the following aromatase inhibitor (AI) doses for at least 21 days prior to registration and plans to continue for at least an additional 180 days after registration. Patients may have received any number of prior AI therapies, but the first AI therapy must have started no more than 36 months prior to registration.
 - 1. anastrozole (Arimidex®) 1 mg daily
 - 2. letrozole (Femara®) 2.5 mg daily
 - 3. exemestane (Aromasin®) 25 mg daily

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

- _____ c. Patients must have aromatase inhibitor (AI) associated musculoskeletal symptoms that began or increased after starting AI therapy. New musculoskeletal pain must not be due specifically to fracture or traumatic injury.
- _____ d. Patients must have completed the **S1202** Brief Pain Inventory-Short Form (BPI-SF) within 7 days prior to registration. Patients must have an "average pain" of at least 4 on the BPI-SF (item #4).
- _____ e. Patients must have Zubrod performance status of 0-2 (see [Section 10.3](#)).
- _____ f. Patients must have no known allergy or hypersensitivity to duloxetine or any of the inactive ingredients in the matching placebo.
- _____ g. Patients must not have any contraindicated concurrent illnesses listed on the duloxetine package insert including:
- Current primary psychiatric diagnosis (schizophrenia, psychosis) or suicidal ideation, history or bipolar disorder, or seizure disorder
 - History of alcohol or other substance abuse or dependence within 365 days prior to registration.
 - Chronic liver disease
 - End stage renal disease
 - Uncontrolled narrow-angle glaucoma
 - Clinically significant coagulation disorder
- _____ h. Patients must not take MAO-Inhibitors for 14 days before registration or any time during study treatment. Concomitant therapy with heparin and warfarin is also not permitted at registration or while on protocol treatment. Aspirin is permitted (see [Section 8.2](#)).
- _____ i. Patients must have a calculated creatinine clearance > 30 mL/min. The serum creatinine value used in the calculation must have been obtained within 28 days prior to registration.
- Calculated creatinine clearance = $\frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85}{72 \times \text{creatinine (mg/dL)}}$
- _____ j. Patients must have adequate hepatic function as evidenced by all of the following within 28 days prior to registration: AST and ALT both within 3 x Upper Limit of Normal based on institutional values, and total bilirubin within the upper limit of normal based on institutional values.
- _____ k. Patients must not require selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants during study participation. Patients must have been able to taper and discontinue treatment with these medications at least 7 days prior to registration (28 days for fluoxetine), and must not be experiencing antidepressant withdrawal symptoms (e.g., dizziness, nausea, sleep disturbance, or other sensory disturbances). **Patients must not have previously taken the serotonin norepinephrine reuptake inhibitors (SNRI) duloxetine or milnacipran.** Prior venlafaxine is allowed as long as it was not taken for treatment of pain (eg, prior treatment for hot flashes is permitted).

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

(Section 5.2k contd.)

NOTE: Patients requiring antidepressants for management of depression are not appropriate candidates for this placebo-controlled study, but those who are on antidepressants for other indications, such as hot flash management, may be able to tolerate a time off of antidepressant therapy.

- _____ l. Patients who are receiving treatment with narcotics, tramadol, gabapentin, and/or pregabalin must have been taking a stable dose for at least 30 days prior to registration.
- _____ m. Patients must be able to complete study questionnaires in English or Spanish.
- _____ n. Patients must not have concurrent medical/arthritis disease that could confound or interfere with evaluation of pain or efficacy including: inflammatory arthritis (rheumatoid arthritis, systemic lupus, spondyloarthropathy, psoriatic arthritis, polymyalgia rheumatica) and cancer involving the bone. Patients with osteoarthritis are eligible.

5.3 Specimen Submission Criteria

- _____ a. Patients must be willing to submit blood samples for correlative studies as outlined in [Section 15.0](#). Baseline samples must be obtained prior to beginning protocol treatment.

5.4 Regulatory Criteria

- _____ a. All patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.
- _____ b. As a part of the OPEN registration process (see [Section 13.3](#) for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

Patient randomization will be dynamically balanced according to the following stratification factors: baseline pain score (BPI-SF item #4) (4-6 vs 7-10); and prior taxane use (yes vs. no).

7.0 TREATMENT PLAN

For treatment or dose modification related questions, please contact Dr. Lynn Henry (norahh@umich.edu) at 734/936-4991, or Dr. Anne Schott (aschott@umich.edu) at 734/936-4991.

7.1 Treatment

Agent	Dose	Schedule
Blinded drug (duloxetine 30 mg or placebo)	1 capsule PO Daily	Days 1-7
Blinded drug (duloxetine 30 mg or placebo)	2 capsules PO Daily	Days 8-84
Blinded drug (duloxetine 30 mg or placebo)	1 capsule PO Daily	Days 85-91

7.2 Study Plan

a. Initial Visit

Before beginning the intervention, patients will have a general physical exam (including recording of weight and height) and a mandatory blood draw for whole blood and serum (see [Section 15.1](#)). The patient will complete the **S1202** Brief Pain Inventory–Short Form (BPI-SF) prior to registration to confirm eligibility (see [Section 5.2d](#)). Patients will complete the following questionnaires prior to beginning treatment with blinded study drug:

S1202 Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index (Version 3.1)

S1202 Modified-Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH)

S1202 FACT – ES Trial Outcome Index (Version 4)

S1202 Patient Health Questionnaire-9 (PHQ-9)

It should take the patient about 20-25 minutes to complete the questionnaires. See [Section 15.2](#) for instructions for administration of the questionnaires.

The nurse or CRA must complete the **S1202** Cover Sheet for Patient-Completed Questionnaires.

Bottle #1 and #2 are dispensed at this visit. Patients will take 1 capsule daily for the first 7 days, then increase the dose to 2 capsules daily. The dose that should be taken each day should be listed on the patient calendar (see [Section 15.2c.1](#)).

b. Follow-up Visits

Follow-up visits will occur on Day 15, 43, 85, and 169 after start of treatment. Drug adherence will be ascertained by the nurse or CRA by review of the patient completed **S1202** Intake Calendar on Day 15, 43, and 85, as well as count of blinded drug capsules on the Day 43 and 85 visits. After the Day 85 pill count, the nurse or CRA must dispense bottle #3 to the patient to complete the Day 85 to Day 91 taper. Counts of blinded drug capsules remaining should be recorded on the **S1202** Treatment Form and the patient's medical record through the Day 85 visit. Adherence to AI should be recorded on the **S1202** Treatment Form at every visit. Adverse events will be assessed and recorded on the **S1202** Adverse Event Summary Form through the Day 85 visit. Use of pain medications, steroids, physical therapy, and acupuncture will be recorded on the **S1202** Supplemental Agents Reporting Form.

The nurse or CRA will contact the patient by telephone on Day 99 to assess adverse events following study drug discontinuation. Adverse events will be recorded on the **S1202** Adverse Event Summary Form

Patients will be instructed to complete the following questionnaires at the Day 15, 43, 85, and 169 visits. It takes about 20-25 minutes to complete the questionnaires.

