SBI ALApharma Canada Inc.

SBI-CIP 20-002

A prospective multi-center clinical study evaluating the use of PD G 506 A and the Eagle V1.2 Imaging System for the visualization of carcinoma during breast conserving surgery

Revision:	v1.8
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NCT04815083

CLINICAL STUDY PROTOCOL

A prospective multi-center clinical study evaluating the use of PD G 506 A and the Eagle V1.2 Imaging System for the visualization of carcinoma during breast conserving surgery

Protocol Number: SBI-CIP 20-002
Amendment Number: 8

Short Study Name: Fluorescence imaging of carcinoma during breast conserving surgery

Sponsor: SBI ALApharma Canada Inc.
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Toronto, Ontario, M5G 1Z8
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Protocol Version: 1.8

Previous Protocol Versions: 1.7

Title	A prospective multi-center clinical study evaluating the use of PD G 506 A and the Eagle V1.2 Imaging System for the visualization of carcinoma during breast conserving surgery
Protocol Number	SBI-CIP 20-002
Version Date	Mar 11, 2024
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1. Investigator Signature:

I agree to conduct the study in accordance with the relevant, current protocol.

I agree to personally conduct or supervise this study.

I agree to perform and conduct the study as described in the protocol and in accordance with the relevant laws/regulations and standards outlined in the Clinical Trial Agreement.

I will ensure that the requirements relating to obtaining informed consent and Ethics Committee (EC) or Institutional Review Board (IRB) review and approval are met.

I agree to maintain adequate and accurate study records and to make those records available for inspection by the Sponsor, the Sponsor's authorized representatives, and/or other applicable regulatory entities.

I agree to promptly report to the EC/IRB all changes to the study and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes to the study without Sponsor and EC/IRB approval, except where necessary to eliminate apparent immediate hazards to study patients.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____ (print name and title)

Signature: _____ Date (DD/MMM/YYYY): _____

Sponsor Signatory:

_____ _____

Dr. Ralph DaCosta, PhD Date (DD/MMM/YYYY)

CEO and CTO SBI ALApharma Canada Inc.

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2. Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Version/Date**
Original Protocol	1.0
Amendment 1	1.1/January 7, 2021
Amendment 2	1.2/March 28, 2021
Amendment 3	1.3/April 14, 2021
Amendment 4	1.4/September 30, 2021
Amendment 5	1.5/March 24, 2022
Amendment 6	1.6/November 25, 2022
Amendment 7	1.7/November 13, 2023
Amendment 8	1.8/March 11, 2024

Amendment # (DD-MMM-YYYY): Amendment 8 (11-Mar-2024), Version 1.8

Overall Rationale for Amendment: Improve study logistics (in response to site feedback). Removal of optional procedures (specimen tagging) and removal of images required from the cavity after lumpectomy is performed (primary cavity).
Change in primary endpoint and key secondary endpoints, as well as changes in the sample size calculation taking into consideration only the primary outcome (P 1.1 – conversion rate among all patients included in the study) These changes were made to corroborate with FDA recommendations in the type D meeting (03 Aug 2023).
Removing the modified ASTRO/SSO definitions and all endpoints related to the modified guideline, as well as the modified definition of true positive and true negative.
Defining positive margins as per the latest consensus from the Society of Surgical Oncology (ASTRO/SSO). Removal of some of the surgeon's assistant requirements, such as training on the sterile field and suturing experience.
In addition, extending diagnostic imaging requirements to 90 days prior to the surgery date (drug administration).

Summary of Changes

Section	Changes/rationale
General	1. Reorganisation of protocol numbering for sections – starting with revision history for section 1. 2. Updating the table of content to reflect all changes made in the protocol.

Section 4	1. <u>Study Synopsis:</u> - Moved to Appendix 1 – To improve the flow of the protocol and to have the synopsis easily accessible for investigators and research teams. 2. <u>Schedule of Activities (SOA):</u> - Moved to section 13, to be part of the study procedures and schedule.
Section 5	1. Moved before definitions to improve the readability (flow) of the protocol.
Section 6	<u>Definitions:</u> 1. Reorganised definitions to include essential/fundamental definitions (6.1) and additional definitions (6.2). - Adding essential definitions at the beginning of the list to introduce the basic definitions for the study and facilitate readability. - Adding "additional" definition as the more complex definitions that requires previous comprehension from the essential definitions. 2. Updated definitions for surgical cavity, shave types, final margins, true positive/negative and re-excisions. - Making the definitions more clear and comprehensive. 3. Redefined positive margins according to the 2014 & 2016 SSO/ASTRO guidelines - Better define the guidelines that will be used in the study to define positive margins and calculate endpoints as well as study analysis. 4. Removed modified SSO/ASTRO guidelines for positive margin and all the endpoints related to the modified definition (p2.29, p2.30 and p2.31). 5. Removed modified true positive and modified true positive definitions.
Section 8	Objectives and Endpoints: 1. Updated Primary and secondary objectives and endpoints as per FDA recommendations in the type D meeting held in Aug/2023. 2. Updated Primary Endpoint as Requested by FDA (P.1.1) – conversion rate among all patients for the study. 3. Updated key secondary objectives and endpoints (5.2.1) – P (2.1; 2.2;2.3): - Sensitivity, Specificity and Conversion rate among patients with positive margin after SoC as per FDA recommendations. 4. Updated numbering of secondary endpoints. 5. Removed endpoints p2.29, p2.30 and p2.31: - Related to modified SSO/ASTRO guideline assessment.

	6. Removed endpoint 23: - Related to assessment of optional procedure – Specimen Tagging. The assessment will no longer be performed for the study. 7. Removed endpoints 9 and 10: - Related to modified true positive and modified true negative definitions. 8. Corrected the "Specificity" formula in endpoint P(2.6) which was previously P(2.4) in v1.7.
Section 13	<u>Study Procedures and Schedule:</u> 1. Enrollment and randomization: - Extending the diagnostic imaging timeline from ≤ 45 to ≤ 90 days prior to Day 1. This will improve site logistics, patient screening and study workflow. 2. Intra-operative procedures: a) Removal of Specimen Tagging: - To reduce the OR time for the patient as well as for the surgeons and to allow the surgeon's assistant to be an individual that does not need to be trained in suturing, which will improve site recruitment as well as patient recruitment. b) Removal of the requirement to image the primary cavity: - To allow the surgeon's assistant to be an individual that does not need to be trained to operate in the sterile field.
Section 16	<u>Statistical Considerations</u>: 1. Sample size estimation (16.2): - Readjusted the primary outcome that is now driving the sample size of the study – primary endpoint P(1.1) and recalculated the sample size taking into consideration the 1% null hypothesis threshold recommended by the FDA in the last type D meeting (Aug/2023). 2. Modified intention to treat analysis population (16.4.1): - Adjusted the definition as per FDA's recommendation dated 22/11/2021.
Appendix 2	1. Adjusted Study Workflow to Reflect the Changes made in the Protocol: a) Removed the intra-operative procedure: Specimen tagging. b) Removed imaging of the primary cavity. c) Readjusted the wording and numbering to make the steps more clear and concise.

3. List of Abbreviations

A	anterior
AE	adverse event
AF	autofluorescence
ALA	aminolevulinic acid
ALA HCl	aminolevulinic acid hydrochloride
ALAT	alanine transaminase
ASAT	aspartate aminotransferase
ASTRO	American Society for Radiation Oncology
BCS	breast conserving surgery
BW	body weight
CCD	Contact Charging Device
CIP	clinical investigational plan
CRF	case report form
CSP	clinical study protocol
CSS	Custom Sterile Sleeve
CTCAE	Common Terminology Criteria for Adverse Events
DCC	data control centre
DCIS	ductal carcinoma *in situ*
DIB	Dark Imaging Box
DIS	Dark Imaging Sheet
DOR	diagnostic odds ratio
DSMB	data safety monitoring board
ECG	electrocardiogram
ECH	External Communication Hub
eCRF	electronic case report form
EDC	electronic data capture
EPR	electronic patient record
FDA	Food and Drug Administration
FOV	field of view
FL	fluorescence
FN	false negative
FN_o	false negative orientation
FN_{ps}	false negative primary specimen
FP	false positive
FP_o	false positive orientation
FP_{ps}	false positive primary specimen
GCP	Good Clinical Practice

GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HCl	hydrochloride
HFC	Handheld Fluorescence Camera
I	inferior
IV	intravenous
ITT	intention-to-treat
L	lateral
LED	light emitting diode
M	medial
mITT	modified intention-to-treat
NPV	negative predictive value
P	posterior
PA	pathologist's assistant
PI	principal investigator
PMCC	Princess Margaret Cancer Centre
PO	per os
PPIX	protoporphyrin IX
PPV	positive predictive value
PSC	Protective Storage Cradle
REB/IRB	Research Ethics Board / Institutional Review Board
S	superior
SAE	serious adverse event
SPF	sun protection factor
SoC	standard of care
SSO	Society for Surgical Oncology
SUSAR	Suspected Unexpected Serious Adverse Reaction
TN	true negative
TN_o	true negative orientation
TN_{ps}	true negative primary specimen
TP	true positive
TP_o	true positive orientation
TP_{ps}	true positive primary specimen
UHN	University Health Network
UV	ultraviolet
WL	white light
WOCBP	women of child-bearing potential
UP	unanticipated problem
UADE	Unanticipated Adverse Device Effect

4. General Information

4.1. Identification of the Clinical Investigational Plan (CIP)

Protocol title: A prospective multi-center clinical study evaluating the use of PD G 506 A and the Eagle V1.2 Imaging System for the visualization of carcinoma during breast conserving surgery

4.2. Sponsor Information

Sponsor: SBI ALApharma Canada Inc.

4.3. Identification of Investigators

Lists of Investigators responsible for conducting the trial, clinical laboratories and other medical and/or technical departments and/or institutions involved in the trial are provided as separate documents.

4.4. Contract Research Organization

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4.5. REB/IRB Contact Information

List of REB/IRBs responsible for reviewing the trial are provided as separate documents.

4.6. Laboratory Contact Information

List of clinical laboratories involved in the trial are provided as separate documents.

4.7.Pharmacovigilance/Medical Inquiries

Name: spmd – strategies for health, Inc.
Contact: Dr. Diana Witticke (PV Project Management)
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4.8.Monitoring Information

Name: Allucent
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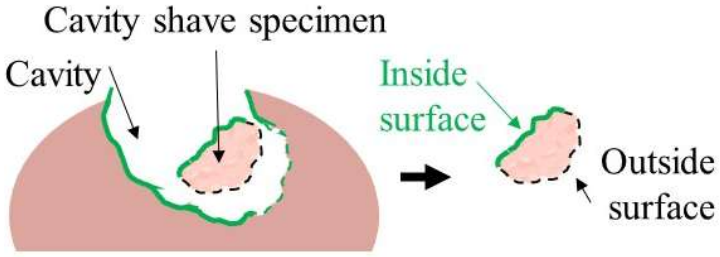
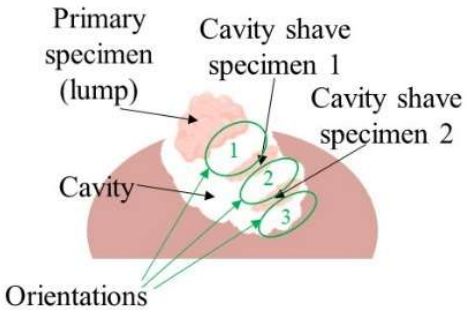
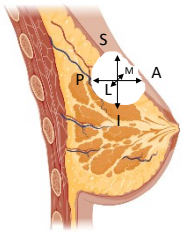
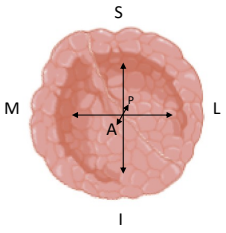
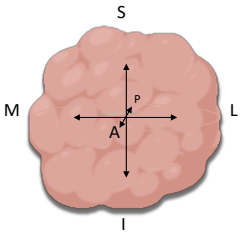
5. Definitions

5.1. Essential/Fundamental Definitions

a) Definitions of surface and orientations	
Surface	A border (i.e., one of many borders) of a ***cavity*** or ***excised tissue specimen*** that was surgically resected during the excision of said specimen. A surface is defined as inside (deep) surface, which is the contiguous margin of the most recently resected tissue. The outside (superficial) surface is the margin that was continuous with the remaining breast tissue. 
Orientation	An ***orientation*** is comprised of two contiguous tissue ***surfaces*** that have been resected or separated surgically. An orientation is described based on the anatomical location of the contiguous tissues (e.g. Superior, Medial, Posterior, Lateral, Inferior, Anterior)  Orientation 1 = outside surface of primary specimen + inside surface of cavity shave specimen 1 Orientation 2 = outside surface of cavity shave specimen 1+ inside surface of cavity shave specimen 2 Orientation 3 = outside surface of cavity shave specimen 2+ inside surface of final cavity

	Viewed from the lateral perspective  	Viewed from the anterior perspective  	Viewed from the anterior perspective 
	S = superior (towards the head) M = medial (towards the midline of the body) P = posterior (towards the chest wall) L = lateral (towards the ipsilateral arm) I = inferior (towards the feet) A = anterior (towards the front of the patient)		
b) Definition of cavity and excised tissue			
Cavity (Surgical Cavity)	The tissue void in the breast remaining after tissue has been resected as part of a breast conserving surgery procedure. A cavity is composed of 6 anatomical ***cavity surfaces*** (Superior, Medial, Posterior, Lateral, Inferior, Anterior).		
Final Cavity after FGR	The ***cavity*** after ***FL-guided resection*** (***FGR***) is complete. If no ***FL-driven cavity shave specimens*** are collected in a patient randomized to receive ***FGR***, then the ***final cavity after FGR*** is equivalent to the ***final cavity after SoC***.		
Final Cavity after SoC	The ***cavity*** after SoC resection is complete (including resection of the ***primary specimen*** and any ***SoC-driven cavity shave specimen(s).***		
Positive Cavity	A positive cavity occurs when postoperative analysis identifies carcinoma that is positive on histopathology either inside the surgical cavity during SoC lumpectomy or after FGR resection.		

Cavity Shave Specimen(s)	Tissue specimen(s) excised from the ***cavity*** after the ***primary specimen*** has been removed; ***cavity shave specimen(s)*** The surfaces of a ***cavity shave specimen*** are described with reference to the primary specimen (not relative to the cavity/patient). The ***outside surface*** of a ***cavity shave specimen*** is the surface that was continuous with the remaining breast tissue. The ***inside surface*** of a cavity shave margin is the surface that is continuous with most recently resected tissue.
Primary Specimen	Also known as the "lump" or main mass refers to the primary piece of tissue resected during a standard of care lumpectomy. It contains most (or all) of the primary tumor mass
Shave types (Excised tissue)	I. Shave: any tissue removed from the lumpectomy cavity walls after the main specimen is removed.
	II. Standard of care (SoC) cavity shave: any piece of tissue excised from a specific location of the lumpectomy cavity wall after the primary specimen has been removed, as per surgeon's decision per SoC.
	III. Fluorescence-driven shave specimen(s): any piece of tissues excised from a specific location of the lumpectomy cavity wall indicated by PD G 506 A-induced tissue fluorescence after SoC resection has been completed.
c) Definition of margins and re-excision	
Margin Assessment	The procedure(s) performed to evaluate the outside surface of the last resected tissue(s) and/or cavity. Given that ***FL-guided resection*** occurs after completion of SoC, margin assessment may be based on SoC methods (***SoC margin assessment***) or FL-imaging (***FL margin assessment***). ***SoC margin assessment*** may include WL palpation, visualization, specimen radiology and intraoperative ultrasound (patients undergoing intraoperative histopathological assessment are excluded from participating).

<table>
<tr><td>Final Margin(s)</td><td>Final margin is comprised of the outside surface of the last resected tissue(s) for each anatomical surface and the final cavity at that margin.

Final margins are evaluated to determine whether the patient has positive or -negative margins based on postoperative clinical pathology assessment.

For each patient, final margins after SoC and final margins after FGR will be evaluated histopathologically.

If there are no FL-driven cavity shave specimens collected in a patient randomized to receive FGR, then the final margins after FGR are equivalent to the final margins after SoC.</td></tr>
<tr><td>Positive Margins</td><td>Determined postoperatively wherein histopathological analysis identifies carcinoma within a defined distance from the inked surface of an excised tissue specimen.

Positive margins are defined using the latest consensus from the Society of Surgical Oncology as follows:

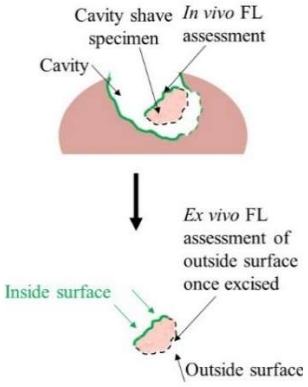
-For invasive cancer with or without associated ductal carcinoma in situ (DCIS): cancer cells or DCIS present on ink (per Moran et al. 2014[1])
-For pure DCIS lesions: DCIS present less than 2 mm from ink (per Morrow et al. 2016[2]).</td></tr>
<tr><td>True Positive Orientation and True Negative Orientation</td><td>
<table>
<tr><td></td><td colspan="3">Surface histopathology status</td></tr>
<tr><td></td><td></td><td>Positive</td><td>Negative</td></tr>
<tr><td rowspan="2">Surface fluorescence status</td><td>Positive</td><td>True positive (TP)</td><td>False positive (FP)</td></tr>
<tr><td>Negative</td><td>False Negative (FN)</td><td>True Negative (TN)</td></tr>
</table>
a. A TP orientation contains at least 1 True Positive surface.
b. A FN orientation contains at least 1 False Negative surface and no True Positive surface.
c. A FP orientation contains at least 1 False Positive surface and no True Positive or False Negative surfaces.
d. A TN orientation contains only True Negative surfaces.
</td></tr>
</table>

Re-excisions	A re-excision is defined as a surgical procedure performed in the ipsilateral breast following the primary lumpectomy because of positive margins found from the initial lumpectomy procedure. The re-excision procedure can be a separate surgical procedure to excise further breast tissue or a mastectomy.