S1202 Brief Pain Inventory Short Form (BPI-SF)

S1202 Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index (Version 3.1)

S1202 Modified-Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH)

S1202 FACT – ES Trial Outcome Index (Version 4)

S1202 Global Ratings of Change in Joint Pain and Stiffness

Patients will also be instructed to complete the following self-administered questionnaire at the Day 43 and 85 visits. It takes about 5-10 minutes to complete the assessment.

S1202 Patient Health Questionnaire-9 (PHQ-9).

The nurse or CRA will also complete the **S1202** Cover Sheet for Patient-Completed Questionnaires at each visit to indicate whether or not the patient completed the questionnaires, if the patient required assistance and the method for completing the questionnaires. If one or more of the questionnaires was not completed, an overall reason must be indicated on the Cover Sheet. See [Section 15.2](#) for detailed instructions for administration of the questionnaires.

Additionally, at the Day 85 visit, blood will be drawn for serum biomarkers (see [Section 15.1](#)).

All patients must taper off study drug after the Day 85 visit by decreasing the dose to 1 capsule daily for 7 days. After completing the taper of the study drug, if a patient wishes to take commercially-available duloxetine, she should take at least 7 days of duloxetine 30 mg daily prior to increasing the dose to 60 mg daily, in order to minimize the chance of developing side effects. She is permitted to start this at any time following completion of the taper of the study drug (Day 92).

7.3 Drug Compliance Documentation

Drug compliance will be recorded by patients in the Intake Calendar (see [Appendix 18.2](#)). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each visit. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking patient compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.4 Criteria for Discontinuation from Protocol Intervention

- a. Evidence of new cancer (except for basal squamous skin cancer or in situ cervical cancer) or cancer recurrence at any time.*
- b. Unacceptable toxicity.*
- c. Delay of study drug for any reason > 28 days.
- d. Completion of 13 weeks of treatment.
- e. Discontinuation of AI therapy or change to a different aromatase inhibitor medication during protocol treatment.* (Note: a delay of 28 days or more will be considered discontinuation of AI therapy.)
- f. The patient may withdraw from the study at any time for any reason.*

* If a patient is taking 2 capsules of blinded study drug daily and discontinues therapy prior to the Day 85 visit, she should decrease the dose to 1 capsule daily for 7 days prior to permanently stopping the blinded study drug. If a patient goes off protocol intervention for any reason before the Day 85 visit, the **S1202** Supplemental Agents Reporting Form and the patient questionnaires required at each subsequent visit should continue to be administered according to the protocol assessment schedule. See [Section 14.4i](#) for off protocol intervention data submission requirements.

7.5 Discontinuation of Treatment

All reasons for discontinuation of intervention must be documented in the Off Treatment Notice – Prevention Studies.

7.6 Follow-Up Period

No further follow-up will be required once the patient completes 24 weeks of study participation.

7.7 Unblinding

Patients may be unblinded to their treatment assignment on request at the end of the study, after follow-up for all patients is complete. Institutions will be notified when patient unblinding information is available for the study. For emergency unblinding criteria and procedures, see [Section 18.3](#).

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

The CTEP Version 4.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE), will be utilized for AE reporting. The CTEP 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 CTEP Version 4.0 of the CTCAE.

8.2 General Considerations

Patients who are taking narcotics, tramadol, gabapentin, and/or pregabalin at study registration should continue to take a stable dose of medication or should decrease their dose during study participation, as tolerated. Dose increases for these medications should be discouraged.

Patients who need additional analgesic medication during study participation are requested to take acetaminophen. Patients should not undergo therapy with other treatment modalities such as physical therapy, acupuncture, systemic steroids, or intra-articular steroid injections during study participation unless medically necessary. Usage of all medications and other therapies for treatment of pain should be documented on the **S1202** Supplemental Agents Reporting Form.

Caution should be taken if patients take aspirin or non-steroidal anti-inflammatory drugs during study participation because of the increased risk of bleeding when these medications are used in combination with duloxetine.

Caution should be taken if patients take triptan medications, tramadol, linezolid, or other serotonergic medications during study participation because of the increased risk of serotonin syndrome when these medications are used in combination with duloxetine.

Duloxetine has been associated with an increased risk of suicide. Therefore, at the day 43 and 85 study visits, the answer to question #9 on the PHQ-9 should be reviewed before the patient leaves the clinic. In addition, all patients should be asked about suicidal thoughts or actions at the Day 15 study visit and Day 99 telephone call. If a patient reports suicidal thoughts or actions, or answers anything other than "Not at all" to question #9, the treating physician should be immediately notified.

NOTE: Concomitant therapy with heparin and warfarin is not permitted while on study treatment.

8.3 Dose Modifications

Grade 1 and Grade 2 Toxicity

If Grade 1 or 2 toxicities occur that are felt to be possibly, probably, or definitely related to study drug, monitor as needed until problem has resolved (i.e., Grade 0), stabilized (i.e., remains as Grade 1 or Grade 2), or is otherwise explained. If Grade 1 or Grade 2 symptoms persist, the local SWOG investigator will assess whether symptom management should be initiated, or whether the dose should be reduced from 2 capsules per day to 1 capsule per day. If Grade 1 or 2 symptoms persist while taking 1 capsule per day, the local SWOG investigator will assess whether symptom management should be initiated (if that has not already been done), or whether the patient should be removed from protocol treatment. No dose re-escalations are allowed. Follow-up will be conducted at the intervals specified in the protocol.

Grade 3 or Grade 4 Toxicity

If a patient develops any Grade 3 toxicity possibly, probably, or definitely related to the study drug, the patient should decrease the dose to 1 capsule daily for 7 days (if deemed medically safe to do so). If the symptoms resolve to Grade 0-2, the dose should be continued at 1 capsule per day. This dose may be maintained if Grade 3 toxicity does not recur. If at the 1 capsule a day dose the participant is still experiencing problems, she can be given a 1 week drug holiday from the blinded study drug. Subsequently, the patient may be re-challenged at the 1 capsule per day dose. Follow-up will continue at the intervals specified in the protocol. If symptoms do not recur (i.e., if symptoms resolve to Grade 0), the dose should be maintained, and no dose re-escalations are allowed. If Grade 3 drug-related toxicity does not improve to a Grade 0, 1, or 2 level within 1 week at the reduced dose, the patient should be removed from all protocol treatment. If the patient develops any Grade 4 toxicity possibly, probably, or definitely related to the study drug, the patient should decrease the dose to 1 capsule daily for 7 days (if deemed medically safe to do so) and then be removed from protocol treatment. Patient will also be removed from protocol treatment if there is a delay of study intervention >28 days.

8.4 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Lynn Henry at 734/936-4991 (norahh@umich.edu), or Dr. Anne Schott at 734/936-4991 (aschott@umich.edu).

8.5 Adverse Event Reporting

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 Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

	α		\dagger		π		γ		δ	
	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk
REQUIRED STUDIES	0	1	2	3	4	5	6	7	8	9
	D	D	D	D	D	D	D	D	D	D
PRE STUDY	1	8	15	22	29	36	43	50	57	64
PHYSICAL										
History *										
Physical Exam (Height, Weight and Performance Status)										
Toxicity Assessment			X				X			X
Drug Compliance (Intake calendar, pill count & AI adherence)			X				X			
Assessment of suicidality δ			X				X			X
LABORATORY										
FSH (if necessary)										
AST/ALT										
Total bilirubin										
Serum creatinine										
PATIENT COMPLETED QUESTIONNAIRES Σ										
S1202 BPI-SF			X				X			X
S1202 WOMAC		X	X				X			X
S1202 M-SACRAH		X	X				X			X
S1202 FACT-ES		X	X				X			X
S1202 Global Ratings of Change in Joint Pain and Stiffness			X				X			X
S1202 PHQ-9		X					X			X

Calendar continued on next page.
Click here to see [footnotes](#).

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org). Forms submission guidelines may be found in [Section 14.0](#).

NOTE: Timing of the follow-up assessments are based on the start date of protocol treatment.



Footnotes

- α Patient reported questionnaires and blood draw must be completed prior to starting blinded drug.
- Ω On Day 15, review only the intake calendar and record AI adherence in the patient record. Do not perform pill count. See [Section 7.2b](#).
- δ Adverse events will be collected on the phone call. Report adverse events on the **S1202** Adverse Event Summary Form. Phone call must be completed within +/- 2 days from Day 99.
- ≠ [See Section 15.1](#).
- † Assessments must be completed during Day 15-21.
- π Assessments must be completed during Day 40-46.
- ✓ Assessments must be completed during Day 79-85.
- ✕ Assessments must be completed within +/- 7 days from Day 169.
- β After the pill count, return enough pills to the patient to complete the Day 85-91 taper. See [Section 7.2b](#).
- Σ Administer questionnaires at the scheduled assessments even if the patient goes off protocol treatment prior to Day 85 for any reason. **S1202** Cover Sheet for Completed Questionnaires must be completed and included with the submission of patient questionnaires. See [Section 7.2](#) and [15.2](#).
- ο Patient is to take study drug daily. See [Section 7.1](#).
- * A statement that musculoskeletal symptoms started or worsened since initiation of adjuvant AI therapy must be documented in the patient's medical record at prestudy.
- ~ Must be performed within 28 days prior to registration.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Primary Outcome

Reduction in average joint pain according to the Brief Pain Inventory – Short Form (BPI-SF) average pain score (item #4). This item has a scale of 0 to 10 with 0 indicating “No pain” and 10 indicating “Pain as bad as you can imagine” (assessed at Weeks 2, 6 and 12).

10.2 Main Secondary Outcome

Reduction in worst joint pain according to the BPI-SF worst pain score (item #2) at 12 weeks. This item has a scale of 0 to 10 with 0 indicating “No pain” and 10 indicating “Pain as bad as you can imagine”.

10.3 Performance Status

Participants will be graded according to the Zubrod performance status scale.

<u>POINT</u>	<u>DESCRIPTION</u>
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 Primary Objective

Joint pain will be assessed using “average pain” according to the BPI-SF. Enrollees must currently be taking AIs and must exhibit joint pain with a minimum BPI-SF average pain score of 4; scores of 4 to 10 are considered to reflect moderate to severe pain. (42) Patients will be stratified at randomization by the use of average baseline pain according to the BPI (4-6 vs 7-10) and prior taxane use (yes vs. no). The primary assessment time of 12 weeks, upon which power calculations are based, corresponds to completion of the intervention and allows cross-trial comparisons to be made with S0927, which is evaluating a different pharmacologic agent for treatment of AIMSS in the same patient population.

This study stipulates an $\alpha=0.05$ two-sided test, with an estimated 5% non-adherence (reducing the nominal effect size) and 15% dropout rate (increasing the total required sample size) at 12 weeks after randomization. (16, 43) In addition, the design will

incorporate a 10% contamination rate (which also reduces the nominal effect size) based on the assumption that a portion of the patients will not benefit from intervention based on joint pain with a different etiology that is not associated with AI treatment (this has a similar impact on power calculations as a “drop-in” rate).[\(44\)](#)

The proposed sample size incorporates adjustments for loss, non-adherence, and contamination. The power for the design will be a function of the difference detected and the standard deviation at 12 weeks after randomization.

Difference Detected: Although a difference of 2 points in the BPI has been identified as representing a clinically meaningful *individual* level difference, for power calculations assessing group-level differences, we will test a smaller effect. [\(45\)](#) Specifically, an incremental difference in pain reduction due to duloxetine over placebo of about 1.0 points at 12 weeks has been repeatedly found in the setting of fibromyalgia. [\(43,46\)](#)

Standard Deviation: Multiple studies of AI-induced joint pain have found the standard deviation for BPI “average pain” at follow-up on placebo to be about 2.0 to 2.5 points. [\(47,8\)](#) The design assumes a common standard deviation between arms; a similar standard deviation has been observed in a pilot study of duloxetine. [\(16\)](#) We assume a SD of 2.3 points at 12 weeks for this study (the estimated average SD found in Arnold, Clin J Pain, 2009). [\(8\)](#)

For a 1.0 point difference and a 2.3 point SD at 12 weeks, with other parameters as specified above, 270 eligible patients would be required for 80% power under a two-arm normal design. Power will be higher with lower observed standard deviation or a larger observed difference.

The following considerations clarify the impacts of loss, non-adherence, and contamination on the sample size calculations:

- A two-arm normal design with $\alpha=.05$ two-sided test and a 2.3 point SD to detect a difference of 1.0 points requires approximately 166 patients (83 per arm) for 80% power.
- An estimated 5% non-adherence and 10% contamination both reduce the nominal effect size, from 1.0 points to 0.85 points. This increases the required sample size to 230 total patients (115 per arm).
- To account for an estimated 15% dropout rate, the total required sample size must be further increased by 15%, as in $230/0.85 = 270$ total patients.

The primary analysis will rely on longitudinal measures of BPI at Weeks 2, 6, and 12 for improved power. (Thus the proportion of patients with zero follow-up observations will likely be less than the specified 5% non-adherence and 15% dropout at 12 weeks used for power calculations.) Assessment windows of +/- 7 days, +/- 14 days, and +/- 14 days will be allowed for the 2, 6, and 12 week timepoints. (Given the primary analysis is based on longitudinal measures, a sensitivity analysis will consider all observations within 14 weeks of registration.) The analysis will be performed using mixed models, adjusted for baseline average pain and the stratification factors. To minimize missed assessments, SWOG utilizes an electronic system to remind institutions in real-time that patients are due for follow-up assessment. If the proportion of missing follow-up data is >20% (the sum of the specified targets for non-adherence and dropout), plots of mean pain levels over time for patients grouped by number of follow-up responses will be examined to check for patterns of informative missing data. Should these plots suggest that data may not be missing at random, pattern mixture models, which models missingness patterns through stratification, will be utilized for analysis of the longitudinal BPI pain data. [\(48, 49\)](#)

Under the intention-to-treat principle, the primary analysis will be based on all eligible, randomized patients. To allow for an ineligibility rate of 8%, as found on our recent Symptom Control study [S0715](#), a total of 294 patients will be enrolled to achieve 270 eligible patients.

11.2 Accrual Monitoring

Accrual is expected to be rapid given the common use of AIs for adjuvant therapy in postmenopausal women with breast cancer. Allowing for 6 months ramp-up and IRB approval time, accrual of 15 patients/month would allow completion of the study in approximately 2 years. Accrual will be assessed at 1.5 years after study activation. If monthly average accrual in quarters 5-6 after study activation is < 50% of projected accrual, efforts will be made to increase accrual over the succeeding 6 month period. If after 2 years, monthly accrual remains < 50% of projected accrual, study revision will be considered.