5.2. Additional Definitions

Fluorescence-Guided Resection (FGR)	Resection of tissue based on the results of PD G 506 A- induced PpIX fluorescence imaging using the Eagle V1.2 Imaging System and the surgeon's best clinical judgement. ***FGR*** is performed after SoC is declared complete by the ***surgeon***. Any patient that undergoes fluorescence imaging with the intent to resect tissue is considered to have undergone ***FGR***, even if no ***FL-driven cavity shave specimens*** are resected.
Fluorescence (FL) Positive Surface	Determined intraoperatively wherein the surgeon identifies PD G 506 A-induced PpIX fluorescence on any specimen ***surface*** or cavity ***surface*** when performing imaging with the Eagle V1.2 Imaging System.
FL-positive orientation	An orientation wherein either (or both) of the two surfaces which make up said orientation were determined intraoperatively to be positive for PD G 506-A-induced PpIX fluorescence (FL-status = FL-positive).
FL-negative orientation	An orientation wherein both of the two surfaces which make up said orientation were determined intraoperatively to be negative for PD G 506-A-induced PpIX fluorescence (FL status = FL-negative).
FL-positive orientation-*in vivo*	Orientation with FL-positive status of the cavity surface (or the ***inside surface*** of a ***cavity shave specimen*** if removed due to ***FGR***); fluorescence is assessed *in vivo*
FL-negative orientation-*in vivo*	Orientation with FL-negative status of the cavity surface (or the ***inside surface*** of a ***cavity shave specimen*** if removed due to ***FGR***); fluorescence is assessed *in vivo*
FL-positive orientation-*ex vivo*	Orientation with FL-positive status of the surface of the ***primary specimen*** or ***outside surface*** of a ***cavity shave specimen***; fluorescence is assessed *ex vivo*
FL-negative orientation-*ex vivo*	Orientation with FL-negative status of the surface of the ***primary specimen*** or ***outside surface*** of a ***cavity shave specimen***; fluorescence is assessed *ex vivo*

Inking – Specimen or Surface	A procedure performed as part of SoC, wherein a specific colour of ink is applied to a specific surface or margin of a tissue specimen for the purposes of orienting tissue blocks during histopathological analysis. Up to six colours may be used to orient the ***primary specimen or shaves***.
Index Surgery/ Surgical Procedure	The first surgery performed to remove a primary breast cancer.
***In vivo* Fluorescence assessment / inside surface**	Determination of the FL status of tissue based on FL imaging of tissue that is inside the patient (not yet resected). The ***inside surface*** of ***cavity shave specimen(s)*** and the ***final cavity after FGR*** can undergo ***in vivo FL assessment.***
***Ex vivo* Fluorescence assessment / outside surface**	Determination of the FL status of tissue based on FL imaging of resected tissue ***specimen(s)*** after removal from the patient (i.e., outside the patient). The ***outside surface*** of the ***primary specimen***, ***final margins after SoC*** and outside surface of ***cavity shave specimen(s)*** can undergo ***ex vivo FL assessment.***
Orientation-level endpoint	An endpoint for which ***orientation***-based analysis is performed. An ***orientation-level*** analysis would evaluate each ***orientation*** as a single data point with a total of at least 5 ***orientations*** per patient (in cases where an area of skin is removed with the lump, there may be n = 5 data points per patient). ***Orientation-level*** analysis evaluates efficacy based on the performance characteristics (accuracy) in each anatomical location of the entire surgical cavity.
Patient-level endpoint	An endpoint for which patient-based analysis is performed. A ***patient-level*** analysis evaluates each patient as a single data point.
Surgeon	The surgeon responsible for performing the SoC breast conserving surgery procedure and real-time intraoperative interpretation of the Eagle V1.2 Imaging System data.



Surgeon's Assistant	The individual responsible for performing Eagle V1.2 Imaging System fluorescence imaging of the ***primary specimen*** and any ***SoC cavity shave specimens*** prior to opening of the randomization envelope. The ***surgeon's assistant*** may be a qualified staff ***surgeon***, surgical fellow, resident, nurse, physician's assistant, research manager or research coordinator.
True Positive Orientation (TP_o)	Orientation that is fluorescence positive and histopathology positive.
True Negative Orientation (TN_o)	Orientation that is fluorescence negative and histopathology negative.
False Positive Orientation (FP_o)	Orientation that is fluorescence positive and histopathology negative.
False Negative Orientation (FN_o)	Orientation that is fluorescence negative and histopathology positive.
True Positive Patient	Patient has at least one ***TP orientation*** without any ***FN orientations***
True Negative Patient	Patient has all ***TN orientations***
False Positive Patient	Patient has at least one ***FP orientation*** without any ***FN*** or ***TP orientations***
False Negative Patient	Patient has at least one ***FN orientation***

6. Introduction

6.1. Study Rationale

6.1.1. Clinical Need

Breast conserving surgery (BCS) is performed on patients with breast cancer to resect and completely remove the primary malignancy while conserving as much of the surrounding normal tissue as possible. Currently, surgeons rely on a multitude of methods to assess the adequacy of the margins intra-operatively including visual assessment and palpation, specimen radiology, intraoperative ultrasound and intraoperative histopathology (in specific cases). There is no consensus on intraoperative resection adequacy and definitive margin assessment requires histopathological assessment, which is not real-time and impractical in the intra-operative setting. Despite intra-operative measures to obtain clean margins in BCS, the need for re-excision via a subsequent surgery is not uncommon. In Canada, 57,840 BCS procedures were performed between 2007-2010 for primary invasive unilateral breast cancer (before 2014 ASTRO/SSO guidelines[3]), with 23% of patients requiring re-excision (n=38,517; range:17-56%) within 1 year of the ***index*** BCS to establish acceptable clear/negative margins[4, 5]. The average US re-excision rate for invasive breast cancer or *ductal carcinoma in situ* (DCIS) was 23.6% (range: 18.4-26.5%) between 2004[6][7][8] and risk of local [4, 9-16]. Re-excisions due to final positive margins also increase the risk of disease local recurrence and decrease disease-specific survival[4, 9-15]. [17, 18]. Optimizing surgery to improve resection guidance and positive margin assessment during initial BCS would be highly [19], leading to a decreased need for 2nd or subsequent surgeries.

Emerging technologies (including drugs and devices) have aimed to address the need for real-time margin assessment during BCS. Among these, only MarginProbe (Dune Medical) and OTIS (Perimeter Medical Imaging) have received FDA clearance. MarginProbe is indicated for the detection of carcinoma at the margins of tissue, but requires time consuming evaluation of tissues using a probe with a small sampling area that produces an auditory (non-image based) output indicating the presence or absence of carcinoma. OTIS provides an image output but is indicated for imaging tissue microstructures, not carcinoma. Both technologies are limited to the evaluation of the surgical specimen and cannot be used to evaluate residual disease in the surgical cavity. Thus, an urgent clinical need exists for real-time intraoperative (imaging) methods to assess both the surgical cavity and excised specimens during BCS.

6.1.2. Fluorescence Imaging During Surgery

The pro-drug ALA is a non-fluorescent non-protein amino acid that is converted into the fluorophore protoporphyrin IX (PpIX) as part of the heme biosynthesis pathway and preferentially accumulates in malignant tissue such as in cultured breast cancer cell lines of a variety of phenotypes[20]. This selectivity has been demonstrated to extent to murine breast cancer models where it was found to be a good marker for early tumorigenic processes in the mouse mammary gland. In a number of clinical trials, ALA has been administered orally for the purpose of

fluorescence-based imaging of a variety of other cancer types such as rectal carcinomas (n = 2)[21], malignant gliomas (n > 500)[22-32], and palpable breast tumours (n = 16 and n=7)[33, 34]. In the case of malignant gliomas, a multicentre Phase III randomized controlled study (n = 322) demonstrated complete tumour resection in 65% of the ALA HCl dosed patients undergoing ***fluorescence-guided resection (FGR)*** compared with 36% in those that underwent conventional resection based solely on white light guidance (clinicaltrials.gov identifier: NCT00241670)[32]. ALA HCl has received marketing authorization by SBI ALApharma Canada's affiliate companies for use in patients undergoing surgery for high grade glioma in over 40 countries, including GLEOLAN™ in the United States of America[35, 36].

6.1.3. Previous Clinical Experience

Fluorescence imaging of breast cancer was previously investigated in an investigator-initiated trial (PI: Dr. Wey Leong), conducted at Princess Margaret Cancer Centre, Toronto, Canada (Study #10-0633, clinicaltrais.gov identifier: NCT01837225), using a handheld and portable fluorescence imaging device, called PRODIGI, in patients undergoing BCS (both lumpectomies and mastectomies). This device was developed by Dr. Ralph DaCosta at Princess Margaret Cancer Center, University Health Network, and uses violet-blue light (405 nm) to excite fluorescence which is detected at 500-550 nm (green) and 600-660 nm (red) in real time using an optically-modified high-resolution consumer-grade digital camera.

In the first stage of Study #10-0633 in which patients did *not* receive ALA HCl, PRODIGI autofluorescence imaging of excised breast tissue specimens demonstrated healthy breast connective tissue appeared bright green autofluorescent and adipose tissue appeared dull pinkish-brown autofluorescent. However, tissue autofluorescence alone resulted in poor tumour-to-normal tissue contrast. The conclusion of this stage of the study was that an exogenous (fluorescence) contrast would be required to achieve the desirable tumor-to-normal imaging contrast.

In the second stage of Study #10-0633, ALA HCl was investigated as a fluorescence contrast agent to improve the detection of breast carcinoma compared with autofluorescence alone. Study patients were randomly assigned to one of three dose cohorts (n = 15/cohort): 0 mg/kg (Cohort 1, autofluorescence only), 15 mg/kg (Cohort 2), or 30 mg/kg (Cohort 3) of ALA HCl. Analysis of the *ex vivo* specimen(s) only (lumpectomy or mastectomy) was performed in the first n = 5 patients in each cohort. In the subsequent n = 10 patients/cohort both intraoperative white light and fluorescence imaging of the surgical cavity, as well as *ex vivo* fluorescence and white light imaging of the excised specimen were performed.

The primary objective of the second stage of Study #10-0633 was to determine preliminary sensitivity and specificity estimates of ALA HCl-induced PpIX fluorescence, as visualized with the PRODIGI imaging device in *ex vivo* specimens. ALA HCl substantially improved tumour-to-normal tissue contrast relative to autofluorescence alone. At final analysis of all patients who received ALA HCl, a total of 93 biopsies were collected in areas of healthy tissue, tumour tissue

and tumour adjacent tissue. The sensitivity and specificity to detect breast carcinoma in the *ex vivo* specimens based on ALA HCl-induced red PpIX fluorescence using 15 or 30 mg/kg BW ALA HCl is presented in **Table 6.1:**

Table 6.1: Diagnostic measures ALA HCl-induced red PpIX fluorescence to detect breast cancer tumours using PRODIGI

	Low Dose (15 mg/kg)		**High Dose (30 mg/kg)**	
	-Tumor	**+Tumor**	**-Tumor**	**+Tumor**
-Red FL	22	7	20	7
+Red FL	4	13	5	15
PPV % (95%CI)	76.5% (50.1 – 93.2)		75.0% (50.9 – 91.3)	
NPV % (95%CI)	75.9% (56.5 – 89.7)		74.1% (53.7 – 88.9)	
Sensitivity % (95%CI)	65.0% (40.8 – 84.6)		68.2% (45.1 – 86.1)	
Specificity % (95%CI)	84.6% (65.1 – 95.6)		80.0% (59.3– 93.2)	

The secondary objective of Study #10-0633 was to evaluate the safety and feasibility of intraoperative fluorescence imaging of the surgical cavity following excision of the lumpectomy or mastectomy specimen. No adverse events were associated with the experimental procedures (ingestion of ALA HCl and intraoperative imaging) and there was minimal interruption to the standard clinical workflow. Intraoperative imaging added ~5-10 minutes to the procedure time. However, while the initial design of the PRODIGI device was optimal for imaging of flat surfaces such as those of the resected specimens, it did not perform as well for intracavity imaging. As a result of its bulky form factor, PRODIGI could not enter the surgical cavity and the illumination of the cavity surface using 405 nm light was not optimal for imaging within an enclosed space, such as the surgical cavity.

To overcome this challenge, a next generation prototype (Eagle 1.1 Imaging Device) was designed for testing in combination with 20 mg/kg body weight (BW) ALA HCl in the third stage of Study #10-0633. Eagle 1.1 Imaging Device has a smaller form factor and is intended to enter and image inside the surgical cavity; however, the white light and fluorescence imaging capabilities are not integrated into a single device. For example, there are two distinct devices which are designed to perform white light and fluorescence imaging, respectively. The reason for this was to enable technical optimization of both imaging modalities separately, prior to physically combining both white light and fluorescence imaging functions into a single handheld device design.

To this end, SBI ALApharma Canada Inc. has developed and manufactured the Eagle V1.2 Imaging Device which has an optimized design that integrates the white light and fluorescence imaging functions and an improved user interface based on results of formative human factors

testing. Additionally, a suite of accessories have been developed to improve the usability of the device in the intraoperative setting during ***FGR.*** Collectively, the imaging device and accessories are referred to as the "Eagle V1.2 Imaging System".

6.2.Potential Risks and Benefits

A detailed description of the chemistry, pharmacology, efficacy, and safety of PD G 506 A is provided in the Investigator's Brochure and a detailed description of the Eagle V1.2 Imaging System performance testing and safety is found in the Instructions for Use.

6.2.1. Previous clinical trials using ALA HCl

No major side effects are anticipated from the consumption of ALA HCl (based on previous studies[33]). A Phase I study involving 21 healthy male subjects compared the absolute bioavailability of oral (20 mg/kg BW) relative to i.v. (2 mg/kg BW) ALA HCl administration and evaluated the duration of photosensitization of the skin by observing the minimal erythemal dose and corresponding PpIX plasma concentrations after oral treatment. Just 1 adverse event (AE) occurred in 1 subject 2.02 hours after oral administration. The symptom was mild nausea, assessed as probably drug related. The AE resolved without any action taken after 3 hours. There were no effects of the ALA HCl on laboratory values of clinical chemistry, hematology, and urinalysis; vital signs; electrocardiogram (ECG) parameters; or physical findings. Overall, both oral and i.v. formulations were assessed as safe and tolerable.

The administration of low (< 60 mg/kg BW) doses of ALA has no known long-term risks and is associated with minimal side effects[38]. In the case of 139 patients given 20 mg/kg orally for contrast in malignant glioma[33] a toxicological safety analysis noted no concerns. Oral doses of 40 mg/kg[34] were also well tolerated, with transient minor side effects (facial erythema, peri-nasal swelling) dissipating within 72 hours of the applied dose. The same study also reported 5 patients who received doses as high as 60 mg/kg, which increased the intensity (but not the duration) of these side effects and was also associated with nausea in 3 of the 5 patients.

6.2.2. Anticipated adverse drug effects

Detailed information about anticipated adverse drug effects can be found in the Investigator's Brochure.

6.2.3. Residual device risk and mitigation

There is a potential risk that the imaging end of the Eagle V1.2 Imaging System may reach up to 50 degrees Celsius (122 degrees Fahrenheit) if used for a long time without turning off the white or blue lights on the camera. This temperature may cause burns.

No burns linked to the use of the Eagle V1.2 Imaging System have been reported. To minimize this risk, the Eagle V1.2 Imaging System has temperature indicators to alert the user of increases

in temperature before the imaging end reaches a temperature that may burns. Additionally, the lights will automatically turn off to minimize the risk of burns.

All users will be trained on how to use the Eagle V1.2 Imaging System in a way that minimizes the risk of causing burns.

Intraoperative imaging will be performed of the surgical cavity and excised tissue (lumpectomy, standard of care revisions and FL-guided revisions) following SoC BCS. The Eagle V1.2 Imaging Device will be covered in a custom sterile surgical sleeve in order to maintain sterility of the sterile operating field. The previous study conducted at Princess Margaret Cancer Centre (study #10-0633) has demonstrated no adverse events or any effect on standard histopathological analysis of specimens for clinical diagnosis related to the study imaging procedure.

6.2.4. Anticipated adverse device effects

There are no known or anticipated adverse device effects.

6.2.5. Anticipated clinical benefit

Study patients who receive PD G 506 A (i.e., all participants in Part A and Part B patients randomized to Arm 2) may experience a clinical benefit as a result of their participation in the study. Arm 2 patients with residual carcinoma in the cavity or on the ***final margins after SoC*** may have the residual carcinoma in the cavity resected and/or the final margins converted from carcinoma-positive after SoC to carcinoma-negative as a result of ***FGR.*** If ***FGR*** improves (decreases) the positive margin rate after surgery, Arm 2 patients may also benefit from not having to undergo a second surgery to achieve negative margins.

6.2.6. Risks associated with participation and risk-to-benefit ratio

Patients choosing to participate in this trial may experience side effects related to the investigational drug. To minimize the potential photosensitizing effect of PpIX, patients will be provided with oral and written instructions on how to protect themselves from possible photosensitivity reactions within the first 48 hours following ingestion, including avoiding exposure to sunlight, wearing sunscreen while outside, maintaining dim lighting, and wearing protective clothing (e.g. clothes covering the limbs, hat). Additional sunscreen will be given to the patient to take home following discharge.

Patients choosing to participate in this trial may experience a slightly longer surgical procedure (~5-10 minutes) than those not participating in this trial. Arm 1 participants will receive SoC BCS. In all Part A study patients and in Part B patients randomized to Arm 2, additional ***cavity shave margins*** will be resected when red fluorescence is observed following SoC BCS. ***FL-guided cavity shave specimens*** will be collected when red fluorescence is observed on any ***cavity surface*** and/or specimen ***surface*** (e.g. anterior, posterior, lateral, medial, inferior, superior) until no additional red PpIX fluorescence is observed or the clinician determines resection of additional tissue is either

not possible or not in the patient's best interest based on the ***surgeon's*** clinical judgement. All Part A patients and patients randomized to Arm 2 in Part B may have additional tissue removed from their breast as compared to SoC as a result of the ***FGR***, which may affect the cosmetic outcome of the procedure. However, the literature suggests that resection of non-targeted (circumferential) ***cavity shave specimens*** following SoC decreases the rate of positive margins with no or minimal effect on cosmesis[37, 38]. Arm 2 participants will undergo directed shaving of fluorescence-positive margins and therefore are not expected to experience any negative impact on cosmetic outcomes. Obtaining ***cavity shave specimens*** is a standard procedure performed as part of ***SoC margin assessment*** (e.g. in response to a positive specimen radiographic finding).