11.3 Secondary Endpoints

The following secondary analyses will be conducted:

- a. Multiple linear regression analyses of the individual assessment timepoints will be conducted to identify potential critical effectiveness timepoints and to allow comparisons to other studies. These analyses will include the baseline score (as a covariate) as well as the pre-specified stratification factors.
- b. At weeks 2, 6, and 12, we will investigate whether duloxetine 60 mg daily:
 1. Decreases worst joint pain according to the BPI.
 2. Improves functioning, pain, and stiffness in the knees/hips according to the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) scale. Differences between the two study arms of at least two points on the WOMAC Index are of interest. [\(50, 51\)](#) We will also evaluate clinically meaningful change for the WOMAC Index with respect to the $\frac{1}{3}$ to $\frac{1}{2}$ standard deviation during the study period of 12 weeks.
 3. Improves function, pain and stiffness in the hands according to the Modified Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH). Differences between the two study arms of at least two points on the M-SACRAH are of interest. [\(50, 51\)](#) We will also evaluate clinically meaningful change for the M-SACRAH with respect to the $\frac{1}{3}$ to $\frac{1}{2}$ standard deviation during the study period of 12 weeks.
 4. Improves functional quality of life as measured by the Functional Assessment of Cancer Therapy-Endocrine Scale (FACT-ES). [\(52, 53\)](#) Trial Outcome Index (TOI). Clinically meaningful change in FACT-ES TOI scores will also be based on $\frac{1}{3}$ to $\frac{1}{2}$ of a standard deviation. [\(53-55\)](#)
 5. Improves the proportion of patients reporting changes for the better versus worst as measured by the Global Rating of Change Scale. The GRCs for joint pain and for joint stiffness will be used to identify patients who report they are worse (combining scores of -1 through -3), the same score (score of 0), or better (combining scores of +1 through +3) since the last time they completed the questionnaire. [\(54-56\)](#) Mean scores for the WOMAC Index, BPI, M-SACRAH, and FACT-ES TOI will be compared for groups based on those patients who select “a little better” and “a little worse” on the GRC ratings to identify minimally important change. [\(54-56\)](#)

6. Reduces depression as measured by the Patient Health Questionnaire (PHQ-9). Differences between the two arms of at least five points on the PHQ-9 at 12 weeks will be of interest. (57) Clinically meaningful change in PHQ-9 scores will also be based on $\frac{1}{3}$ to $\frac{1}{2}$ of a standard deviation. (57)
 7. Decreases analgesic use.
 8. Increases adherence to, and reduces the discontinuation rate for, AI therapy.
 9. Affects measures of pain interference.
 10. Reasons for treatment discontinuation will also be described.
- c. Interaction tests between treatment and stratification variables will be conducted to explore whether these factors are predictive of average pain scores.
 - d. A logistic regression analysis of responders will be conducted, where a response to intervention is defined as a reduction of 2 or more points in average pain according to the BPI. (50)
 - e. In addition, we will explore the relationship between the severity of arthralgias and degree of benefit from therapy in each of the treatment groups and inherited variants in genes responsible for duloxetine metabolism and activity (COMT, HTR3A, SLC6A2, SLC6A4, CYP1A2, CYP2D6) and aromatase (CYP19A1). Finally, we will explore the relationship between baseline and change in serum inflammatory cytokine levels with 12 weeks of treatment and the degree of benefit from therapy in each of the treatment groups.

For linear scales, secondary endpoints will be analyzed using multiple linear regression analyses including the baseline score as a covariate and the pre-specified stratification factors. For binary outcomes, logistic regression will be used.

11.4 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 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 6 months from the SWOG 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. Given the anticipated rapid accrual to this protocol (≤ 2 years total), insufficient data will be available while the study is still accruing to conduct an interim analysis. Thus no formal interim analysis is planned.

12.0 DISCIPLINE REVIEW

There will be no formal discipline review for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than five working days prior to planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. 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 Web site (enter credentials at <https://www.ctsu.org>; then click on the Register tab) or by calling the PMB at 240/276-6575 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinic 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 by entering credentials at <https://www.ctsu.org>.

Requirements for site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

- a. Institution CTEP ID
- b. Protocol Number
- c. Registration Step
- d. Treating Investigator
- e. Cooperative Group Credit
- f. Credit Investigator
- g. Patient Initials
- h. Patient's Date of Birth

- i. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)
- j. Country of Residence
- k. ZIP Code
- l. Gender (select one):
 - Female Gender
 - Male Gender
- m. Ethnicity (select one):
 - Hispanic or Latino
 - Not Hispanic or Latino
 - Unknown
- n. Method of Payment (select one):
 - Private Insurance
 - Medicare
 - Medicare and Private Insurance
 - Medicaid
 - Medicaid and Medicare
 - Military or Veterans Sponsored NOS
 - Military Sponsored (Including Champus & Tricare)
 - Veterans Sponsored
 - Self Pay (No Insurance)
 - No Means of Payment (No Insurance)
 - Other
 - Unknown
- o. Race (select all that apply):
 - American Indian or Alaska Native
 - Asian
 - Black or African American
 - Native Hawaiian or other Pacific Islander
 - White
 - Unknown

13.4 Registration procedures

- a. All site staff will use OPEN to enroll patients to this study. OPEN is a web-based application and can be accessed at <https://open.ctsu.org>, or from the OPEN tab on the CTSU members' side of the website at <https://www.ctsu.org>, or from the OPEN Patient Registration link on the SWOG CRA Workbench.
- b. Prior to accessing OPEN site staff should verify the following:
 - All eligibility criteria have been met within the protocol stated timeframes. Site staff should refer to [Section 5.0](#) to verify eligibility.
 - All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.
- To perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

- d. Further instructional information is provided on the **OPEN** tab on the CTSU members' side of the website at <https://www.ctsu.org> or at <https://open.ctsu.org>. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctscontact@westat.com.

13.5 Exceptions to SWOG 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.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

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

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see [Section 14.3a](#) for details.

14.3 Data Submission Procedures

- a. SWOG institutions must submit data electronically via the Web using Medidata Rave® at the following url:

<https://login.imedidata.com/selectlogin>

1. If prompted, select the 'CTEP-IAM IdP' link.
2. Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU members' web site and OPEN.

- b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (<http://swog.org>) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG 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,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view 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 difficulties with the CRA Workbench, please email technicalquestion@crab.org.

- c. Institutions participating through Cancer Trials Support Unit (CTSU) please refer to the CTSU Participation Table on [Page 4](#).

14.4 Data Submission Overview and Timepoints

- a. AFTER REGISTRATION BUT PRIOR TO BEGINNING PROTOCOL TREATMENT:

Submit baseline whole blood for DNA and blood for serum biomarkers as outlined in [Section 15.1](#). The SWOG Specimen Tracking System must be used for specimen submission.

- b. WITHIN 7 DAYS OF REGISTRATION:

Submit the following:

S1202 Onstudy Form

S1202 Cover Sheet for Patient-Completed Questionnaires

S1202 Brief Pain Inventory Short Form (BPI-SF)

S1202 Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index (Version 3.1)

S1202 Modified-Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH)

S1202 FACT-ES Trial Outcome Index (Version 4)

S1202 Patient Health Questionnaire-9 (PHQ-9)

Institutional surgical pathology report to confirm diagnosis of ER/PgR status

c. WITHIN 14 DAYS OF DAY 15, 43, 85 STUDY ASSESSMENTS:

Submit the following:

S1202 Treatment Form

S1202 Adverse Event Summary Form

S1202 Supplemental Agents Reporting Form

S1202 Cover Sheet for Patient-Completed Questionnaires

S1202 Brief Pain Inventory Short Form (BPI-SF)

S1202 Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index (Version 3.1)

S1202 Modified-Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH)

S1202 FACT-ES Trial Outcome Index (Version 4)

S1202 Global Ratings of Change in Joint Pain and Stiffness

d. WITHIN 14 DAYS OF DAY 43 AND 85 ASSESSMENTS:

In addition to the forms listed in [Section 14.4c](#), submit the **S1202** Patient Health Questionnaire-9 (PHQ-9)

e. WITHIN 14 DAYS OF DAY 85 ASSESSMENT:

In addition to the forms listed in [Sections 14.4c](#) and [14.4d](#), submit the **S1202** Patient Treatment Satisfaction Form

f. AT THE DAY 85 STUDY ASSESSMENT:

Submit blood for serum biomarkers as outlined in [Section 15.1](#). The SWOG Specimen Tracking System must be used for specimen submission.

g. WITHIN 14 DAYS OF THE DAY 99 TELEPHONE CALL TO PATIENT:

Submit the **S1202** Adverse Event Summary

h. WITHIN 14 DAYS OF THE DAY 169 FINAL STUDY ASSESSMENT:

Submit the following:

S1202 Supplemental Agents Reporting Form

S1202 Cover Sheet for Patient-Completed Questionnaires

S1202 Brief Pain Inventory Short Form (BPI-SF)

S1202 Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index (Version 3.1)

S1202 Modified-Score for the Assessment and Quantification of Chronic Rheumatoid Affections of the Hands (M-SACRAH)

S1202 FACT-ES Trial Outcome Index (Version 4)

S1202 Global Ratings of Change in Joint Pain and Stiffness

i. WITHIN 14 DAYS OF REMOVAL FROM PROTOCOL INTERVENTION:

Submit the following:

Off Treatment Notice-Prevention Studies

Final **S1202** Treatment Form

Final **S1202** Adverse Event Summary

Final **S1202** Supplemental Agents Reporting Form

NOTE: If the patient goes off protocol intervention prior to Day 91 for any reason (see [Section 7.4](#)), the **S1202** Supplemental Agents Reporting Form and the patient-completed questionnaires should continue to be administered according to the protocol assessment schedule.

j. WITHIN 14 DAYS OF A DIAGNOSIS OF NEW OR RECURRENT CANCER OCCURRING UP TO DAY 169 ASSESSMENT:

Submit the Follow-up Form.

NOTE: If the patient was on protocol intervention at the time of new or recurrent cancer diagnosis then also submit the forms listed in [Section 14.4i](#).

k. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH OCCURRING UP TO 168 DAYS AFTER REGISTRATION:

If patient was on **S1202** protocol intervention, submit:

Notice of Death documenting death information

S1202 Treatment Form

S1202 Adverse Event Summary

S1202 Supplemental Agents Reporting Form

If patient was off **S1202** protocol intervention, submit:

Notice of Death documenting all death information

15.0 SPECIAL INSTRUCTIONS

15.1 Correlative Studies and Banking

Specimens for correlative studies and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) (required for patient):

- a. Specimens must be submitted at the following times ** (see [Section 9.0](#)):
 1. 6 cc of whole blood for DNA at baseline*
 2. 10 cc of blood for serum at baseline* and Day 85

* Baseline specimens must be obtained after registration, but before the start of protocol treatment.

** With patient consent, leftover specimens will be banked for future unknown use.
- b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (<http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp>), or via the link on the **S1202** protocol abstract page on the SWOG website (www.swog.org).
- c. Specimen collection kits are not being provided for this study; sites will use institutional supplies.

15.2 Patient Questionnaires: Instructions for Administration

- a. It is important to note that the time frame for providing ratings differs depending on the scale the patient is completing. The **S1202** BPI-SF, **S1202** WOMAC Index, **S1202** M-SACRAH, **S1202** FACT-ES TOI, and **S1202** PHQ-9 should be rated with respect to the past 7 days. The **S1202** Global Ratings of Change in Joint Pain and Joint Stiffness are answered with respect to the last time the patient filled out the questionnaire.

If treatment is delayed for any other reason, the assessment schedule for the Day 15, 43, 85, and 168 assessments should be defined from the treatment start date.

- b. Administration of Questionnaires
 1. The first time the patient completes the questionnaires: Please read to the patient the instructions attached to each patient questionnaire. Explain the specific administration times for this protocol. Patients should be directed to report all symptoms and limitations whether or not they are related to the cancer or its treatment.
 2. It is permissible to assist patients with completing the questionnaires being careful not to influence the patient's response. Note on the **S1202** Cover Sheet for Patient-Completed Questionnaires what assistance was required and indicate reason (e.g., elderly, too sick, etc.). Discourage family members from: 1) being present while the patient completes the questionnaire and/or 2) influencing patient responses to the questions.
 3. It is very important to review the questionnaires after the patient has completed them to be sure all of the questions have been answered and that only one answer is marked. a) If the patient has marked more than one answer per question, ask the patient which answer reflects how she is feeling. b) If the patient has skipped a question, tell the patient that a question was not answered and ask if she would like to answer the question. Always give the patient the option to refuse. Indicate on the form by the question that the patient did not want to answer this question.

4. If a patient refuses or cannot complete the questionnaire for some reason, then this must be documented on the **S1202** Cover Sheet for Patient Completed Questionnaires and submitted to the Data Operations Center in Seattle (see [Section 14.3](#)).
 5. If a patient misses an appointment or is too sick to complete the questionnaires on the scheduled date, the questionnaire can be mailed to the patient or sent home with her. A telephone interview must be scheduled and completed within one week of the originally scheduled time. Patient responses to questionnaire items are to be obtained during the telephone interview while the patient is looking at her copy of the questionnaire.
- c. Additional quality control procedures:
1. When a patient is registered on **S1202**, a calendar should be made with dates of upcoming patient-completed questionnaires noted. A copy of this calendar can be given to the patient with the notation that the questionnaires should be completed before receiving treatment. You may wish to photocopy the Study Calendar, [Section 9.0](#), and include the patient's name and specific dates. A copy of this should be kept in the patient file.
 2. If a patient goes off study intervention prior to the protocol-defined end of intervention at 85 days, administer the patient-completed questionnaires according to the protocol-defined assessment schedule (timed from the treatment start date).
 3. If a patient refuses or cannot complete the patient questionnaires at one time point, she should be asked to do so at the next scheduled administration time. Submit the **S1202** Cover Sheet for Patient-Completed Questionnaires documenting the reason why the questionnaires were not done.
 4. Anyone involved in the collection of quality of life data in SWOG trials should review the training program available on the SWOG website accessible from three locations. On the SWOG Home Page (prior to member login), in the **QUICKLINKS** section on the bottom right corner of the page, there is a link to the Patient Reported Outcomes Training. The other two locations that the training is available are after SWOG member login on the CRA Workbench. The Training section and the New CRAs! Section both contain access to the Patient Reported Outcomes (PROs) training module. The training program is a narrated set of slides designed to standardize the way quality of life data is collected from patients. Questions regarding the quality of life assessments can be addressed to Dr. Henry (734/936-4991) or the SWOG Data Operations Office (206/652-2267).
- d. **S1202** Cover Sheet for Patient-Completed Questionnaires
- For each time point, the nurse or CRA completes the **S1202** Cover Sheet for Patient-Completed Questionnaires. The Cover Sheet is submitted with the set of patient-completed forms at each scheduled assessment. The Cover Sheet is very important for tracking how and when the patient forms were completed. When a patient-completed form is not administered at a scheduled time point, it