Overall, there is minimal risk associated with participation in the study and participants may benefit from having the need for a second surgery due to ***histopathology-positive margins*** following the ***index surgical procedure*** eliminated (in Part A patients and Part B Arm 2 patients).

7. Objectives and Endpoints

7.1. Primary Objective and Endpoint

Primary Objective	Primary Endpoint		
	Parameter Description	**Parameter Formula**	**Abbreviated Description**
1. To evaluate the efficacy of PD G 506 A by demonstrating the clinical usefulness of PDG 506A to identify additional malignant breast tissue during BCS after SoC	Percentage of patients with at least one histopathology-positive margin following SoC who then have ALL histopathology-negative margins following FGR, among all patients imaged.	P(1.1) Conversion Rate = $\frac{\text{\# patients with at least one histopathology-positive margin following SoC and histopathology negative final margins after FGR}}{\text{All patients imaged (Arm 2)}}$ x 100%	Conversion rate among all patients

7.2.Secondary Objectives and Endpoints

7.2.1. Key Secondary Objectives

Secondary Objective	Parameter Description	Parameter Formula	Abbreviated Description
1. To evaluate the efficacy of PD G 506 A by demonstrating the clinical usefulness of PDG 506A to identify additional malignant breast tissue during BCS (Arm 2 only).	Percentage of patients with at least one histopathology-positive margin following SoC who then have histopathology-negative margins following FGR (participant-level analysis; Arm 2 only).	P(2.1) = # patients with at least one histopathology-positive margin following SoC and histopathology negative final margins after FGR / # patients with histopathology positive final margins after SoC x 100%	Conversion rate among patients with SoC positive margins
To characterize the diagnostic performance of PDG 506A to identify malignant breast tissue (Arm 2 only).	2. Patient-level specificity of PD G 506 A-induced fluorescence (following SoC BCS) to determine the presence or absence of residual cancer in the surgical cavity at the initial fluorescence assessment at the end of SoC as compared to the final margin histopathology.	P(2.2) Specificity = TN Patient / TN Patient + FP Patient x 100%	Patient-level specificity to identify residual carcinoma at the initial fluorescence assessment at the end of SoC

Secondary Objective	Parameter Description	Parameter Formula	Abbreviated Description
	3.Patient-level sensitivity of PD G 506 A-induced fluorescence (following SoC BCS) to determine the presence or absence of residual cancer in the surgical cavity at the initial fluorescence assessment at the end of SoC as compared to the final margin histopathology.	P(2.3) Sensitivity = TP Patient / (TP Patient + FN Patient) x 100%	Patient-level sensitivity to identify residual carcinoma at the initial fluorescence assessment at end of SoC

7.2.2. Secondary Objectives

Secondary Objectives	Parameter Description	Parameter Formula		Abbreviated Description
4. To characterize the diagnostic performance of imaging of PD G 506 A to identify malignant breast tissue (Arm 2 only)	Orientation-level diagnostic performance of PD G 506 A-induced fluorescence to determine the presence or absence of residual cancer in the surgical cavity at the end of SoC as compared to the final margin histopathology.	P(2.4) Sensitivity = $\frac{\text{TP Orientation}}{\text{TP Orientation + FN Orientation}}$	x 100%	Orientation level diagnostic performance to identify carcinoma with FGR after SoC
		P(2.4) Specificity = $\frac{\text{TN Orientation}}{\text{TN Orientation + FP Orientation}}$	x 100%	
		P(2.4) PPV = $\frac{\text{TP Orientation}}{\text{TP Orientation + FP Orientation}}$	x 100%	
		P(2.4) NPV = $\frac{\text{TN Orientation}}{\text{TN Orientation + FN Orientation}}$	x 100%	
5. To characterize the diagnostic performance of imaging of PD G 506 A to identify malignant breast tissue (Arm 2 only)	Orientation-level diagnostic performance of PD G 506 A-induced fluorescence to determine the presence or absence of residual cancer in the surgical cavity at the end of FGR as compared to the final margin histopathology.	P(2.5) Sensitivity = $\frac{TP\ Orientation}{TP\ Orientation + FN\ Orientation}$	x 100%	Orientation level diagnostic performance to identify carcinoma at the end of FGR
		P(2.5) Specificity = $\frac{TN\ Orientation}{TN\ Orientation + FP\ Orientation}$	x 100%	

Secondary Objectives	Parameter Description	Parameter Formula		Abbreviated Description
		P(2.5) PPV = $\frac{TP\ Orientation}{TP\ Orientation + FP\ Orientation}$	x 100%	
		P(2.5) NPV = $\frac{TN\ Orientation}{TN\ Orientation + FN\ Orientation}$	x 100%	
6. To characterize the diagnostic performance of imaging of PD G 506 A to identify malignant breast tissue (Arm 2 only).	Patient-level sensitivity of PD G 506 A-induced fluorescence (following SoC BCS) to determine the presence or absence of residual cancer in the surgical cavity at the end of FGR as compared to the final margin histopathology.	P(2.6) Sensitivity = $\frac{\text{TP Patient}}{\text{TP Patient + FN Patient}}$	x 100%	Patient-level sensitivity to identify residual carcinoma after FGR is complete.
	Patient-level specificity of PD G 506 A-induced fluorescence (following SoC BCS) to determine the presence or absence of residual cancer in the surgical cavity at the end of FGR as compared to the final margin histopathology.	P(2.6) Specificity = $\frac{\text{TN Patient}}{\text{TN Patient + FP Patient}}$	x 100%	Patient-level specificity to identify residual carcinoma after FGR is complete.

Secondary Objectives	Parameter Description	Parameter Formula		Abbreviated Description
7. To characterize the diagnostic performance of PD G 506 A to identify malignant breast tissue (Arm 2 only).	Patient-level Positive Predictive Value (PPV) of PD G 506 A-induced fluorescence (following SoC BCS) to determine the presence or absence of residual cancer in the surgical cavity at the initial fluorescence assessment at end of SoC as compared to the margin histopathology.	P(2.7) PPV = $\frac{\text{TP Patient}}{\text{TP Patient + FP Patient}}$	x 100%	Patient-level PPV to identify residual carcinoma at the initial fluorescence assessment at end of SoC.
	Patient-level Negative Predictive Value (NPV) of PD G 506 A-induced fluorescence (following SoC BCS) to determine the presence or absence of residual cancer in the surgical cavity at the initial fluorescence assessment at end of SoC as compared to the margin histopathology.	P(2.7) NPV = $\frac{\text{TN Patient}}{\text{TN Patient + FN Patient}}$	x 100%	Patient-level NPV to identify residual carcinoma at the initial fluorescence assessment at end of SoC.
8. To characterize the diagnostic performance of PD G 506 A to identify malignant breast tissue (Arm 2 only).	Patient-level diagnostic performance characteristics of sensitivity, specificity, PPV and NPV to determine the presence or absence of cancer in the surgical cavity after SoC BCS. For this analysis, all orientations following SoC through the end of FGR are considered in definitions of TP Patient, TN Patient, FP Patient and FN Patient.	P(2.8) Sensitivity = $\frac{\text{TP Patient}}{\text{TP Patient + FN Patient}}$	x 100%	Patient-level diagnostic performance of PD G 506 A to detect cancer after SoC BCS.
		P(2.8) Specificity = $\frac{\text{TN Patient}}{\text{TN Patient + FP Patient}}$	x 100%	
		P(2.8) PPV = $\frac{\text{TP Patient}}{\text{TP Patient + FP Patient}}$	x 100%	
		P(2.8) NPV = $\frac{\text{TN Patient}}{\text{TN Patient + FN Patient}}$	x 100%	

Secondary Objectives	Parameter Description	Parameter Formula		Abbreviated Description
9 To characterize the diagnostic performance of PD G 506 A to identify malignant breast tissue (Arm 2 only).	Percentage of patients assessed as residual tumor negative at the end of FGR (i.e., the final surgical cavity after FGR is completely FL-negative as are the corresponding final margin surfaces) who had positive margins on histopathology.	P(2.9a) = FN Patient / #patients assessed residual tumor negative by FL imaging at the end of surgery(i.e., TN patient + FN patient)	x100%	Patient-level false negative rate of carcinoma at the end of FGR.
		P(2.9b) = FN Patient / All patients imaged (Arm 2)	x100%	
10. To characterize the diagnostic performance of PD G 506 A to identify malignant breast tissue after SoC BCS (Arm 2 only).	Percentage of patients assessed as residual tumor positive by FL imaging at the initial fluorescence assessment at end of SoC (i.e., at least one orientation having a surface that was FL-positive either in the cavity or on the corresponding final shave or specimen margin at the end of SoC) who had negative margins on pathology following SoC and no cancer identified in any FL-guided shave specimen.	P (2.10a) = # patients with ≥ 1 FL-positive orientation at the end of SoC and all carcinoma-negative final margins after SoC and carcinoma-negative FL-driven cavity shave specimens / # patients assessed residual tumor positive by FL imaging at the end of SoC	x100%	Percentage of patients in whom SOC final margins were carcinoma negative and all FL-driven shave specimens were carcinoma-negative (patient-level false positive rate).
		P (2.10b) = # patients with ≥ 1 FL-positive orientation at the end of SoC and all carcinoma-negative final margins after SoC and carcinoma-negative FL-driven cavity shave specimens / All patients imaged (Arm 2)	x100%	

Secondary Objectives	Parameter Description	Parameter Formula		Abbreviated Description
11. To determine how often FGR with PD G 506 A will result in the removal of any additional carcinoma	Percentage of patients with histopathology-negative margins at the initial fluorescence assessment at the end of SoC who have at least one orientation that was both FL-positive and histopathology-positive. This analysis is only done in those patients who have a FL driven shave obtained as a result of FL-positive orientation identified after SoC. Patients who have cancer anywhere in a FL driven shave obtained as a result of the FL-positive orientation can contribute to the numerator of this endpoint.	P(2.11a) = # patients with histopathology-negative final margins after SoC and at least one FGR TP orientation / # patients with histopathology-negative final margins after SoC	x100%	Percentage of patients with carcinoma-negative margins after SoC found to have residual tumor following SoC that was identified intraoperatively with combined FL imaging.
		P(2.11b) = # patients with histopathology-negative final margins after SoC and at least one FGR TP orientation / All patients imaged (Arm 2)	x100%	
12.To characterize the diagnostic performance of PD G 506 A to identify malignant breast tissue after SoC BCS (Arm 2 only).	Percentage of patients with no fluorescence identified at the initial fluorescence assessment at the end of SoC (in either the cavity or on the corresponding final margin surfaces after SoC) in whom all final margins after SoC are histopathologically confirmed to be negative for carcinoma.	P(2.12a) = # patients with only FL-negative orientations after SoC and histopathology negative final margins after SoC (i.e. TN Patient after SoC) / # patients with only FL-negative orientations after SoC	x100%	
		P(2.12b) = # patients with only FL-negative orientations after SoC and histopathology negative final margins after SoC (i.e. TN Patient after SoC) / All patients imaged (Arm 2)	x100%	
13. To characterize the diagnostic performance of in vivo imaging of PD G 506 A	Patient-level in vivo diagnostic performance of PD G 506 A-induced fluorescence (following SoC BCS) to	P(2.13) Sensitivity = TP Patient (*in vivo*) / TP Patient (*in vivo*) + FN Patient (*in vivo*)	x100%	Patient-level in vivo diagnostic performance to

Secondary Objectives	Parameter Description	Parameter Formula		Abbreviated Description
to identify malignant breast tissue (Arm 2 only).	determine the presence or absence of residual cancer in the surgical cavity at the end of FGR as compared to the final margin histopathology. Only FL-positive orientation-in vivo and FL-negative orientation-in vivo orientations are included in the patient-level diagnostic performance definitions for this analysis. FL-assessment of in vivo tissue in the final cavity will be compared to histopathological status of final margins of the ex vivo tissue specimens.	P(2.13) Specificity = $\frac{\text{TN Patient}}{\text{TN Patient + FP Patient}}$	x100%	identify residual carcinoma after FGR is complete.
		P(2.13) PPV = $\frac{\text{TP Patient } (\textit{in vivo})}{\text{TP Patient } (\textit{in vivo}) + \text{FP Patient } (\textit{in vivo})}$	x100%	
		P(2.13) NPV = $\frac{\text{TN Patient } (\textit{in vivo})}{\text{TN Patient } (\textit{in vivo}) + \text{FN Patient } (\textit{in vivo})}$	x100%	
14. To determine the frequency with which fluorescence is found only on one of the opposing surfaces in an orientation.	Percentage of orientations where in vivo FL imaging disagrees with ex vivo FL imaging (e.g., FL-negative cavity surface but FL-positive corresponding shave or specimen margin surface, or vice versa). FL imaging at all points during the surgery (not just at the end) are used for this endpoint.	P(2.14) = $\frac{\text{\# orientations where FL status of Orientation-}\textit{in vivo}\text{ is discordant with FL status of Orientation-}\textit{ex vivo}}{\text{All Orientations}}$	x100%	Percentage of orientations with discordant FL status.
15. To characterize the impact of FGR on the rate of 2nd surgery within 1 year	Percentage of patients receiving a 2nd surgery on the ipsilateral breast within 1 year of index BCS to remove	P(2.15a) Arm 1 only =	x100%	Patient-level re-operation rate due to suspected residual disease.

Secondary Objectives	Parameter Description	Parameter Formula		Abbreviated Description
following index BCS (Arm 1 and Arm 2).	suspected residual disease (patient-level analysis; Arm 1 and Arm 2).	P(2.15b) Arm 2 only = $\frac{\text{\# of patients in Arm 1 that underwent a 2nd surgery on the ipsilateral breast within 1 year of index BCS}}{\text{\# of patients in Arm 1}}$ $\frac{\text{\# of patients in Arm 2 that underwent a 2nd surgery on the ipsilateral breast within 1 year of index BCS}}{\text{\# of patients in Arm 2}}$	x100%	
16. To characterize the impact of FGR on the rate of 2nd surgery shortly after index BCS (Arm 1 and Arm 2).	Percentage of patients receiving an early 2nd surgery (planned or actual) on the ipsilateral breast related to positive final margins prior to radiation or medical management (patient-level analysis; Arm 1 and Arm 2).	P(2.16a) Arm 1 only = $\frac{\text{\# of patients in Arm 1 that underwent or are scheduled to undergo a 2nd surgery on the ipsilateral breast due to positive SoC final margins following initial BCS prior to radiation or medical management}}{\text{\# of patients in Arm 1}}$	x100%	Patient-level early re-operation rate.
		P(2.16b) Arm 2 only = $\frac{\text{\# of patients in Arm 2 that underwent or are scheduled to undergo a 2nd surgery on the ipsilateral breast due to positive FGR final margins following initial BCS prior to radiation or medical management}}{\text{\# of patients in Arm 2}}$	x100%	

Secondary Objectives	Parameter Description	Parameter Formula	Abbreviated Description
17. To characterize the impact of FGR during BCS on the amount of tissue removed (Arm 1 and Arm 2).	Sum of the weight (mg) of all tissue removed based on SoC compared to the sum of the weight (mg) of all tissue removed based on FGR (patient-level analysis; Arm 1 and Arm 2).	P(2.17a) = Mean SoC tissue weight (mg) Arm 1 and Arm 2: SoC tissue weight = Primary specimen (mg) + SoC-driven cavity shave specimen(s) (mg) P(2.17b) = Mean FGR tissue weight (mg) Arm 2 only: Total tissue weight = FL-driven cavity shave specimen(s) (mg)	Amount of tissue removed with FGR beyond SoC.
18.To characterize the impact of FGR during BCS on the patient-reported cosmetic outcome (Arm 1 and Arm 2).	Patient satisfaction with the cosmetic outcome of breast conserving surgery performed based on SoC in combination with PD G 506 A and the Eagle V1.2 Imaging System compared to SoC (patient-level analysis; Arm 1 and Arm 2) This endpoint will be assessed at 3, 6, and 12 months.	P(2.18a) = Mean Breast-Q Breast Conserving Therapy Module satisfaction with breasts score before and after SoC surgery. P(2.18b) = Mean Breast-Q Breast Conserving Therapy Module satisfaction with breasts score before and after SoC surgery + FGR.	Patient satisfaction.

7.3.Exploratory Objectives and Endpoints

Exploratory Objective	Parameter Description	Parameter Formula	Abbreviated Description
19. To characterize the diagnostic performance of *ex vivo* imaging of PD G 506 A to identify	Patient-level *ex vivo* diagnostic performance of PD G 506 A-induced fluorescence to determine the presence or absence of residual	P(E.19) Sensitivity = $\frac{\text{TP Patient (}ex\ vivo\text{)}}{\text{TP Patient (}ex\ vivo\text{) + FN Patient (}ex\ vivo\text{)}}$ x 100%	Patient-level *ex vivo* specificity to identify residual carcinoma after FGR is complete.

Exploratory Objective	Parameter Description	Parameter Formula	Abbreviated Description
malignant breast tissue (Arm 2 only).	cancer in the surgical cavity at the <u>end of FGR</u> as compared to the final margin histopathology. Only FL-positive orientation- *ex vivo* and FL-negative orientation- *ex vivo* orientations are included in the patient-level diagnostic performance definitions for this analysis.	P(E.19) Specificity = $\frac{\text{TN Patient (}ex\ vivo\text{)}}{\text{TN Patient (}ex\ vivo\text{) + FP Patient (}ex\ vivo\text{)}}$ x 100%	
		P(E.19) PPV = $\frac{\text{TP Patient (}ex\ vivo\text{)}}{\text{TP Patient (}ex\ vivo\text{) + FP Patient (}ex\ vivo\text{)}}$ x 100%	
		P(E.19) NPV = $\frac{\text{TN Patient (}ex\ vivo\text{)}}{\text{TN Patient (}ex\ vivo\text{) + FN Patient (}ex\ vivo\text{)}}$ x 100%	
20. To determine the frequency with which PD G 506 A-induced fluorescence is visualized but that tissue is not resected (Arm 2 only).	Percentage of patients who did not have a FL-guided shave although indicated by FL imaging.	P(E.20a) = $\frac{\text{\#Patients with} \geq 1\ \text{FL-positive orientation where no FL-driven shave was resected}}{\text{\#Patients with} \geq 1\ \text{FL-positive orientation}}$ x 100%	Fluorescence-positive tissue that cannot be resected.
		P(E.20b) = $\frac{\text{\#Patients with} \geq 1\ \text{FL-positive orientation where no FL-driven shave was resected}}{\text{\#Patients in Arm 2}}$ x 100%	
		P(E.20c) Clinical outcomes (e.g., positive final margin rate, need for 2nd surgery) will also be reported for patients ≥ 1 FL-positive orientation but the FL-driven shave(s) was not resected	

Exploratory Objective	Parameter Description	Parameter Formula	Abbreviated Description
21. To characterize the diagnostic performance of imaging of PD G 506 A to identify malignant breast tissue (Arm 2 only).	Percentage of FL guided shaves that had no cancer on histopathology.	$P(E.21) = \frac{\text{\# FL-driven shave specimens with no carcinoma anywhere}}{\text{\# of FL-driven shave specimens}} \times 100\%$	Carcinoma negative FL-driven shave specimens.
22. To investigate the depth of carcinoma tissue that can be visualized by PD G 506 A using the Eagle V1.2 Imaging System.	Depth of tumor identified by FL imaging relative to the inked surface, reported by tumor type (invasive carcinoma and DCIS), using descriptive statistics (e.g., mean, median, and range).	--	Depth of FL visualization.
23. To investigate the depth of carcinoma tissue that can be visualized by PD G 506 A using the Eagle V1.2 Imaging System.	Percentage of specimens where invasive carcinoma was located only below the inked surface (i.e., inked surface cancer free) for the surfaces imaged *ex vivo* (primary specimen or shave specimens) where FL detected invasive carcinoma.	$P(E.23) = \frac{\text{\#FL-positive orientations-}ex\ vivo \text{ where invasive carcinoma was located only below the inked surface (i.e., inked surface cancer free)}}{\text{\#FL-positive orientations } ex\ vivo \text{ with invasive carcinoma}} \times 100\%$	Fluorescence visualization of invasive carcinoma below the imaged surface.
24. To investigate the depth of carcinoma tissue that can be visualized by PD G 506 A using the Eagle V1.2 Imaging System.	Percentage of specimens where DCIS was only located deeper than 2 mm below the inked surface (i.e., DCIS not within 2 mm of the inked surface) for the surfaces imaged *ex vivo* (primary specimen or shaves) where FL detected DCIS.	$P(E.24) = \frac{\text{\#FL-positive DCIS orientations-}ex\ vivo \text{ where DCIS was only located deeper than 2 mm below the inked surface (i.e., DCIS not within 2 mm of the inked surface)}}{\text{\#FL-positive orientations-}ex\ vivo \text{ with DCIS}} \times 100\%$	Fluorescence visualization of DCIS > 2 mm below the imaged surface.

Exploratory Objective	Parameter Description	Parameter Formula	Abbreviated Description
25. To characterize the diagnostic performance of imaging of PD G 506 A to identify malignant breast tissue (Arm 2 only).	For those primary specimens containing cancer anywhere on the bisected surfaces, the proportion that displayed fluorescence in any area/region. Primary specimen examination will only be conducted at a subgroup of clinical sites.	P(E.25)= $\frac{\text{\# sectioned primary specimens with carcinoma anywhere and positive fluorescence anywhere}}{\text{\# sectioned primary specimens with carcinoma anywhere}}$ x 100%	Sensitivity of PD G 506 A to identify carcinoma inside the primary specimen.
26. To characterize the diagnostic performance of PD G 506 A using the Eagle V1.2 Imaging System to identify malignant breast tissue in the primary specimen (Arm 2 only).	Diagnostic performance of PD G 506 A-induced fluorescence to determine the presence or absence of cancer inside the sectioned primary specimen. Primary specimen examination will only be conducted at a subgroup of clinical sites.	P(E.26) Sensitivity = $\frac{TP}{TP + FN}$ x 100% P(E.26) Specificity = $\frac{TN}{TN + FP}$ x 100% P(E.26) PPV = $\frac{TP}{TP + FP}$ x 100% P(E.26) NPV = $\frac{TN}{TN + FN}$ x 100%	Diagnostic performance of PD G 506 A to detect cancer in the primary specimen.

Exploratory Objective	Parameter Description	Parameter Formula	Abbreviated Description
27. To characterize the diagnostic performance of *ex vivo* imaging of PD G 506 A to identify malignant breast tissue (Arm 2 only).	Sensitivity, specificity, NPV, and PPV of *ex vivo* FL imaging of primary specimen margin surfaces and all cavity shave specimen(s) (SoC or FL-guided). SSO/ASTRO definitions of histopathology positive/negative will be used.	P(E.27) Sensitivity = $\frac{\text{TP Orientation (}ex\ vivo\text{)}}{\text{TP Orientation (}ex\ vivo\text{)} + \text{FN Orientation (}ex\ vivo\text{)}}$ x 100%	Orientation-level *ex vivo* diagnostic performance for all specimens using SSO/ASTRO definitions (direct ground truth only).
		P(E.27) Specificity = $\frac{\text{TN Orientation (}ex\ vivo\text{)}}{\text{TN Orientation (}ex\ vivo\text{)} + \text{FP Orientation (}ex\ vivo\text{)}}$ x 100%	
		P(E.27) PPV = $\frac{\text{TP Orientation (}ex\ vivo\text{)}}{\text{TP Orientation (}ex\ vivo\text{)} + \text{FP Orientation (}ex\ vivo\text{)}}$ x 100%	
		P(E.27) NPV = $\frac{\text{TN Orientation (}ex\ vivo\text{)}}{\text{TN Orientation (}ex\ vivo\text{)} + \text{FN Orientation (}ex\ vivo\text{)}}$ x 100%	

Exploratory Objective	Parameter Description	Parameter Formula	Abbreviated Description
28. To characterize the diagnostic performance of *ex vivo* imaging of PD G 506 A to identify malignant breast tissue (Arm 2 only).	Sensitivity, specificity, NPV, and PPV of *ex vivo* FL imaging of the imaged surfaces of the primary bisected specimen as compared to the histopathology of the corresponding biopsies.	P(E.28) Sensitivity = $\frac{\text{TP primary specimen biopsy}}{\text{TP primary specimen biopsy} + \text{FN primary specimen biopsy}} \times 100\%$	Diagnostic performance inside the primary specimen.
		P(E.28) Specificity = $\frac{\text{TN primary specimen biopsy}}{\text{TN primary specimen biopsy} + \text{FP primary specimen biopsy}} \times 100\%$	
		P(E.28) PPV = $\frac{\text{TP primary specimen biopsy}}{\text{TP primary specimen biopsy} + \text{FP primary specimen biopsy}} \times 100\%$	
		P(E.28) NPV = $\frac{\text{TN primary specimen biopsy}}{\text{TN primary specimen biopsy} + \text{FN primary specimen biopsy}} \times 100\%$	

7.4.Safety Objectives and Endpoints

Safety Objective	Safety Endpoints		
	Parameter Description	Parameter Formula	Abbreviated Description
Characterize the safety of PD G 506 A and the Eagle V1.2 Imaging System in patients undergoing fluorescence imaging during breast cancer surgery (Arm 1 and Arm 2).	Rate of procedure-related WHO grade 3-5 adverse events.	P(S.1) = # of procedure related AEs (WHO grade ≥3)	Safety of the procedure.
	Rate of drug-related WHO grade 3-5 adverse events.	P(S.2) = # of drug related AEs (WHO grade ≥3)	Safety of the drug.
	Rate of device-related WHO grade 3-5 adverse events.	P(S.3) = # of device related AEs (WHO grade ≥3)	Safety of the device.

Safety assessments will include:

- Adverse events
- Serious adverse events
- Blood analysis: complete blood count, aspartate aminotransferase, alanine transaminase, total bilirubin level, creatinine

8. Study Design

8.1. Description of the Study Design

This pivotal study is a 2-part, double -blind (pathologist(s) & patient – blinded) randomized placebo-controlled trial (Arm 1: placebo + SoC BCS, Arm 2: SoC BCS + Eagle V1.2 Imaging System + PD G 506 A) to evaluate the ***patient-level*** clinical usefulness, as well as ***patient-*** and ***orientation-level*** diagnostic performance and safety of PD G 506 A-induced fluorescence for the real-time visualization of carcinoma missed by SoC lumpectomy for breast cancer. Part A is an open-label training phase of the study to optimize workflow and train ***surgeon's*** and ***surgeon's assistant*** on the day 1 study-specific procedures; Part B of the study is randomized and double -blind and will serve as the pivotal portion of the study. The Eagle V1.2 Imaging System will be used for the visualization of fluorescence. SBI ALApharma Canada requires completion of the Investigator Training Program to ensure the controlled distribution and safe use of PD G 506 A investigational drug and the Eagle V1.2 Imaging System investigational medical device to trained surgeons for use in clinical trials.

Part A will not be randomized; all participants in Part A will receive PD G 506 A. The Day 1 procedures for Part A patients will be carried out with support and oversight from the Sponsor. Part A will include approximately 75 patients. Data acquired from the first 30 patients in Part A will be used to optimize the study workflow and to confirm the sample size for Part B. The remaining approximately 45 patients on Part A will be allocated to training for ***surgeon's*** and ***surgeon's assistants*** prior to their enrolling patients into Part B. All ***surgeon's*** and ***surgeon's assistants*** must complete at least 1 procedure in Part A, before enrolling a patient into Part B. A given site can only be enrolling patients for either Part A or Part B at any given time. In the event a new ***surgeon*** is brought onto the study after the site has begun enrolling patients into Part B, they must shadow a study surgeon for at least one Arm 2 patient procedure. In the event a new ***surgeon's assistant*** is brought onto the study after the site has begun enrolling patients into Part B, they must shadow a study surgeon assistant for at least one patient procedure before participating in as the ***surgeon's assistant.***

Only data from participants in Part B will be used for the analyses of primary and secondary efficacy. Data from all participants in both Part A and Part B will be used for the evaluation of safety.

In Part B of the study, participants will be randomized in a ratio of 1:6 (Arm 1 [SoC]: Arm 2 [PD G 506 A]).

The randomization will be stratified by breast cancer type (invasive carcinoma with or without in situ carcinoma vs. in situ carcinoma alone). This will ensure an approximate ratio of 1:6 within each type of breast cancer. Preoperative diagnosis based on diagnostic tissue sampling performed during screening (e.g. percutaneous core needle biopsy, fine-needle aspiration cytology) will be

used for stratification. Permuted blocks will be used to construct the randomization schedule and the randomization will be implemented using an interactive web response system.

Data from the SoC arm (Arm 1) will not be used for statistical analysis of the primary and most secondary endpoints. The purpose of the SoC arm is to compare resected tissue weight, patient reported cosmetic outcomes, re-excision prior to initiation of adjuvant therapies, re-excision within 1-year of index BCS, and safety between study arms as well as to minimize bias introduced into the SoC procedure if the ***surgeon*** is aware that they have an opportunity to revise the margins further after SoC is complete. A 3-month, 6-month and 1-year follow-up will be performed to evaluate patient reported cosmetic outcomes as well as the rate of re-excision across both study arms. The 6-month and 1-year follow-up data will be collected as an extension phase to the study, meaning database lock and analysis of all other endpoints will be performed following the last patient's 3-month follow-up data is collected. Analysis of 6-month and 1-year data will occur after the last patients 1-year visit. The clinical study report will be appended to include the 6-month and 1-year data, when available.

8.2. Patient and Study Completion

A study patient is considered to have completed the study if she has completed all phases of the study, including the post-operative follow-up visit (10 -14 days after their surgical procedure), and data through the 1-year follow-up has been retrieved and recorded. A study site will be closed only after all follow-up data through 1-year are collected on all patients from that site.

For analyses of Primary and Secondary efficacy endpoints, the end of the study is defined by the receipt of the 3-month follow-up data from the last patient in the study. The end of the extension phase of the study is defined as the date the 1-year follow-up data is retrieved and recorded for the last participant in the study.

8.3.Minimizing Bias

The following precautions are in place to minimize bias in data collection:

- No personnel involved with the surgical procedure (i.e., ***surgeon***, ***surgeon's assistant***) will be aware of the participant's randomized treatment assignment nor be present when the participant is provided with the study drug to ingest.
    - Blinded research personnel will be instructed not to solicit any information from the participant regarding the taste and/or smell of the investigational drug.
- The participant will be blinded to whether they have been randomized to Arm 1 or Arm 2 for the duration of the study.
- The ***surgeon*** will be blinded to whether a participant has been randomized to Arm 1 or Arm 2 until the time at which the ***surgeon*** declares the SoC lumpectomy is complete.
- The individual (e.g. pathologist's assistant, pathologist) processing the surgical specimen(s) will be blind to the manner (e.g. SoC vs. ***FGR***) by which samples are obtained and the FL status of the samples. This individual will also be blind to the fluorescence

imaging data collected of the bisected/serially sectioned primary specimen during the perioperative procedures.

- The pathologist performing the histopathological evaluation will be blind to the manner (e.g. SoC vs. ***FGR***) by which the samples are obtained and the FL status of the samples.
- To ensure FL-imaging does not influence ***SoC margin assessment***, intraoperative data collection tools will document the completion of SoC prior to the ***surgeon*** being given access to any previously acquired FL imaging data and performing additional FL imaging.

8.4.Scientific Rationale for Study Design

ALA is an endogenous molecule and a precursor of heme. Exogenous administration of ALA leads to accumulation of PpIX in cells.

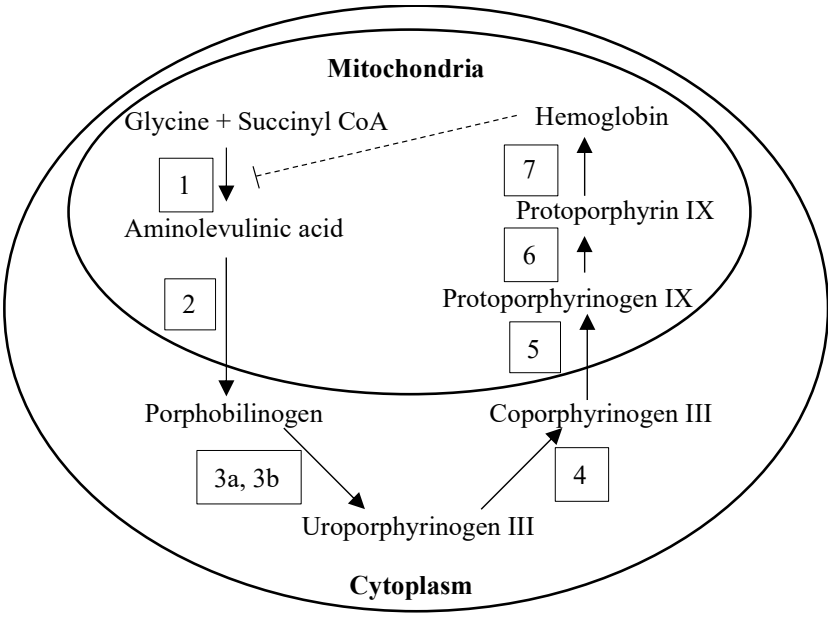


Figure 8.1 Biosynthesis of Heme[39-41].
Heme biosynthesis with ALA as the starting product. Enzymes involved are: 1, ALA synthase; 2, porphobilinogen synthase; 3a, PBGD; 3b, uroporphyrinogen-III synthase, 4, uroporphyrinogen decarboxylase; 5, copro-porphyrinogen oxidase; 6, protoporphyrinogen oxidase; 7, ferrochelatase.

The primary pharmacodynamic effect of exogenous ALA HCl administration is the specific accumulation of porphyrins, especially PpIX. This accumulation is due to an increase in the biosynthesis of these porphyrins. Figure 8.1 shows a schematic representation of heme biosynthesis.

Since mammalian cells require hemoproteins, i.e. cytochromes, for aerobic energy metabolism (oxidative phosphorylation), all nucleated cells have at least a minimal capacity to synthesise heme. Moreover, heme is the prosthetic group of several other key proteins, such as hemoglobin,

myoglobin, catalase, and peroxidase. Heme biosynthesis is tightly controlled by various feedback loops. In hepatocytes, feedback inhibition of ALA synthase is mediated by a free heme pool[42], i.e. free heme is involved in the regulation of its own synthesis. Therefore, the rate of PpIX synthesis is also mediated by the availability of free heme. Details of the regulation of heme biosynthesis have been reviewed[42-44].

In animal studies, PpIX has been proven to be the predominant metabolite after exogenous ALA administration by means of *in vivo* and *ex vivo* fluorescence spectroscopy[45-48] as well as HPLC analysis of tissue extracts[49-51]. However, considerable amounts of hydrophilic porphyrins, e.g. uroporphyrin and coproporphyrin, have been identified in experimental tumours[52-55] and tissue cultures[56].

Literature data show that malignant cells accumulate more ALA-induced PpIX than non-malignant cells from which they are derived[20, 57-61]. This may be related to different enzyme profiles in abnormal and normal tissue. Increased activity of porphobilinogen deaminase (PBGD or hydroxy-methylbilane synthase), as well as reduced activity of ferrochelatase, may contribute to enhanced PpIX accumulation[54, 62, 63]. The specific mechanisms, however, have not been elucidated. Since ferrochelatase converts PpIX into heme by the insertion of ferrous iron into the porphyrin macrocycle, iron availability *in situ* may also limit the activity of ferrochelatase in cells and tissues[64, 65], thereby contributing to the enhanced accumulation of PpIX in malignant cells. PpIX accumulates preferably in tissues and tumours of both epithelial and mesenchymal origin[33, 41, 45].

PpIX has maximum light absorption from violet light at 405 nm. To induce maximum fluorescence (without emitting high levels of harmful UV light), the Eagle V1.2 Imaging System utilizes violet LEDs with a narrow range of wavelengths centered around 405 nm to excite the PpIX. Using violet-blue light excitation (peak emission 405 nm), the Eagle V1.2 Imaging System can visualize ALA-induced red PpIX fluorescence emitted by malignant cells in patients who have received oral-ALA prior to surgery.