is important to know why the assessment did not occur; the form includes potential reasons for a patient not completing a form. See [Section 14.0](#) for data submission guidelines.

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).

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.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

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 18.1](#) for general and background information about expedited reporting.

b. Reporting method

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). The NCI's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

In the rare event when internet connectivity is disrupted an electronic report MUST be submitted immediately upon re-establishment of internet connection.

- c. When to report an event in an expedited manner

When the adverse event requires expedited reporting, submit the report within 10 calendar days of learning of the event.

- d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

- e. Expedited reporting for commercial agents

Commercial reporting requirements are provided in [Table 16.1](#). The commercial agent used in this study is duloxetine. 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 Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1. Expedited reporting requirements for adverse events experienced by patients on study within 30 days of the last administration of the commercial agent. The agent used in the study is commercial agent.

ATTRIBUTION	Grade 4		Grade 5 ^a	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			CTEP-AERS	CTEP-AERS
Possible, Probable, Definite	CTEP-AERS		CTEP-AERS	CTEP-AERS
CTEP-AERS: Indicates an expedited report is to be submitted via NCI CTEP-AERS within 10 calendar days of learning of the event ^b .				
^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 within 5 calendar days by fax to 210-614-0006.				

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18.0 APPENDIX

- 18.1 Determination of Expedited Adverse Event Reporting Requirements
- 18.2 **S1202** Intake Calendar
- 18.3 Guidelines for Emergency Unblinding of Coded Drug
- 18.4 IND Exemption Let

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18.1 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 16.1.](#)

All serious adverse events determined to be reportable to the Institutional Review Board responsible for the oversight of the patient must be reported according to local policy and procedures. Documentation of this reporting should be maintained for possible inspection during quality assurance audits.

Steps to determine if an adverse event is to be reported in an expedited manner
(This includes all events that occur while on treatment or within 30 days of the last dose of protocol treatment.)

Step 1: Determine whether the patient has received an investigational agent, commercial agent, or a combination of investigational and commercial agents.

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 with sequential administration all expedited reporting of adverse events should follow the guidelines for the type of agent being given. For example, if the patient begins the study on the investigational agent(s), then all expedited reporting of adverse events should follow guidelines for the investigational agent(s). Once the patient begins receiving the commercial agent(s) then all expedited reporting of adverse events should follow the guidelines for commercial agent(s).

Step 2: 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.

Step 3: Grade the event using the NCI CTCAE version specified in the protocol for reporting serious adverse events.

Step 4: Determine if the adverse event is Expected or an Exception to Expedited Reporting. **Expected** events are those that have been previously identified as resulting from administration of the agent and are listed in one of the following:

- The current NCI SPEER (Specific Protocol Exceptions to Expedited Reporting) for treatments using agents provided under an NCI-held IND, or an equivalent listing for treatments using agents provided under a Non-CTEP-held IND; located in [Section 3.0](#) of the protocol.
- For treatments using commercial agents, the current CAEPR (Comprehensive Adverse Event and Potential Risks), ASAE (Agent Specific Adverse Event List), or other list of expected toxicities located in [Section 3.0](#) of the protocol, or the drug package insert.

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 one of the areas outlined above.

Step 5: Determine whether the adverse event involved hospitalization or a prolongation of hospitalization (≥ 24 hours).

Step 6: Additionally, for commercial drugs, determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite. Consult the appropriate table for expedited reporting criteria for commercial agent(s).

NOTE: Any event that occurs more than 30 days after the last dose of study agent and is attributed (possible, probable, or definite) to the study agent(s) must be reported according to the instructions above and as outlined in the appropriate table in [Section 16.1](#).

18.3 Guidelines for Emergency Unblinding of Coded Drug

a. The following events MAY require emergency unblinding of Coded Drug:

- A compelling medical need as determined by a physician, e.g., occurrence of a severe or life-threatening reaction, inclusive of an adverse drug reaction, which may have been attributable to Coded Drug, or existence of a condition where the knowledge of the patient's treatment assignment would directly influence or affect his/her immediate care;
- ingestion of the Coded Drug by persons other than the patient or in excessive quantity;
- exposure of a pregnant woman to the Coded Drug;
- exposure of a child to the Coded Drug;

Note: Adverse drug reactions should be reported as required per [Section 16.0](#) of this protocol.

b. Procedure for Emergency Unblinding

The procedure for unblinding the treatment assignment for a patient is as follows:

- All unblinding must be done by the registering physician or designee.
- Call the Washington Poison Control (WPC) collect at 206/526-2121 or at 800/732-6985 if calling from within Washington State. The WPC is accessible 24 hours per day, 365 days per year for unblinding calls. Informational calls should be directed to the Data Operations Center in Seattle during standard business hours.
- Provide the WPC with the following information:
Study number: **S1202**
SWOG patient number
Patient name
Coded Drug ID number and bottle number
Name and telephone number of the caller
Reason unblinding is required
- Unblinding for ingestion of the Coded drug by a pregnant woman will not require the authorization of a resource physician. (The resource physicians for this study are listed at the end of this section.)
- Unblinding for ingestion of the Coded Drug by a child will not require the authorization of a resource physician.
- Unblinding for ingestion of the drug either in excessive amounts or by a person other than the patient will be done ONLY when a compelling medical need exists and/or unblinding has been authorized by a resource physician.
- Unblinding for a "compelling medical need" must be authorized by a physician designated as a resource physician for this protocol.

The treating physician (or designee) would provide the WPC with the information needed to determine if unblinding is required for the patient. The WPC would contact the resource physician, provide the required information, and obtain the authorization to unblind, if necessary. Based on the decision of the resource physician, the WPC would call the treating physician with either the unblinded treatment assignment or a treatment recommendation from the resource physician.

If a resource physician cannot be reached by the WPC, treatment of the patient should proceed as if the drug ingested were an active agent.

- Unblinding of Coded Drug for any reason must be documented on the **S1202** Treatment Form and the **S1202** Off Treatment Notice.

All unblinded participants are taken off treatment and followed per the requirements of the Southwest Oncology Group protocol.