The increased accumulation of PpIX in malignant cells (compared of healthy cells) as well as the unique photophysical properties of PpIX which allows it to be detected with an appropriately configured device, this provides surgeons a means by which to visualize breast carcinoma in real-time. This phase 3 pivotal trial will evaluate the clinical usefulness, diagnostic performance and safety of PD G 506 A for the visualization of breast carcinoma during BCS.

8.5. Justification for Dose

The 20 mg/kg ALA HCl dose is supported by the safety data from Gleolan in the visualization of glioma, the global post-marketing data in glioma and bladder cancer and Parts 1 and 2 Study #10-0633 (Princess Margaret Cancer Centre – Investigator-Initiated Trial).

In Parts 1 and 2 of Study #10-0633, both the 15 mg/kg and 30 mg/kg doses of PD G 506 displayed similar measures of diagnostic accuracy and no major adverse events occurred with either dose.

Both doses were lower than the only dose of ALA (40 mg/kg) previously reported for clinical use in breast cancer[33].

Therefore, it was decided that a dose between the low and high doses, and identical to the dose previously approved by FDA for Gleolan would be appropriate for PD G 506 A as well, leading to the selection of the 20 mg/kg dose for the proposed study.

Based on ALA pharmacokinetics the optimal imaging timeframe for fluorescence detection occurs over a period between 3-5 hours after administration when ALA has been sufficiently converted into PpIX and is still retained in the cells[21, 66]. In studies of ***FGR*** in glioma, patients are typically administered ALA HCl approximately 3 hours prior to anesthesia[23, 25, 32].

As described in **Section 10.1.2.4**, PD G 506 A will be administered approximately 3 hours prior to anesthesia, with a minimum time of 2 hours and a maximum time of 4 hours. This dosing time aligns with the previously characterized optimal imaging timeframe[21, 66] and is consistent with FDA-approved Gleolan labeling.

Ultimately, the proposed Phase 3 study is required to objectively test if the 20 mg/kg dose will deliver the anticipated clinical usefulness and diagnostic accuracy.

9. Study Population

9.1. Description of the population to be studied

Participants will be adult female surgical patients with breast cancer undergoing BCS.

9.2. Inclusion criteria

1. Female, 18 years or older
2. Histologically or cytologically confirmed primary breast cancer (includes invasive lobular carcinoma, invasive ductal carcinoma, inflammatory breast cancer, papillary breast cancer, adenoid cystic carcinoma of the breast, mucinous breast cancer, metaplastic breast cancer, cribriform carcinoma and ductal carcinoma *in situ,* alone or in combination with invasive disease)
3. Scheduled for a lumpectomy (including bilateral lumpectomy) of a breast malignancy [eligibility for breast conserving surgery/partial mastectomy based on clinical staging using TNM staging system (AJCC Cancer Staging Manual: Breast Cancer, 8th Edition[67])].
4. Patient must have normal organ and bone marrow function and be appropriate surgical candidate per site standard of care
5. Women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) starting the day entering the study, and for the duration of the study period (until the Week 2 visit)

9.3. Exclusion criteria

Disease and SoC treatment:

1. Currently on (neo)adjuvant therapy to treat another cancer
2. Receiving or intended to receive neoadjuvant therapy to treat the primary breast cancer (including chemotherapy, endocrine therapy and radiotherapy)
3. Stage 4 cancer, inclusive of metastatic disease
4. Non-invasive diseases of the breast (includes lobular carcinoma *in situ*, phyllodes and Paget's disease of the breast)
5. Patients who have had the following procedures performed on the involved breast:
   a) Surgery for a benign lesion(s) within 1 year of the BCS date
   b) Breast implants inserted within 1 year of the BCS date
   c) Breast reduction, surgery for malignant disease or mastectomy (at any time prior to the BCS date)
   d) Surgery for a benign lesion(s) or insertion of implants >1 year prior to the BCS date and who have signs of ongoing inflammation, active tissue healing and/or extensive scarring
   e) Radiation at any time prior to the BCS date and who have signs of ongoing inflammation, active tissue healing and/or extensive scarring
6. Patients for whom intraoperative frozen section analysis is planned

Concomitant diseases:

7. Patients who have not recovered from adverse events due an investigational pharmaceutical or diagnostic agents administered more than 30 days prior to their scheduled surgical procedure
8. History of hypersensitivity to ALA HCl or porphyrins
9. Known or documented personal or family history of porphyria
10. Patient has a recording of any parameter as defined below:
    Bilirubin: Above upper limit of normal
    AST (SGOT): > 2.5 X institutional upper limit of normal
    ALT (SGPT): > 2.5 X institutional upper limit of normal
11. Patient has an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2, calculated using the MDRD (Modification of Diet in Renal Disease Study) equation for estimating GFR.
12. Uncontrolled concurrent illness, that in the opinion of the Investigator would prevent the patient from participation in the study, including but not limited to:
    a. Ongoing or active infection;
    b. Cardiovascular disease (e.g. symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia).
13. Patients who have the following collagen vascular diseases:
    a. Lupus
    b. Scleroderma
    c. Sjogren's Syndrome

Concomitant medications:

14. Use of an investigational drug within 30 days of their scheduled surgical procedure
15. Simultaneous use of other potentially phototoxic substances (such as St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones and tetracyclines), and topical preparations containing ALA for 24 hours during the perioperative period.

Consent/compliance/other:

16. Social or medical situations including uncontrolled psychiatric illnesses that would in the opinion of the Investigator limit compliance with study requirements (e.g. ability to travel for follow-up)
17. Patients who are pregnant or become pregnant (it is unknown if ALA HCl is teratogenic or has abortifacient effects)
18. Patients who are breast feeding (there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ALA HCl, breastfeeding should be discontinued if the mother is treated with ALA HCl)
19. Inability to consent

9.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details and eligibility criteria.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if the eligibility criteria leading to the screen failure has changed since initial screening and the patient has not yet undergone surgery.

10. Treatments

10.1. Treatments Administered

10.1.1. Investigational Drug and Placebo

10.1.2. Investigational Drug Acquisition

The investigational drug will be provided to the PI by SBI ALApharma Canada Inc. The investigational drug will be acquired from SBI Pharmaceuticals Co., Ltd. (Tokyo, Japan) and imported with appropriate regulatory authorization from the importing country.

10.1.2.1. Formulation, Appearance, Packing and Labeling

The formulation intended for oral administration is aminolevulinic acid hydrochloride (ALA HCl) dissolved in drinking water. The investigational drug is supplied as 1.5 g of granulated aminolevulinic acid hydrochloride (equivalent to 1.17 g aminolevulinic acid), for oral solution in a white, aluminum/polyethylene laminated film sachet.

A single filled sachet is provided in a cardboard sleeve which is placed into a cardboard box and labeled as follows:

Sponsor/Promoteur: SBI ALApharma Canada Inc.
180 Dundas St. W, Suite 430, Toronto, ON, M5G 1Z8

Protocol/Protocole: SBI-CIP-20-002
1.5 g PD G 506 A
Aminolevulinic acid hydrochloride granules for oral solution
Reconstitution in water and dosage according to protocol
Exp: Apr/25 Lot No: ATE01
Do not store above 25°C / Ne pas conserver au-dessus de 25°C

FOR CLINICAL TRIAL USE ONLY
Investigational Drug – To be used by qualified investigators only
POUR UTILISATION ESSAI CLINIQUE UNIQUEMENT
Drogue de recherche – Réservée uniquement à l'usage des chercheurs qualifiés

Caution: New Drug – Limited by Federal (or United States) law to investigational use

The container from which the PD G 506 A or placebo will be consumed will be prepared by the site pharmacy and labeled as follows:

PD G 506 A or placebo in drinking water for (PATIENT NAME HERE)
Dosage: 20 mg/kg
Reconstituted solution: 30 mg/ml
Preparation Date: MM/DD/YYYY
Expiry Date: MM/DD/YYYY
Store at 25 degrees Celsius
Study Participant #:
Study Randomization #:

10.1.2.2. Product Storage and Stability

PD G 506 A should be stored at controlled room temperature [25°C (77°F) with excursions permitted to 15-30°C (59-86°F)]. The shelf-life at these storage conditions is 60 months. The supplied sachets will have an expiration date listed on the interior and exterior labels.

Following reconstitution in drinking water, the solution of PD G 506 A can be stored for up to 24 hours at controlled room temperature [25°C (77°F) with excursions permitted to 15-30°C (59-86°F)] prior to administration.

10.1.2.3. Preparation of the Investigational Drug

PD G 506 A powder must be reconstituted prior to administration (≤ 24 hours) according to the following instructions:

1. Determine the total number of sachets needed to achieve the intended dose for the patient according to the equation below (rounded up to the nearest whole sachet):

$$\#\ sachets = \frac{Patient\ Weight\ (kg)}{75\ kg/sachet}$$

2. Carefully tear open the sachet and transfer the entire contents to a suitably sized, glass container (e.g., flask, graduated cylinder). To facilitate storage after reconstitution, the volumetric measuring device/container should have a suitable closure (e.g., stopper).
3. Using an appropriate volumetric measuring device (e.g., flask, graduated cylinder, dosing syringe), measure 50 mL of drinking water per sachet used and add to the container of PD G 506 A powder.
4. Gently swirl the container to completely dissolve PD G 506 A.
5. The resulting reconstituted solution is clear and colorless to slightly yellowish and contains 30 mg of ALA HCl per mL of solution.
6. If required, replace the closure of the appropriately labeled reconstitution container and store reconstituted solution for up to 24 hours at room temperature prior to administration.

10.1.2.4. Dosing and Administration of the Investigation Drug

Calculate the administration volume, in mL, to achieve the intended dose according to the following:

$$Administration\ Volume\ (mL) = \frac{Patient\ Weight\ (kg) \times 20\ mg/kg}{30\ mg/mL}$$

For the calculation of administration volume, the patient's body weight, measured ≤ 7 days prior to administration of the study drug, should be used.

Using a disposable volumetric syringe, remove the administration volume of reconstituted solution (prepared according to **Section 10.1.2.4** from the dosing container and transfer to a separate amber oral dosing container. Administer orally 3 hours (range 2 to 4 hours) prior to induction of anesthesia.

10.1.2.5. Preparation and Administration of the Placebo

Participant's randomized to Arm 1 will receive drinking water as the placebo. Calculate the administration volume, in mL, according to the following:

$$Administration\ Volume\ (mL) = \frac{Patient\ Weight\ (kg) \times 20\ ml}{30\ kg}$$

10.1.2.6. Route of Administration

The investigational drug and placebo will be provided by an oral route of administration.

10.1.2.7. Handling/Storage/Accountability

1. The investigator or trained designee must confirm appropriate temperature conditions have been maintained during transit for all investigational drug received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive the investigational drug and only authorized site staff may supply or administer the investigational agent.
3. The investigational agent must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to authorized site staff.
4. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused investigational drug are provided in the Study Pharmacy Manual.

The site will return any unused investigational drug to SBI ALApharma Canada Inc. under the following circumstances: the study is completed or discontinued; the drug is expired; the drug is damaged or unfit for use (e.g., change in colour). Excess prepared drug that is left over following a participant's surgical procedure will be disposed of in accordance with the site's disposal policies and procedures.

In the event that there is a deviation in the investigational drug accountability procedures (e.g. temperature deviation), as defined by SBI ALApharma Canada Inc., the 3rd party responsible for dispensing the investigational drug (e.g. trial site pharmacist) will not dispense the drug and will notify the Sponsor (SBI ALApharma Canada Inc.) within 1 business day of identification of the deviation. The Sponsor (SBI ALApharma Canada Inc.), in consultation with the site, will determine the appropriate course of action.

10.1.3. Investigational Medical Devices

1. The sponsor (SBI ALApharma Canada Inc). manufactured medical devices provided for use in this study include the following components of the Eagle V1.2 Imaging System:

    a. **Handheld Fluorescence Camera (HFC) (Figure 10.1):** A handheld, battery-powered, imaging camera with 405 nm and white light illumination light sources and dual imaging sensors with optical filters for imaging of PD G 506 A-induced PpIX fluorescence and standard full spectrum visible (white) light, respectively. When performing fluorescence imaging, red (PpIX) fluorescence from malignant cells is detected simultaneously against a background tissue (green) autofluorescence emitted mainly by connective tissues (which do not produce excess PpIX), thereby producing a composite fluorescence image (or video); noting that adipose tissue appears dull-brown in colour in fluorescence images of breast tissues. To accomplish this, a custom dual bandpass emission filter is placed in front of the camera sensor. The two regions of light that are being imaged are green (500 – 545 nm) and red (600 – 660 nm). The Handheld Fluorescence Camera has mechanical buttons to capture images and videos as well as switch between white light and FL imaging modes. The device's built-in color touchscreen is used to view and annotate images and videos in real-time. The device can be connected to an external monitor for viewing of images and videos on a larger screen visible to all members of the operating room team in real-time. The information displayed on the monitor is a mirror of the information displayed on the device screen.

    b. **Custom Sterile Sleeve (CSS):** A clear plastic film with an optically transparent cap used to enclose the Handheld Fluorescence Camera and maintain sterility, enabling the intraoperative use of the device in a sterile surgical environment. The Custom Sterile Sleeve is a patient contacting single-use accessory (ISO 10993-1: external communicating device, in contact with tissue, for a limited duration ≤ 24 hours).

    c. **Dark Imaging Box (DIB):** An accessory to be used to create a dark environment to enable fluorescence imaging of excised tissue specimens when ambient light levels are not acceptable for fluorescence imaging. The Dark Imaging Box consists of a reusable imaging stand and a detachable single-use black plastic drape.

    d. **Dark Imaging Sheet (DIS):** A nonfluorescent plastic sheet to be used as a consistent and standardized background for performing fluorescence imaging of excised tissues placed upon it. The Dark Imaging Sheet is a single-use accessory that will be used within a sterile environment.

    e. **Contact Charging Device (CCD):** Charging station that uses a charging pin connection for charging the Handheld Fluorescence Camera's battery

    f. **Protective Storage Cradle (PSC):** Stand used for holding the Handheld Fluorescence Camera while not in use and protecting the device during

transportation. The stand is compatible with conventional sterilization methods to allow for use in a sterile surgical environment.

Figure 10.1 Handheld Fluorescence Camera
Renderings of the (A) front (target-facing), (B) back (user-facing) and (C) side of the Handheld Fluorescence Camera, including the distal imaging tip (A, inset) and the mechanical buttons which control image/video capture, imaging mode, and device power (B). (D) Representative photograph of user-facing side of Handheld Fluorescence Camera being used to perform fluorescence imaging in a dark environment.

g. **External Communication Hub (ECH):** Intended to simultaneously display the image/video seen on the Handheld Fluorescence Camera's display on the larger ECH Display Monitor through a wireless connection. The ECH is comprised of:

- ECH Display Monitor
- ECH PC – a small form factor computer with encrypted USB Flash Drive (32 Gb) and numeric pad

- ECH Router
- ECH HDMI Link Assembly, and ECH USB Cable
- ECH Power Supplies and Extension Cables
- ECH Power Bar
- Cart (ECH Cart)
- The ECH supports connecting up to two (2) Handheld Fluorescence Cameras at once. When two (2) Handheld Fluorescence Cameras are connected, the ECH can: save data captured on either device; be used to review data from one HFC on the other HFC, and vice versa; cast (i.e. mirror) the display from only 1 HFC at a time.

2. Instructions for medical device use are provided in the Eagle V1.2 Imaging System Instructions for Use document.
3. All medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see **Section 13**).

10.1.3.1. Handling/Storage/Accountability

The Eagle V1.2 Imaging System labels and labeling will be clearly identified by the Sponsor/Manufacturer as an investigational device. The PI and designees are responsible for maintaining control over the investigational device equipment maintained by the site. The investigational equipment must be segregated and provided only to participating investigators.

The following procedures will be followed to account for devices used in the clinical trial:

- All Handheld Fluorescence Cameras will be serialized
- The serial IDs of all serialized components of the Eagle V1.2 Imaging System will be recorded by the sites in the Device Accountability and Device Return/Repair/Destruction logs which will identify the storage location, date shipped, requested by, assigned to, date returned and include a record any issue(s) found with the system
    - These logs must be stored in the same location as the Eagle V1.2 Imaging System
- Device serial numbers will be recorded on the Intraoperative Data Collection Tool at the beginning of each procedure
- All devices will be issued an RMA (return material authorization) number for return that will be listed on the packing slip when shipping. Details about cleaning before returning, should be documented in the Device Return/Repair/Destruction and communicated to the Sponsor prior to shipment.
- All devices will be shipped in a protected case
- The Eagle V1.2 Imaging System is to be used for the trial purpose only

Investigators will be responsible for maintaining all devices dedicated to the trial according to the study protocol and device manual/instructions for use to ensure optimal performance. The need

for any non-routine maintenance will be reported by the investigator to the device manufacturer (SBI ALApharma Canada Inc.) as soon as the issue is observed. The device manufacturer will be responsible for performing and documenting any routine and non-routine device maintenance.

10.2. Method of Treatment Assignment

All participants will be centrally assigned to randomized study treatment using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information & directions for the IWRS will be provided to each site. Study treatment will be dispensed at the Day 1 study visit as summarized in the Schedule of Activities. Unused dispensed reconstituted investigational drug should be disposed of and should not be re-dispensed to another participant. The IVRS/IWRS will be used for both Part A and Part B as the first step for enrollment of a participant; all subjects in Part A will receive PD G 506 A and in Part B subjects will be randomized to receive PD G 506 A or placebo.

10.3. Blinding

Part A of the study is not blinded as all participants will receive PD G 506 A. Although surgeons will not be blinded to treatment in Part A, they will follow all of the same procedures as in Part B and will not perform any fluorescence assessments until SoC resection is complete. In the main study, Part B, the participants and pathologist(s) (and pathologist's assistant) will be blinded to the treatment assignment for the duration of the trial. The ***surgeon*** and ***surgeon's assistant*** will be blinded to the treatment assignment up until the time that the SoC lumpectomy procedure is complete, at which point they will be unblinded. The ***surgeon*** will also be blinded to the fluorescence imaging data collected by the ***surgeon's assistant*** during SoC (e.g. imaging data of the, ***primary specimen*** and ***SoC-driven cavity shaves***) until such time that they are intentionally unblinded per protocol.

At clinical sites where specimen biopsies are collected from inside the sectioned specimen, the individual grossing the specimen (e.g. pathologist's assistant) will remain blind to the fluorescence imaging data collected by the ***surgeon*** or ***surgeon's assistant***.

In order to maintain this blind, an otherwise uninvolved 3rd party (e.g. pharmacist) will be responsible for the reconstitution and dispensation of the study drug and dispensation of the placebo (drinking water) and will endeavor to ensure that there are no differences in time taken to dispense following randomization. The investigational drug or placebo will be administered by a blinded qualified medical professional (e.g. nurse). Neither the ***surgeon*** nor ***surgeon's assistant*** can administer the study drug due to the potential risk that the patient's reaction to consuming the investigational product accidentally unblinds the individual dosing them.

The sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment

will affect the immediate management of the participant's condition. In this case, the investigator must notify the Sponsor's pharmacovigilance vendor, spmd (spmd will notify the Sponsor) within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

For participants that are withdrawn or are terminated, the investigator may be unblinded to the treatment allocation following documentation of the participants withdrawal/termination.

If any member of the blinded research team (e.g. ***surgeon***, ***surgeon's assistant***, research nurse or pathologist) is inadvertently unblinded at any time other than as defined by the study protocol, data collection will continue as per protocol. The time that the blind was broken and individual that was unblinded will be noted in the eCRF.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.

10.4. Treatment Compliance

To minimize the risk of a phototoxic skin reaction all participants will be required to comply with written sun/light protection instructions provided by the Sponsor (SBI ALApharma Canada Inc.). See **Appendix 3** for more details.

10.5. Concomitant Therapy

Any medication for concomitant diseases of the patient will be allowed during the course of the clinical study.

Participants will be provided with sunscreen to apply prior to leaving the hospital and for a minimum of 48 hours after administration of investigational drug when exposed to sunlight.

10.6. Prophylactic Medications, Treatments and Procedures

The participant may be administered antiemetics to mitigate the side effects of PD G 506 A, as medically required.

Participants will be advised to keep out of direct sunlight for at least 48 hours and given a small bottle of sunscreen (minimum sun protection factor (SPF) 60) as further prevention against photo-sensitization. Sunscreen will be self-administered by participants. While in the hospital and when possible, participants will be exposed to low light environment conditions (e.g. inpatient room will be turned off) following administration of the investigational drug.

10.7. Warnings and Precautions

Reduce direct exposure to sunlight or room lights for at least 48 hours after oral administration of the investigational drug.

10.8. Prohibited Medications, Treatments and Procedures

Patients taking PD G 506 A who are exposed to a photosensitizing agent may experience a phototoxic skin reaction. Due to the risk of possible phototoxic reactions, study participants should avoid administering phototoxic drugs such as St. John's Wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones, and tetracyclines, and topical preparations containing ALA for 24 hours before and after administration of investigational drug.

Information regarding use of prohibited medications, treatments and procedures will be collected during screening and at all study visits. Treatment with any the above listed medications will not be permitted unless discussed with and approved by the investigator and Sponsor. If treatment with any of the above listed medications is commenced prior to administration of the study drug, the participant will be terminated early. If treatment with any of the above listed medications is commenced following administration with study drug, early termination will require discussion and approval by the investigator and sponsor.

11. Termination of Participation/Withdrawal Criteria

The following criteria apply to participants who have been enrolled in the study. An enrolled participant will be automatically withdrawn from the study if their surgery is re-scheduled at a site other than a study site or if their treatment plan is modified such that they no longer meet the study eligibility criteria. A participant may verbally withdraw at any time by contacting her surgeon or appropriate study staff (e.g. study coordinator).

An investigator may terminate a patient's participation in the study if: any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.

Reasons for withdrawal or termination will be recorded in the participant's study record.

11.1. Handling of Participant Withdrawals or Termination

All data collection relating to a withdrawn or terminated participant, excluding safety data for participants that have received PD G 506 A, will cease at the time of withdrawal/termination. Clinical care in all withdrawn or terminated participants will continue as per standard of care.

In order to maintain the required number of study subjects, any participant that withdraws or is terminated prior to completion of the Week 2 visit will be replaced. Participants that withdraw or are terminated after the Week 2 visit but prior to the 1 year follow-up will not be replaced.

11.2. Loss to Follow Up

A participant will be considered lost to follow-up if they fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

For the purposes of the 6-month and 1-year follow-up, any participant who may have died within 6-months or 1 year of their index BCS procedure or for whom follow-up data cannot be retrieved (either through medical record review and/or telephone contact with the participant), will be considered lost to follow-up for the extension phase of the study. Data from participants that are lost to follow-up for the extension phase will still be used for analysis of all endpoints that are based upon data collected through the Month 3 visit.

12. Study Procedures and Schedule

- Immediate safety concerns should be discussed with spmd immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g. diagnostic imaging and histopathology, bloodwork) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

12.1.Schedule of Activities

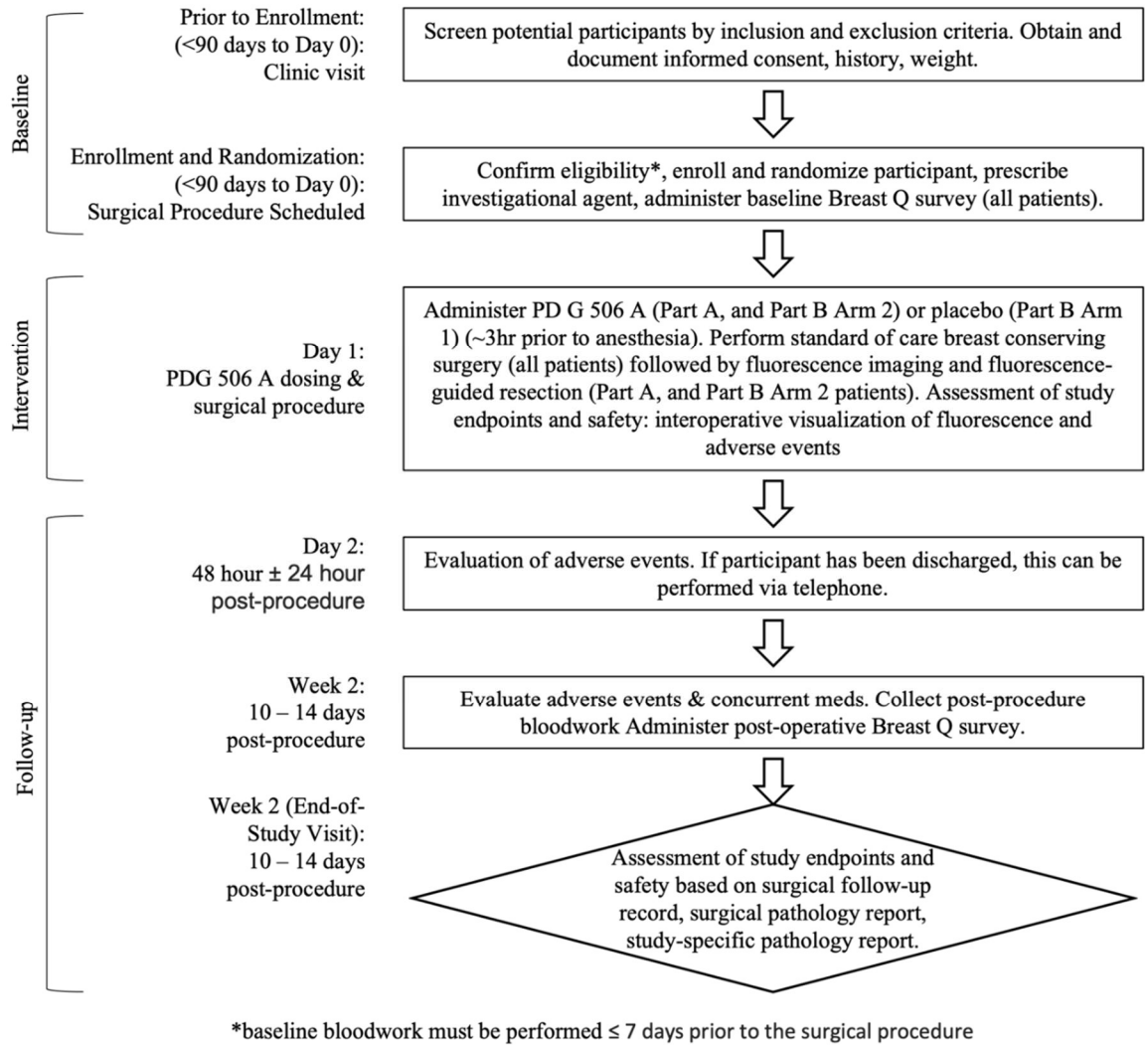


Figure12.1: Schematic of Study Visits and Procedures through Week 2 Visit

Table 5.1: Schedule of Study Assessments and Procedures.

List of study specific assessments and procedures to be performed at each study visit.

Study Assessment or Procedure	Baseline	Day 1				Day 2	Week 2	3-month Follow-up[r]	6-month Follow-up	1 Year Follow-up
								(In-Person Visit not Required)		
	≤ 90 to Day 0 before procedure	Before PD G 506 A dosing & surgical procedure	PD G 506 A dosing	Surgical procedure	After PD G 506 A dosing & surgical procedure	24 – 48 hours post-procedure[n]	10 days – 14 days post-procedure (Last In-Person Study Visit)	80 – 90 days post-procedure	168 – 182 days post-procedure	365 – 379 days post-procedure
Informed consent	X									
Eligibility criteria	X	X								
Demographics and Medical history	X									
Randomization	X									
Adverse event evaluation[s]	X	X	X	X	X[o]	X	X[p]			
Concurrent meds	X	X				X	X			
Physical Examination[a]	X[b]	X[b]					X			
Vital signs		X	X		X					
CBC, AST, ALT, TBL, creatinine [c, d, e]	X						X			
IMAGING (at least one of: mammography, ultrasound, MRI)[f, g]	X									
Diagnostic tissue sample collection (e.g. PCNB, FNAC)[g, h]	X									
Breast-Q questionnaire	X						X	X	X	X
Pregnancy Test[i]	X[j]	X[k]								
PD G 506 A / placebo [l, m]			X							
Sunscreen application and sun protection instructions					X					
SoC lumpectomy				X						
Eagle V1.2 Imaging System assessment				X						
FL-guided resection				X						
Resected tissue weight					X					
Pathology assessment							X			

Study Assessment or Procedure	Baseline	Day 1				Day 2	Week 2	3-month Follow-up[r]	6-month Follow-up	1 Year Follow-up
								(In-Person Visit not Required)		
	≤ 90 to Day 0 before procedure	Before PD G 506 A dosing & surgical procedure	PD G 506 A dosing	Surgical procedure	After PD G 506 A dosing & surgical procedure	24 – 48 hours post-procedure[n]	10 days – 14 days post-procedure (Last In-Person Study Visit)	80 – 90 days post-procedure	168 – 182 days post-procedure	365 – 379 days post-procedure
(report) of surgical specimens										
Medical chart review - additional procedures[q]								X	X	X

a. Physical exam includes (at a minimum): height (baseline visit only), weight, vitals (heart rate, blood pressure), auditory assessment of heart and lungs, assessment of skin, eyes, abdomen and lower extremities, assessment of any phototoxic reactions (Day 1, Day 2 and Week 2 visit only).
b. An abbreviated physical exam (including weight, heart rate and blood pressure) may be performed on Day 1 prior to dosing if a complete physical examine (as described in (a)) has been performed no more than 7 days prior to surgery.
c. CBC=complete blood count, AST=aspartate aminotransferase, ALT=alanine transaminase, TBL= Total bilirubin level
d. Phosphorus, uric acid, creatinine kinase, & amylase will be added as clinically necessary/indicated.
e. Baseline must be performed no more than 7 days prior to surgery
f. Type of diagnostic imaging test dependent on site SoC
g. May be performed up to 90 days prior to surgery
h. PCNB=percutaneous core needle biopsy, FNAC=fine-needle aspiration cytology
i. Pregnancy test for women of childbearing potential performed one time prior to surgery either within 7 days prior to surgery or the day of surgery prior to dosing
j. If pregnancy test is performed within 7 days prior to surgery a blood pregnancy test must be performed
k. If pregnancy test is performed on the day of surgery prior to dosing either a urine or blood pregnancy test may be performed
l. PD G 506 A to be dosed 3 hours (target range: 2 hours – 4 hours) prior to anesthesia
m. PD G 506 A is dosed as 20 mg/kg BW. Oral administration is one-time only and based on actual body weight, measured ≤ 7 days prior to administration of the study drug
n. For patients that are discharged on Day 1, Day 2 AE and concurrent medication evaluation will be performed via telephone questionnaire
o. Clinical laboratory tests as required to investigate (S)AEs (e.g. blood work)
p. Any unresolved AEs present at Week 2 visit will be followed for an additional 7 days. Any unresolved SAEs will be followed for an additional 30 days. Patients with elevated liver enzymes will be followed until levels return to baseline.
q. Medical chart reviewed to identify additional therapies related to the breast cancer diagnosis received since the Week 2 visit and within 1 year following Day 1 (e.g. additional surgeries, chemotherapy, radiation therapy, endocrine therapy, immunotherapy). In the event the patient is no longer under the care of the study investigator, the patient will be contacted via telephone.
r. 3-month follow-up data must be collected 80-90 days post-procedure or within 7 days prior to commencement of radiation therapy, whichever occurs first.
s. Includes assessment of neurological AEs (neurological AEs observed in the clinical trials of ALA HCl used for the visualization of glioma during surgical resection may be attributable to the greater amount of tissue resected in patients in the ALA arm as compared to control and are not expected to occur in breast cancer patients; nevertheless investigators must evaluate potential neurological AEs at each AE assessment time point)

12.2. Screening (Days -90 to Day 0)

Screening will take place within 90 days prior to the ***index surgical procedure***. Screening must be completed with sufficient time prior to the scheduled surgery to allow for the investigational drug prescription to be filled. Patients will be pre-screened based on their primary diagnosis. Patients thought to meet the eligibility criteria (**Section 9.2**) will be approached to participate in the study. The ***surgeon*** or a member of the research staff will go through the informed consent process with the patient (**Appendix 4**). Patients will be given adequate time to consider participation (minimum 24 hours if requested). Consented patients will be questioned regarding their eligibility to participate in the study. If a patient meets any of the exclusion criteria, screening will be ceased, and the patient will not be enrolled in the study. Screening will continue for patients that do not meet any of the exclusion criteria and at a minimum meet the following inclusion criteria:

- Female, 18 years or older.
- Histologically or cytologically confirmed primary breast cancer (including invasive lobular carcinoma, invasive ductal carcinoma and mixed invasive and ductal carcinoma in situ) **OR** histology/cytology confirmation pending.
- Women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) starting the day entering the study, and for the duration of the study period (until the Week 2 visit).

Patients meeting the above criteria will be weighed, and their weight will be recorded on the screening data collection tool. A note will be made in the patient's medical record indicating they have consented to participate or are considering participation in the study.

Any additional tests beyond standard of care required to confirm eligibility (e.g. blood work) will be performed/ordered only after the patient has consented to participate. Screening blood work of consented participants must be performed ≤ 7 days prior to administration of the study drug.

Baseline blood work may be collected before obtaining informed consent if both of the following criteria are met:

1. Baseline blood work required to confirm eligibility according to study protocol SBI-CIP 20-002 is performed as part of the site's standard of care for all patients undergoing breast conserving surgery.
2. Standard of care baseline blood work is collected ≤ 7 days prior to surgery.

Baseline blood work **may NOT be collected before obtaining informed consent if the following criterion is met:**

1. Baseline blood work required to confirm eligibility according to study protocol SBI-CIP 20-002 is NOT performed as part of the site's standard of care for all patients undergoing breast conserving surgery.

The participant's weight will be collected ≤ 7 days prior to administration of the study drug and recorded on the eCRF and communicated to an unblinded qualified medical professional (e.g.

pharmacist) responsible for preparing and dispensing the investigational drug or placebo (**Sections 10.1.2.3, 10.1.2.4, 10.1.2.5**). Diagnostic imaging may be performed ≤ 90 days prior to administration of the study drug. Diagnostic histopathology may be performed ≤ 90 days prior to administration of the study drug.

Consented patients will be asked to complete the pre-operative Breast Conserving Therapy Module of the Breast-Q survey to establish their baseline score. Patients may complete this survey anytime between Day -30 and Day 1 (day of surgery).

12.3. Enrolment and Randomization (no visit, Days -30 to Day 0)

Consented patients meeting all eligibility criteria at the time that their surgery is scheduled will be enrolled in the study. Sites must submit the Enrolment Form to the study sponsor for review and approval a minimum of 2 business prior to the patient's scheduled surgery. Enrolment and randomization will take place with sufficient time prior to the scheduled surgery to allow for the investigational drug prescription to be filled. Participants will be notified verbally (in person or via telephone) that they have been enrolled in the study. Consented patients that do not meet the eligibility criteria at the time their surgery is scheduled will not be enrolled in the study and will be notified of such verbally (in person or via telephone).

Study patients scheduled to undergo a bilateral lumpectomy procedure will only have the study procedure performed on one breast. The breast to be included in the study will be identified and documented by the surgeon at the time of enrolment.

Following enrolment, the ***surgeon*** will complete the investigational drug prescription order and submit it to the 3rd party responsible for dispensing the investigational drug (e.g. pharmacist). The prescription order will specify the dose, date and time of pick-up. The 3rd party responsible for dispensing the investigational drug will use the IVRS/IWRS system to identify to which study arm a participant has been randomized.