Any questions regarding unblinding may be directed to one of the following resource physicians:

Norah Lynn Henry, M.D., Ph.D. (Medical Oncology)
University of Michigan
Comprehensive Cancer Center
1500 E. Medical Center Drive, Med Inn Building C450
Ann Arbor, MI 48109
Phone: 734/936-4991
FAX: 734/936-4940
E-mail: norahh@med.umich.edu

Craig R. Nichols, M.D. (Medical Oncology)
Virginia Mason Medical Center
1100 Ninth Avenue, MS: C2-HEM
Seattle, WA 98101
Phone: 206/223-6193
FAX: 206/223-6169
E-mail: craig.nichols@vmmc.org



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117788

EXEMPT IND

SWOG

Attention: Laurence H. Baker, D.O.

Chairman

Operations Office

4201 Medical Drive, Ste 250

San Antonio, TX 78229

Dear Dr. Baker:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Duloxetine (Cymbalta).

After reviewing the information contained in your submission, we have concluded that your study, protocol S1202, entitled "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor-Associated Musculoskeletal Symptoms in Women with Early Stage Breast Cancer" meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct your investigation. In accordance with 21 CFR 312.2(b)(4) of the regulations, FDA will not accept your application.

The IND regulations [21 CFR 312.2(b)] state that the clinical investigation of a drug product, including a biological product, that is lawfully marketed in the United States, is exempt from the requirements for an IND if all of the following apply:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for the drug.
2. The investigation is not intended to support a significant change in the advertising for a prescription drug product.
3. The investigation does not involve a change in route of administration, dosage level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug product.
4. The investigation is conducted in compliance with the requirements for institutional review (21 CFR Part 56) and informed consent (21 CFR Part 50).

5. The investigation is conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective, nor may it be commercially distributed, for the purposes for which it is under investigation.

In addition, 21 CFR 312.2(b)(5) exempts from the IND requirements a clinical investigation that involves use of a placebo if the investigation does not otherwise require submission of an IND. We remind you that exemption from the requirements for an IND does not in any way exempt you from complying with the requirements for informed consent under 21 CFR 50.20 or from initial and continuing Institutional Review Board review under 21 CFR Part 56. You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 U.S.C. §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Please note that, if in the future you submit an application under sections 505, 515, or 520(m) of the FDCA (21 USC §§ 355, 360(e), or 360(j)(m)), or under section 351 of the PHS Act (21 U.S.C. § 262), or you submit a report under section 510(k) of the FDCA (21 USC § 360(k)), the application or submission must be accompanied by a certification that all applicable requirements of section 402(j) of the PHS Act (42 USC § 282(j)) have been met. Where available, such certification must include the appropriate National Clinical Trial (NCT) control numbers (42 USC § 282(j)(5)(B)). Additional information regarding the certification is available at: <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information on registering your clinical trial(s) is available at the Protocol Registration System website (<http://prsinfo.clinicaltrials.gov/>).

For additional information about IND regulations, you can check our web site at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm>

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at (301) 796-1348.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FRANK H CROSS

03/04/2013

Signed for:

Robert L. Justice, M.D., M.S.

Director

Division of Oncology Products 1

Office of Hematology & Oncology Products

Center for Drug Evaluation and Research

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Informed Consent Model for S1202

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/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 SWOG 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 SWOG Operations Office.

Readability Statistics:

Flesch Reading Ease 62.5 (targeted above 55)

Flesch-Kincaid Grade Level 8.5 (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 SWOG.

"SWOG" 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 SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Center, all intergroup studies for which the registration is being credited to SWOG (whether the registration is

through the SWOG Data Operations Center 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 SWOG.

- 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 titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at <https://cissecure.nci.nih.gov/ncipubs> 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.

S1202, "A Randomized Placebo-Controlled Phase III Study of Duloxetine for Treatment of Aromatase Inhibitor (AI)-Associated Musculoskeletal Symptoms in Women with Early Stage 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 been identified as having a history of hormone receptor positive breast cancer, are post-menopausal, are being treated with an aromatase inhibitor, and are experiencing joint pain.

Who is doing this study?

SWOG is sponsoring this trial. SWOG is an adult cancer clinical trials organization. SWOG is funded through the National Cancer Institute, and its network consists of about four thousand physicians at almost three hundred institutions throughout the United States. Your study doctor has met all requirements to be a member of SWOG and to perform National Cancer Institute-funded research through this Group.

Why is this study being done?

The purpose of this study is to assess the effects, good and/or bad, of the medication duloxetine compared to placebo (contains no active ingredient) on your joint pain that is associated with taking aromatase inhibitors. Duloxetine is a drug usually prescribed to treat depression or anxiety, pain caused by nerve damage or fibromyalgia (a painful muscle/bone/nerve disorder) and a muscle and bone pain from a type of arthritis. Researchers on this study want to see if the pain relieving effects of the drug work for your type of pain.

How many people will take part in the study?

About 294 people will take part in this study.

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
- Blood work to check your liver and kidney function
- Blood work to check your menopausal status (if necessary).

You will also complete a questionnaire to collect information about joint pain that you are currently having. This is not part of routine cancer care.

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 procedures.

- Blood sample – Blood (about 3 teaspoons) will be taken before starting the study drug. The blood sample is not part of usual medical care. The blood sample will be submitted for specific biomarker and DNA (genetic) studies. (A biomarker is a biological molecule found in blood, other body fluids, or tissues that is a sign of normal or abnormal process, or of a condition or disease.) You and your study doctor will not know the results of these tests.
- Also, you will be asked if remaining blood from the sample can be kept for future research purposes. Please see separate questions at the end of this document.
- Questionnaires – You will complete four questionnaires (which will take about 20-25 minutes to complete) at the beginning of the study to collect information about how you are feeling physically during your treatment and how you are performing your daily activities. You will be asked to respond to questions regarding aromatase inhibitors and pain medications. You will also be asked questions about other symptoms you may be having, including hot flashes, sleep difficulties, and mood changes. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. We will do our best to make sure that your personal information will be kept private. This is not part of regular cancer care, but is being done as part of this research study.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance, like a flip of a coin. 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 of being placed in either group.

You will receive duloxetine (the study drug) or you will receive placebo (which contains no drug). Neither you nor your doctor will know which medication you are receiving. During the first week, you will take 1 capsule each day. Starting the second week, you will take 2 capsules each day for a total of 11 weeks (77 days). For the last week, you will take 1 capsule each day.

You will be supplied with study drug when you start the study and at 12 weeks.

Your doctor will give you a pill diary to keep track of your medication. You will record your medication intake and your doctor or nurse will review it every month.

At the 2 Week Visit...

The medical team or staff will record:

- Side effects you may be having
- Pain treatments you are receiving
- Aromatase inhibitor use
- Questionnaires – You will complete five questionnaires (which will take about 20-25 minutes to complete) at this appointment to collect information about how you are feeling physically during your treatment and how you are performing your daily activities. You will be asked to rate joint pain, and will be asked to respond to questions regarding aromatase inhibitors and pain medications. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. We will do our best to make sure that your personal information will be kept private.

At the 6 Week and 12Week Visits...