Dissemination of the randomization code will be by sealed, tamper-protected randomization envelopes. Specifically, the 3rd party responsible for dispensing the investigational drug (e.g. pharmacist) will have unblinded access to the electronic database (EDC). Pharmacists will be granted specific EDC permissions that will allow them to see allocation of subjects at their site, to either the study drug, or placebo. When preparing the study drug or placebo for administration 3 hours before the scheduled surgery, the pharmacist will print the Allocation Form off of the EDC. This form will indicate subject ID, allocation to active drug or placebo, date and time of study drug preparation. The pharmacist will place the Allocation Form into an envelope that has been protected from tampering by carbon paper, seal the envelope, and hand it to the study coordinator along with the prepared investigational product for the subject. The study coordinator or a designate (another member of research team staff other than the surgeon or surgeon's assistant), will administer the investigational product and keep subject under observation for 30 minutes, then hand the intact unblinding envelope to the Operating Room staff. Continued monitoring of the patient at hourly intervals following the initial 30-min observation post-administration of the study

drug can be done by trained medical personnel (e.g. the patient's nursing staff). The seal will be broken at the end of the SoC lumpectomy procedure (including resection of the primary specimen and any SoC-driven cavity shave specimens) by the ***surgeon's assistant*** or a designate (another member of the operating room staff) to confirm the participant's allocation, as detailed in **Section 12.4.3**.

12.4. Surgical Procedure (Day 1)

12.4.1. Pre-operative Procedures

Participants will arrive at the site at least 4 hours prior to surgery. Participant eligibility and documented informed consent will be verified. If the day of surgery weight is being used for calculating the investigational drug administration volume, it will be collected and communicated to an unblinded qualified medical professional (e.g. pharmacist) responsible for preparing and dispensing the investigational drug or placebo (**Sections 10.1.2.3, 10.1.2.4, 10.1.2.5**). If the weight used for calculating the investigational drug administration volume was collected prior to day 1 but within 7 days of surgery (**Section 12.2**), the participant's day of surgery weight must still be collected and recorded on the eCRF. In women of child-bearing potential (WOCBP) a negative pregnancy test result must be documented prior to administration of the investigational drug or placebo. The investigational drug or placebo will be administered by a blinded qualified medical professional (e.g. nurse). Participants will be administered PD G 506 A or placebo approximately 3 hours (2 – 4 hr) prior to anesthesia. Neither the ***surgeon*** nor ***surgeon's assistant*** can administer the study drug due to the potential risk that the patient's reaction to consuming the investigational product accidentally unblinds the individual dosing them. Patients must have an IV line in place prior to study drug administration, and must be under medical supervision from the time of dosing until the initiation of anesthesia. Baseline heart rate and blood pressure will be collected prior to administration and post-administration heart rate and blood pressure will be monitored and recorded immediately after and 30 minutes after administration. Post-administration heart rate and blood pressure will continue to be collected at least hourly following the measurement at 30-mins post dosing, until the initiation of anesthesia. The participant will be observed for 30 minutes following administration for any acute (S)AE(s). (S)AE monitoring will continue for the duration of the study period (until the Week 2 visit) as described in **Section 13**
Instructions will be provided to the patient to immediately report any possible symptoms of hypotension (e.g. light headedness, blurry vision, nausea, dizziness, weakness, blurry vision, etc.) after receiving the study drug.

While the patient is under medical supervision from the time of P DG 506 A dosing until the initiation of anesthesia, trained medical personnel and applicable therapies should be immediately available for the treatment of hypotension or any other hypersensitive reactions during administration of PD G506A and the post- administration monitoring period.

Following administration of the investigational drug and prior to surgery all efforts should be made to minimize the participant's exposure to light (e.g. turn room lights off and draw curtains where possible).

Instructions will be provided to the participant regarding steps they should take to minimize the risk of experiencing a phototoxic reaction due to PD G 506 A including sun/light protection instructions and a list of other common photosensitizing medications which should be avoided (**Appendix 3**).

12.4.2. Standard of Care Intraoperative Procedures

In all participants, the ***surgeon*** will perform the lumpectomy following best clinical practice. A lumpectomy is defined as a wide local excision of the intact tumor surrounded by a cuff of tumor-free tissue (determined by palpation and visual inspection). This includes the posterior extent of the resection; routinely excising posteriorly down the chest wall should not be performed. Anterior skin should not be routinely removed unless clinically indicated. Tumor involved margins should be revised as separate margins. Separate incisions should be used for the removal of the primary tumor and the axillary surgery except when they coincide anatomically. Curvilinear incision, concentric with the areolar margin, or transverse incisions are recommended over radial incisions. Drains and approximations sutures should not be used in the breast parenchyma.

For participants who are undergoing sentinel lymph node mapping with blue (or green) dye during their BCS, surgeons should avoid injection of blue dye close to the primary tumor bed if feasible. This may help reduce the presence of blue dye in the tumor tissue and surgical cavity where fluorescence assessments will take place. Current studies demonstrate that the location of dye injection distant to the primary tumor bed does not affect the identification of sentinel nodes[68]. Among study patients who are undergoing lymphatic mapping as part of their index BCS, surgeons must comment on the presence or absence of blue (or green) dye at each specimen surface investigated and in the final cavity surfaces.

The ***primary specimen*** will be palpated/inspected, assessed using intraoperative ultrasound (if applicable) and where indicated (wire localization/guidance) sent for mammography to assess positive margins. Intraoperative pathological assessment of the ***primary specimen*** (e.g. touch cytology, frozen section, etc.) is not permitted (as defined in the exclusion criteria). Based on the results of visual inspection/palpation/imaging (***SoC margin assessment***), the ***surgeon*** will decide if additional tissue should be removed (***SoC-driven cavity shave specimens***).

The ***surgeon*** will remain blinded to all Eagle V1.2 Imaging System assessment data until the SoC lumpectomy procedure (including resection of ***SoC-driven cavity shave specimens***) is complete. All excised specimens must be accurately oriented using orientation sutures (or clips).

Intraoperative inking for orientation is permitted only after all imaging required according to this protocol has been completed.

12.4.3. Study-Specific Intraoperative Procedures

The ***surgeon*** and ***surgeon's assistant*** will perform study-specific imaging using the Eagle V1.2 Imaging System, ***FGR,*** and ***primary specimen*** biopsy collection (if applicable) as outlined in **Appendix 2** and described below. Further note, all videos and images will be automatically timestamped and the Eagle V1.2 Imaging System does not have an audio recording function to annotate actions, therefore all relevant actions must be recorded in the Intraoperative Data Collection Tool. Both Part A and Part B of the study will follow these same procedures.

Imaging acquisition using Eagle V1.2 Imaging System of the excised specimens will occur outside the sterile field, using the Dark Imaging Box (DIB). This will allow the ***surgeon*** to continue with other aspects of the surgical procedure (e.g. lymph node biopsy/dissection, if applicable) while specimen imaging is being performed in real-time.
A second Handheld Fluorescence Camera will be required, as the draped imaging device used to image the final ***cavity*** must remain in the sterile field until the completion of the procedure. ***Note***: all devices used for specimen imaging, including those used outside the sterile field, must be draped within the CSS prior to use. In both scenarios (e.g. imaging inside or outside the sterile field), the excised specimen(s) will be placed on the DIS during imaging.

Immediately following resection of the ***primary specimen*** and prior to the ***surgeon*** performing any ***SoC margin assessment*** (e.g. palpation, specimen radiography and/or intraoperative ultrasound) or collection of any ***SoC-driven cavity shave specimens,*** the ***surgeon's assistant*** will perform FL imaging of ***primary specimen*** inside the DIB.
This is required in order to: (1) minimize the risk of photobleaching in the SoC specimens and surgical cavity while ***SoC margin assessment*** is performed and (2) ensure blinding of the ***surgeon*** is maintained until SoC is complete.
To ensure the FL imaging results do not affect the ***surgeon's*** clinical decision making with regard to ***SoC margin assessment***, the FL imaging results will not be viewed by or shared with the ***surgeon*** at this stage until the ***surgeon*** has formally declared SoC is complete.

- The ***surgeon's assistant*** will collect a FL video of the ***primary specimen*** moving systematically through each margin of the specimen. During video capture, the ***surgeon's assistant*** will capture still images of each of the anatomical surfaces of the ***primary specimen*** and use the device's inbuilt image annotation feature to assign each image an anatomical orientation annotation.
- WL imaging is encouraged if red PpIX fluorescence is detected.

The ***surgeon*** will then perform SoC margin assessment and will verbalize their intention to resect ***SoC-driven cavity shave specimen(s)*** as well as what margin assessment informed that decision. In cases where ***SoC-driven cavity shave specimen(s)*** are indicated (based on white light

visualization/palpation ± intraoperative ultrasound and/or specimen radiography) the ***surgeon's assistant*** will perform FL imaging of all ***SoC-driven cavity shave specimen(s).***

- The ***surgeon's assistant*** will collect a FL video of both the inside and outside surfaces of all ***SoC-driven cavity shave specimen(s).*** During video capture, the ***surgeon's assistant*** will capture still images of each surface of all ***SoC-driven cavity shave specimen(s)*** and use the device's inbuilt image annotation feature to assign each image an anatomical orientation annotation. WL imaging is encouraged if red PpIX fluorescence is detected. ***Cavity shave specimens*** must have an orientation marker (e.g. suture or clip) placed prior to imaging such that the surface being imaged (e.g. inside surface vs. outside surface) can be identified in the image.

Following ***SoC margin assessment*** and resection of all indicated ***SoC-driven cavity shave specimen(s)*** (if any), the ***surgeon*** will verbalize that the SoC lumpectomy procedure is complete (the time will be recorded in the Intraoperative Data Collection Tool) and will proceed to opening the randomization envelope. The time the randomization envelope is opened will be noted on the Intraoperative Data Collection Tool.
Following the procedure, the ***surgeon*** and ***surgeon's assistant*** will electronically sign the Intraoperative Data Collection Tool to acknowledge that the blind was not broken prior to opening of the randomization envelope.

In participants randomized to Arm 1 (SoC), no further imaging or ***cavity shave specimen*** resections will be performed and the procedure will be completed according to SoC.
In participants randomized to Arm 2 (SoC + PD G 506 A + Eagle V1.2 Imaging System assessment), the ***surgeon*** will proceed to review all images collected, acquire additional images/videos using the Eagle V1.2 Imaging System and perform ***FGR***.

In the event the randomization envelope is opened prior to completion of SoC and the ***surgeon*** and ***surgeon's assistant*** are accidently unblinded earlier than required per protocol, the surgeon will remain blinded to the fluorescence imaging data collected by the ***surgeon's assistant*** during SoC to minimize any bias to the surgeon's practice. The reason and/or events leading to the accidental unblinding will be recorded on the Intraoperative Data Collection Tool.

The ***surgeon*** will collect a FL video of the ***final cavity after SoC*** moving systematically through each surface of the cavity. During video capture, the ***surgeon*** will capture still images of all ***cavity surfaces*** and use the device's inbuilt image annotation feature to assign each image an anatomical orientation annotation.

The ***surgeon*** will then review all images collected with the ***surgeon's assistant*** and will assign (and verbalize) a FL-status to all tissue surfaces imaged, including the ***primary specimen*** (all anatomical surfaces), all ***SoC-driven cavity shave specimens*** (if applicable; inside and outside surfaces), and the ***final cavity after SoC***. The FL-status of all tissue surfaces will be recorded in the Intraoperative Data Collection Tool.

The ***surgeon*** will then resect ***FL-driven cavity shave specimens*** based on the FL-status of the surfaces of the ***final cavity after SoC*** and ***final margins after SoC (outside surface of final SoC shave or primary specimen where no SoC driven cavity shave specimen(s) were collected).***

- If none of the ***final margin(s) after SoC*** and ***final cavity surface(s) after SoC*** are classified as FL-positive, the ***surgeon*** will verbalize the completion of Eagle V1.2 Imaging System assessment.
- If ≥1 are classified as FL-positive, the ***surgeon*** will then resect a ***FL-driven cavity shave specimen*** for each cavity surface where either the ***final cavity surface after SoC*** and/or the corresponding ***final margin after SoC*** was identified as FL-positive.

The ***surgeon*** will then perform FL imaging of the inside and outside surface of all ***FL-driven cavity shave specimens*** resected in the previous step and the corresponding ***cavity surfaces.***
The ***surgeon*** will verbalize which (i.e., S, M, P, L, I, A), if any, of the inside and outside surfaces of the ***FL-driven cavity shave specimens*** and corresponding ***cavity surface(s)*** is considered positive for carcinoma based on the visualization of red PpIX FL (i.e. FL-positive).

The FL-status of each ***specimen surface*** and ***cavity surface*** will be recorded in the Intraoperative Data Collection Tool.

- If none are classified as FL-positive, the ***surgeon*** will verbalize the completion of Eagle V1.2 Imaging System assessment.
- If ≥1 are classified as FL-positive, the ***surgeon*** will continue to perform ***FGR*** as described above until such time that either no red PpIX FL is detected on both the outside surface of the last round of ***FL-driven cavity shave specimens*** and ***surgical cavity*** or until no further tissue can be removed based on the ***surgeon's*** best clinical judgment and in the interest of best medical practice for the patient.
- If at the completion of Eagle V1.2 Imaging System assessment, red PpIX FL is still observed on the ***final margins after FGR*** and/or in the ***surgical cavity*** and no further resection is performed, the anatomical surface(s) of residual fluorescence (i.e., S, M, P, L, I, A) and the reason for not performing further ***FGR*** will be recorded.

The ***surgeon*** will then complete the procedure as per SoC and all samples will be sent for histopathological assessment.
In order to maintain the blinding of the individuals responsible for processing and evaluating the specimens (e.g. pathologist's assistant, pathologist) the conditions under which the ***cavity shave specimens*** were resected will not be indicated in the labelling.
In cases where multiple ***cavity shave specimens*** were resected from a single anatomical location (e.g. S, M, P, L, I, A) labelling will indicate the order in which the shaves were collected such that the relative distance of each of the shaves from the primary specimen is known. For example, if 3 sequential ***cavity shave specimens*** are resected from the lateral ***cavity surface***, the first shave (resected directly after the ***primary specimen***) will be identified as lateral ***cavity shave specimen*** 1, the second shave (resected directly after lateral ***cavity shave specimen margin*** 1) will be

identified as lateral ***cavity shave specimen*** 2 and the 3rd shave (resected directly after lateral ***cavity shave specimen*** 2) will be identified as lateral ***cavity shave specimen*** 3.

Throughout the procedure, care will be taken to protect all excised specimens from exposure to light by placing specimens in sealed, black/opaque, light protected containers at all times when they are not being evaluated. All excised specimens must be marked (e.g. using sutures) for the purposes of orientation as per SoC. For example, the ***primary specimen*** can be marked with a long lateral and short anterior suture and the ***cavity shave specimens*** can be marked with a suture on the outside surface of the shave. Sites may use their preferred method of orienting specimens; however, the method must ensure the orientation of all specimens is clear to the pathologist evaluating the specimens.

12.4.4. Peri-operative Procedures

12.4.4.1. Bisected Specimen Biopsy Collection

These procedures will occur at a subset of clinical sites.

This procedure must be performed following completion of SoC and fluorescence imaging of the ***primary specimen.*** Bisecting of the specimen may be performed by any appropriately trained and qualified individual (e.g. ***surgeon***, pathologist, pathologist's assistant) however interpretation of the fluorescence image(s) of the bisected specimen must be performed by the ***surgeon*** or ***surgeon's assistant***.

The ***primary specimen*** will be palpated and a slice will be made through the centre of the palpable mass. In the case of non-palpable tumors, all best efforts will be made to position the slice through the centre of the tumor. Serial slicing of the primary specimen (e.g. 'bread-loafing') may be performed in lieu of bisecting, if serial slicing is part of SoC at the study site. In this case, the slice with the largest tumor diameter should be selected for imaging. Imaging will be performed with the specimen placed on the DIS. Fluorescence images will be collected such that the entire surface (both sides) of the bisected tissue is captured. While recording a FL-video (to document the location where biopsies were collected), the ***surgeon*** or ***surgeon's assistant*** will collect a tissue biopsy (~ ≤5mm x ≤5mm) in an area of positive- and negative-fluorescence as outlined in **Table** . The imaged surface of the biopsy will be inked with specimen ink to enable proper orienting of the biopsy during paraffin embedding. The individual grossing the specimen (e.g. pathologist's assistant) will remain blind to the fluorescence imaging results collected by the ***surgeon*** and/or ***surgeon's assistant***.

Table 12.1: Specimen biopsy collection algorithm

Fluorescence status	Palpable mass in section	Non-palpable mass in section
Section contains areas of **both** positive- and negative-fluorescence	Collect 1 fluorescence-positive biopsy in an area of brightness positive-fluorescence. Collect 1 fluorescence-negative biopsy as far away (at least ≥ 1 cm specimen size permitting) from the border of positive-fluorescence are where the fluorescence-positive biopsy was collected.	
Section contains **only** positive-fluorescence	Collect 1 fluorescence-positive biopsy in an area of brightness positive-fluorescence.	
Section contains **only** negative-fluorescence	Collect 1 fluorescence-negative biopsy as far away (at least ≥ 1 cm specimen size permitting) from the border of palpable mass as is possible.	Collect 1 fluorescence-negative biopsy as far away (at least ≥ 1 cm specimen size permitting) from suspected-carcinoma in an area suspected to be normal tissue.

12.4.4.2. Specimen Grossing

All specimens (excluding biopsies taken from the ***primary specimen***) will be individually weighed prior to fixation in formalin, and the mass (mg) will be recorded on the Pathology Data Collection Tool.

Specimen grossing and fixation will be performed as per SoC, including inking of all surfaces of the ***primary specimen*** and both the inside and outside surface of all ***cavity shave specimens***. To adjudicate the ***orientation-level*** endpoints, the inside and outside surfaces of all ***cavity shave specimens*** must be inked with different colors (visually obvious) of ink. The ***primary specimen*** and any ***cavity shave specimens*** will be submerged in formalin within the site-mandated time post-resection (i.e. ischemic time).

12.4.5. Post-Operative Procedures

Prior to discharge, participants will be evaluated for any adverse events. At the 2-week follow-up visit the ***surgeon*** will assess the participant for any adverse events including any self-reported signs/symptoms. All AEs will be reported in the participants medical record and in the eCRF. The participant will be administered the post-operative Breast-Q survey.

The participant will be provided sunscreen to apply at time of discharge and for a minimum of 48 hours following administration of the investigational drug when exposed to sunlight. Application of sunscreen at time of discharge will be confirmed and recorded in the case report form. The participant may be administered additional medications (e.g. antiemetics) to mitigate the side effects of PD G 506 A, as medically required.