The medical team or staff will record:

- Side effects you may be having
- Pain treatments you are receiving
- Aromatase inhibitor use
- Number of pills remaining in your container
- Questionnaires – You will complete six questionnaires (which will take about 20-25 minutes to complete) at each of these appointments to collect information about how you are feeling physically during your treatment and how you are performing your daily activities. You will be asked to rate joint pain, and will be asked to respond to questions regarding aromatase inhibitors and pain medications. You will also be asked questions about other symptoms you may be having, including hot flashes, sleep difficulties, and mood changes. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. We will do our best to make sure that your personal information will be kept private.

During the Week 12 visit, blood (about 2 teaspoons) will be drawn. After the treatment part of the study is finished the blood will be used to test for biomarkers and the results of these tests will not be part of your medical record.

You will be asked to take 1 capsule of study drug each day for 7 more days (until the end of Week 13).

At the 14 Week Visit...

The medical team or staff will contact you by telephone to ask about side effects you may be having.

At the 24 Week Visit...

The medical team or staff will record:

- Pain treatments you are receiving
- Aromatase inhibitor use
- Questionnaires – You will complete five questionnaires (which will take about 20-25 minutes to complete) at this appointment to collect information about how you are feeling physically and how you are performing your daily activities. You will be asked to rate joint pain, and you will be asked to respond to questions regarding aromatase inhibitors and pain medications. You will also be asked questions about other symptoms you may be having, including hot flashes, sleep difficulties, and mood changes. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. We will do our best to make sure your personal information will be kept private.

How long will I be in the study?

You will be asked to take duloxetine or placebo for a total of 13 weeks. After you are finished taking the study drugs, the study doctor will ask you to visit the office at 24 weeks for a final follow-up visit.

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 since suddenly stopping the study medication can cause side effects. He or she will tell you how to stop safely. It is important that all patients on the study medication taper off slowly according to your doctor's instructions to prevent serious side effects.

It is important to tell the study doctor if you are thinking about stopping so any risks from the study drugs 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 study drugs. 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 duloxetine include those which are:

Likely (occurring in more than 10% of patients) (1/23/14)

- Nausea (*updated 1/23/14*)
- Headache
- Dry mouth
- Fatigue and tiredness
- Difficulty sleeping
- Moved to Less Likely 1/23/14
- Moved to Less Likely 1/23/14
- Moved to Less Likely 1/23/14

Less Likely(occurring in 1-10% of patients) (1/23/14)

- Dizziness (*moved from Likely 1/23/14*)
- Decreased appetite (*moved from Likely 1/23/14*)
- Increased sweating (*moved from Likely 1/23/14*)
- Vomiting, constipation, diarrhea (*moved from Likely 1/23/14*)
- Palpitations
- Lightheadedness leading to loss of consciousness
- Increased blood pressure
- Blurry vision
- Abdominal pain
- Weight loss or gain

- Tremor
- Anxiety
- Sexual problems
- Abnormal dreams
- Yawning
- Hot flashes
- Fever
- Muscle cramps
- Numbness or tingling of fingers or toes
- Cough
- Rash
- Itching
- Low blood sodium level
- Difficulty urinating

Rare but serious (occurring in less than 1% of patients) (1/23/14)

- Suicidal thoughts or behaviors
- Liver failure
- Bleeding
- Serotonin syndrome (a potentially life-threatening drug reaction caused by too much serotonin activity in the body; it may include agitation, hallucinations, coma, other changes in mental status, coordination problems, muscle twitching, racing heartbeat, high or low blood pressure, sweating, fever, nausea, vomiting, diarrhea, muscle rigidity, dizziness, flushing, tremor, and seizures).
- Stevens-Johnson syndrome (severe rash that can occur in the mouth and on the skin and can be associated with fever; this may include skin sloughing-damage to the outer layer of skin causing it to separate from the rest of the skin). You should contact your doctor if skin rash occurs.

After you start taking the study medication, if you have any thoughts about suicide you should contact the study doctor or your oncologist immediately. Your risk of suicide will be monitored during the study.

You must not take MAO-Inhibitors, heparin, or warfarin while on this study. Please discuss with your study doctor if you are taking any of these medications or if you are given a prescription for them while you are on the study. You should also discuss with your doctor if you take aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) as the use of these drugs with the study drug could increase your risk of bleeding. (4/29/14)

The researchers will try to minimize the risk of nausea by gradually increasing the dose of duloxetine when you first start taking the medication, and by gradually decreasing the dose of duloxetine when you stop taking the medication. Most of these side effects are expected to go away when you stop taking the drug.

Blood draws: The risks of drawing blood are minimal, but include discomfort, bruising, fainting or lightheadedness, and, rarely, infection and significant bleeding. To minimize the risks and discomfort, only trained personnel will collect blood from you during this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. We hope that the information from this study will help doctors learn whether duloxetine reduces joint pain in patients receiving aromatase inhibitors. This information could help future patients taking aromatase inhibitors.

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 joint pain without being in a study
- Taking part in another study
- Getting no treatment

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:

- *[List relevant organizations like study sponsor(s), local IRB, etc.]*
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to clinical trials. *(added 9/18/13)*
- SWOG
- Alliance, ECOG-ACRIN, NRG *(added 1/19/15)*
- Eli Lilly & Company, which is providing the study medication

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

[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 associated with this study (except for the research studies done on your blood as discussed below). 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 care.

Eli Lilly will supply the duloxetine or placebo at no charge while you take part in this study.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the duloxetine and placebo to SWOG for some reason. If this would occur, other possible options are:

- You might be able to get the study drug from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no study drug available at all, no one will be able to get more and the study would close.

If a problem with getting the study drug occurs, your study doctor will talk to you about these options.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://m.cancer.gov/topics/clinicaltrials/learningabout/payingfor/howinsurance-companies-decide>. (updated 1/19/15) 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.

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.]

(deleted 4/29/14)

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.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Future Contact

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

Consent Form for Use of Specimens for Research

About Using Specimens for Research

You are going to have blood drawn for biomarker and DNA (genetic) testing in this study. The results of these tests will not be given to you or your doctor and will not be part of your medical record.

We would like to keep some of the blood that is left over for future research. If you agree, this blood 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.

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 SWOG 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.

If your confidential genetic information is discovered, you may suffer from genetic discrimination. Genetic discrimination occurs if people are treated unfairly because of differences in their genes that increase their chances of getting a certain disease. In the past, this could have resulted in the loss of health insurance or employment. Because of this, The Genetic

Information Nondiscrimination Act of 2008, also referred to as GINA, was passed by Congress to protect Americans from such discrimination. The new law prevents discrimination from health insurers and employers. This act was signed into federal law on May 21, 2008, and went into effect May 2009. This law does not cover life insurance, disability insurance and long-term care insurance.

While this study has safeguards in place to protect your confidential genetic information and to make it extremely unlikely that your identity would be connected with any special studies that are performed on your blood, it is possible that this information could be discovered by someone who is unauthorized to have access to it.

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, treat or cure cancer.**

Yes No

2. **My specimens may be kept for use in research about 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

If you decide to withdraw your specimens from a SWOG Specimen Repository in the future, a written withdrawal of consent should be submitted through your study doctor to the SWOG Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the study doctor.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

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

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 _____
(deleted 1/19/15)

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 SWOG. Your doctor does not work for SWOG, 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 SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG 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 SWOG. If more information is needed, SWOG 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 to 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?

SWOG is in charge of making sure that information about you is kept private. SWOG 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).