Participants will receive postoperative treatment (e.g. radiation, chemotherapy, re-operation) as per standard of care. All postoperative treatment that is initiated within the study period (until the Week 2 visit) will be recorded in the eCRF.

12.5. Day 2 Follow-up (24 hours +24 hours post-surgery)

Between 24 – 48 hours after the surgery the participant will be contacted via telephone and asked about their adherence to the sun protection instructions, any self-reported adverse events and concomitant medications.

12.6. Post-operative Pathology Procedures (no visit)

12.6.1. Specimen Blocking and Assessment

The ***primary specimen*** will be blocked according to standard procedures. All ***cavity shave specimen(s)*** will be blocked in total.

Cavity shave specimens must be oriented such that histological sections can be made perpendicularly to the ***inked inside*** and ***outside surfaces.*** Biopsies must be oriented such that histological sections can be made perpendicularly to the ***inked surface*** (i.e., imaged surface).

Primary Specimen:

The pathologist will evaluate the ***primary specimen*** as per SoC and record the following for each anatomical surface (i.e., S, M, P, L, I, A) on the Pathology Data Collection Tool:

i. Presence or absence of carcinoma at each ***inked surface***,
ii. Presence or absence of carcinoma below each inked surface,
iii. Presence or absence of non-malignant abnormal cells (e.g. hyperplastic, dysplastic) at or below each inked surface

If carcinoma is present, record the following additional information on the Pathology Data Collection Tool:

i. Type(s) of carcinoma (e.g. IDC, ILC, DCIS, if other specify)
ii. Shortest distance from the ***inked surface*** to carcinoma

If non-malignant abnormal cells are present, record the following additional information:
Type(s) of abnormal cells (e.g. hyperplastic, dysplastic, etc.)

Cavity Shave Specimens:

The pathologist will evaluate all ***cavity shave specimen(s)*** and record the following on the Pathology Data Collection Tool (note: ***cavity shave specimen(s)*** must be histologically assessed in total):

i. Presence or absence of carcinoma at or below the ***inked outside surface*** of all ***cavity shave specimens***

ii. Presence or absence of carcinoma at or below the ***inked inside surface*** of all ***cavity shave specimens***
iii. Presence/absence of non-malignant abnormal cells (e.g. hyperplastic, dysplastic) at or below the ***inked inside surface*** of all ***cavity shave specimens***

If carcinoma is present, record the following additional information on the Pathology Data Collection Tool:
i. Type(s) of carcinoma (e.g. IDC, ILC, DCIS, if other specify)
ii. Shortest distance from each ***inked surface*** (i.e., inside and outside surfaces) to carcinoma

If non-malignant abnormal cells are present, record the following additional information:
i. Type(s) of abnormal cells (e.g. hyperplastic, dysplastic, etc.)

Tissue Biopsies:
The pathologist will evaluate all specimen biopsies and record the following on the Pathology Data Collection Tool (note: ***biopsies*** must be histologically assessed in total):
i. Presence/absence of carcinoma anywhere in a given biopsy
ii. Presence/absence of non-malignant abnormal cells (e.g. hyperplastic, dysplastic) anywhere in a given biopsy

If carcinoma is present, record the following additional information on the Pathology Data Collection Tool:
i. Type(s) of carcinoma (e.g. IDC, ILC, DCIS, if other specify)
ii. Shortest distance from the inked surface to carcinoma
If non-malignant abnormal cells are present, record the following additional information:
i. Type(s) of abnormal cells (e.g. hyperplastic, dysplastic, etc.)

Lastly, the pathologist will report the final margin status in the participants medical record as well as the Pathology Data Collection Tool.

12.6.2. Specimen Handling, Storage and Future Research

All specimens collected as part of this study will be prepared, handled and stored according to the site's policies and procedures. All tissue blocks will be stored on site and may not be destroyed or discarded prior to the completion of the study and notification by the sponsor that samples are no longer required to be stored. All samples must be logged and tracked over the course of the study and stored in a secure location accessible to research team members delegated responsibility for handling and storing specimens.

During the study and/or at the end of the study, the Sponsor may request specimens collected as part of this study, including unstained histological sections from paraffin embedded tissue blocks and/or tissue blocks (if permitted by the site) in order to answer future research questions. Tissue specimens provided for use in future research will be coded, de-identified and linked to the data

collected as part of this clinical study, including for example: patient demographics, disease characteristics, surgical pathology data, the type of specimen (e.g. SoC-guided vs. FL-guided), and the FL-status and histopathological-status of the tissue block and/or surface from which the tissue block was taken. Tissue specimens sent to the Sponsor may be stored indefinitely and may be used to answer future research questions that are either related or unrelated to the clinical study protocol SBI-CIP 20-002. Tissue specimens may be sent to external laboratories for processing (e.g. histological staining) and evaluation (e.g. analysis of stained histological sections). Tissue specimens will not be used for any genetic research. If future analyses of specimens leads to findings that are relevant to a patient's ongoing health, the patient's surgeon will be informed and findings will be shared with the patient. Specimens provided to the Sponsor may also be shared with 3rd parties for the purposes of answering future research questions unrelated to the current study. Specimens shared with 3rd parties will be coded, de-identified and linked to patient demographics, disease characteristics, surgical pathology data. Specimens shared with 3rd parties will not be linked to any personally identifiable patient information.

12.7. Week 2 Visit (Day 10 – 14)

Clinical usefulness and diagnostic performance endpoint data will be collected at the participant's post-operative surgical follow-up visit.

At this visit, the participant will complete the post-operative Breast Conserving Therapy Module of the Breast-Q survey. To minimize the potential impact of timing of administration of the Breast-Q survey post-op questionnaire, all patients will complete the 2-week post-op questionnaire before they have met with their ***surgeon*** to discuss their surgical pathology report.

The participant's surgical pathology report will be available at this time. Endpoint data will be retrieved from the participant's surgical pathology report and the study-specific Pathology Data Collection Tool. Additional data related to the final pathological tumor staging, pathological features/characteristics and nodal involvement will be retrieved from the participant's surgical pathology report and recorded in the eCRF.

The ***surgeon*** will question the patient about any patient-reported Aes and use of concomitant medications as well as assess and record any ongoing adverse events in the participant's medical record and eCRF.

Blood work (CBC, AST, ALT, TBL, creatinine) will be performed at this visit. If liver enzymes are elevated from baseline (and deemed clinically significant according to the **Table 12.2** below), the patient will be followed until such time that liver enzyme levels return to baseline. Physical examination must include assessment of any phototoxicity reactions and any observed phototoxicity reactions will be followed until resolution.

Table 12.2: Criteria for clinical significant liver enzyme elevation

Criteria	CTCAE v5.0 Grade 2 (moderate) as criterium to judge if elevation of liver enzymes should be deemed clinically significant
Bilirubin: above upper limit of normal	Bilirubin: > 1.5 – 3.0x institutional* ULN if baseline normal > 1.5 – 3.0x baseline if baseline abnormal
AST: > 2.5x institutional ULN	AST: > 3.0 – 5.0x institutional* ULN if baseline normal > 3.0 – 5.0x baseline if baseline abnormal
ALT: > 2.5x institutional ULN	ALT: > 3.0 – 5.0x institutional* ULN if baseline normal > 3.0 – 5.0x baseline if baseline abnormal
AP: n/a	AP: > 2.5 – 5.0x institutional* ULN if baseline normal > 2.5 – 5.0x baseline if baseline abnormal

*"institutional" is included in the study protocol definition, not part of the original CTCAE definition

12.8. 3-Month Follow-up (Day 80 – 90)

The participant will be required to complete the post-operative Breast Conserving Therapy Module of the Breast-Q survey within 80 to 90 days post-surgical procedure. If the participant is scheduled to receive radiation therapy prior to 80 days post-surgical procedure, the survey will be completed within 7 days prior to the initiation of radiation therapy. The survey may be completed during a regular clinic visit (if applicable) or sent and returned via mail. A review of the participant's medical record will be performed 3 months (Day 80 – 90) after their index BCS procedure. Treatments administered for the purposes of treating the primary breast cancer in the ipsilateral breast will be recorded in the eCRF. Treatments may include, but are not limited to, radiation therapy, chemotherapy, hormone, immunotherapy and surgery (e.g. re-excision, lumpectomy, mastectomy). If, at 3 months follow-up, the participant is no longer under the care of the ***surgeon*** who performed the index BCS procedure, the participant will be contacted via telephone to collect the follow-up data.

12.9. Extension Phase

12.9.1. 6-Month Follow-up (Day 168 – 182)

The participant will be required to complete the post-operative Breast Conserving Therapy Module of the Breast-Q survey within 168 to 182 days post-surgical procedure. The survey may be completed during a regular clinic visit (if applicable) or sent and returned via mail. A review of the participant's medical record will be performed 6 months (Day 168 – 182) after their index BCS procedure. Treatments administered for the purposes of treating the primary breast cancer in the ipsilateral breast will be recorded in the eCRF. Treatments may include, but are not limited to, radiation therapy, chemotherapy, hormone, immunotherapy and surgery (e.g. re-excision, lumpectomy, mastectomy). If, at the 6 month follow-up, the participant is no longer under the care of the ***surgeon*** who performed the index BCS procedure, the participant will be contacted via telephone to collect the follow-up data.

12.9.2. 1- Year Follow-up (Day 365 – 379)

The participant will be required to complete the post-operative Breast Conserving Therapy Module of the Breast-Q survey within 365 to 379 days post-surgical procedure. The survey may be completed during a regular clinic visit (if applicable) or sent and returned via mail. A review of the participant's medical record will be performed 1 year (Day 365 + 14 days) after their index BCS procedure. Treatments administered for the purposes of treating the primary breast cancer in the ipsilateral breast within the 1 year period (365 days) following the index BCS procedure will be recorded in the eCRF. Treatments may include, but are not limited to, radiation therapy, chemotherapy, hormone, immunotherapy and surgery (e.g. re-excision, lumpectomy, mastectomy). If, at the 1 year follow-up, the participant is no longer under the care of the ***surgeon*** who performed the index BCS procedure, the participant will be contacted via telephone to collect the follow-up data.

12.10. Early Termination Visit

If early termination occurs prior to administration of the investigational drug (and use of the Eagle V1.2 Imaging System) no additional study specific procedures or evaluations are required and no early termination visit is required. If early termination occurs following administration of the investigational drug (e.g. during the surgery the ***surgeon*** decides it is not in the best interest of the patient to proceed with the study specific data collection), safety data including AEs and medical device problems will be collected and recorded on the procedure day (Day 1). The participant will continue to be followed for AEs until the Week 2 Visit. No specific early termination visit is required.

12.11. Unscheduled Visit

If a participant is seen by their ***surgeon*** following their surgery but prior to the Week 2 Visit, the ***surgeon*** will assess and record AEs (as reported by the participant or observed by the ***surgeon***) and concomitant medications.

13. Assessment of Safety

13.1. Specification of Safety Parameters

13.1.1. Definition of Adverse Events

Investigational **Device**: Eagle V1.2 Imaging System	Investigational **Drug**: PD G 506 A
Adverse Event: Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device which includes: a) Events related to the investigational medical device or the comparator; and b) Events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices. *(Health Canada Guidance Document "Application for Medical Device Investigational Testing Authorization"; Effective: 2018/10/01)*	**Adverse Event:** Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product *(Health Canada Guidance for Industry "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH Topic E2A); H42-2/67-8-1995E; Effective: 1995) FDA 21CFR312.32*

Of note:

- Surgical procedures or other therapeutic interventions themselves are not adverse events, but the condition for which the surgery/intervention is required is an adverse event and should be documented accordingly.
- Planned surgical measures and the condition(s) leading to these measures are not adverse events, if the condition(s) was (were) known before the period of observation (see **Section 13.3**) and did not worsen during study.

13.1.2. Definition of Serious Adverse Events

Investigational **Device**: Eagle V1.2 Imaging System	Investigational **Drug**: PD G 506 A
Serious Adverse Event: An Adverse Event that: a) Led to death; b) Led to serious deterioration in the health of the subject, that either resulted in: i. A life-threatening illness or injury; ii. A permanent impairment of a body structure or a body function; iii. In-patient or prolonged hospitalization; or iv. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. c) Led to foetal distress, foetal death or a congenital abnormality or birth defect; d) Could have led to death or a serious deterioration were it to recur*.	**Serious Adverse Event:** A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: ● Result in death; ● Is life-threatening** ● Requires inpatient hospitalization or prolongation of existing hospitalization; ● Results in persistent or significant disability/ incapacity; ● Is a congenital anomaly/ birth defect; ● Is medically important***
(Health Canada Guidance Document "Application for Medical Device Investigational Testing Authorization"; Effective: 2018/10/01) **added to the definition since those type of events are also reportable to Health Canada*	*(Health Canada Guidance for Industry "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH Topic E2A); H42-2/67-8-1995E; Effective: 1995)*

**The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

***Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject OR may require medical or surgical intervention to prevent one of the outcomes listed in this definition

13.1.3. Definition of an Adverse Drug Reaction

Adverse reactions are defined as all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. Any (S)AEs which are determined to be related to the use of PD G 506 A will be considered adverse drug reactions.

13.1.4. Definition of UADE/ SUSAR

Investigational **Device**: Eagle V1.2 Imaging System	Investigational **Drug**: PD G 506 A
UADE: Unanticipated Adverse Device Effect (US-specific definition): Means: ● any serious adverse effect on health or safety or any life-threatening problem or death ● caused by, or associated with, a device, ● if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), ● or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.	**SUSAR: Suspected Unexpected Serious Adverse Reaction:** Any adverse event (experience) which is considered: ● serious (**Section 13.1.2**); ● causally related to the study medication (**Section 13.2.3**); and ● unexpected in nature, severity or frequency (**Section 13.2.6**)
FDA 21CFR812.3 (s)	*Definition in line with:* *(Health Canada Guidance for Industry "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH Topic E2A); H42-2/67-8-1995E; Effective: 1995) and FDA 21CFR312.32*

13.1.5. Definition of Unanticipated Problem

An unanticipated problem is defined as any incident, experience, or outcome that meets **all** of the following criteria:

1. **Unexpected** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol related documents, such as the REB/IRB-approved research protocol, IB, and informed consent form and (b) the characteristics of the population being studied (i.e., the expected natural progression of any underlying disease, disorder or condition of the participant(s) experiencing the adverse event and the participant's predisposing risk factor profile for the adverse event has altered); AND
2. **Related or possibly related** to participation in the research (i.e., at least a reasonable possibility exists that the incident, experience, or outcome may have been caused by the drugs, devices, or procedures involved in the research); AND
3. Suggests that the research **places participants or others at a greater risk of harm** (including physical, psychological, economic or social harm) than was previously known or recognized.

Only a subset of adverse events occurring in research participants will meet the criteria for an unanticipated problem (UP).

Note: SUSARs and UADE are considered unanticipated problems per definition.

13.2. Classification of an Adverse Event

13.2.1. Severity of Event

All AEs will be assessed by the PI using the protocol defined grading system. The Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 published by the U.S. Department of Health and Human Services (November 27, 2019)[69] will be used to grade the severity of AEs.

For AEs not included in the CTCAE defined grading system, the following guidelines will be used to describe severity[69]:

- **Grade 1, Mild;** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2, Moderate**; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily life (ADL)*.
- **Grade 3, Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- **Grade 4, Life-threatening** consequence; urgent intervention indicated.
- **Grade 5, Death** related to AE.

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

13.2.2. Clarification of the difference in meaning between "severe" and "serious"

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).

This is not the same as "serious", which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Spmd, on behalf of SBI ALApharma Canada Inc., will be responsible for reviewing all AE reports regarding the PI's determination of the severity of the event.

13.2.3. Relationship to Study Intervention

For all collected AEs, the PI will determine the AEs causality based on temporal relationship, alternative explanations (e.g. concurrent disease or other drugs) and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to investigational drug administration or study device use and cannot be explained by concurrent disease or other drugs, chemicals, or devices.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the drug or use of the study device, is unlikely to be attributed to concurrent disease or other drugs, chemicals or devices.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the investigational drug or use of the device). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to investigational drug administration or device use makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs, chemicals, devices or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of investigational drug administration and device use, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Spmd, on behalf of SBI ALApharma Canada Inc., will be responsible for reviewing all AE reports regarding the PI's determination of the relatedness of the event.

13.2.4. Outcome

Outcome of the event will be defined according to the following:

- *Recovered/ Resolved:* The event has fully resolved at the end of the study*.
- *Recovering/ Resolving: The event is improving but has not fully resolved at the end of the study**.
- *Recovered/ Resolved with sequelae*: The event has resolved, but retained pathological conditions resulting from the prior disease or injury.
- *Not recovered/ not resolved:* The event is ongoing at the end of the study*.
- *Fatal:* This event is determined to be the cause of death.

- *Unknown: Outcome information could not be obtained.*

**or at the time of last observation*

13.2.5. Expectedness

13.2.5.1. Expectedness of Adverse Event associated with PD G 506 A

An AE is considered 'unexpected' if it is not listed in IB Section 10.1 "Reference Safety Information", or if it is not listed at the specificity or severity that has been observed.

An AE will be considered unexpected if the:

- nature,
- severity, or
- frequency

of the event is not consistent with the Reference Safety Information previously described for the investigational drug/ product/ procedure.

"Unexpected" also refers to AEs that are mentioned in the study protocol as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

13.2.5.2. Expectedness of Adverse Events associated with Eagle V1.2 Imaging System

An AE is considered 'unexpected' if it is not listed in **Section 6.2.4** of this Protocol, or if it is not listed at the specificity or severity that has been observed.

An AE will be considered unexpected if the:

- nature,
- severity, or
- frequency

of the event is not consistent with the Reference Safety Information previously described for the Investigational Device.

There are no known or anticipated adverse device effects.

13.2.5.3. Obligations of the PI

13.2.5.3.1. Canada

spmd, on behalf of SBI ALApharma Canada Inc., will be responsible for determining whether an SAE is expected or unexpected (see **Figure 13.1**).

13.2.5.3.2. USA

The US PI will be responsible for determining whether an SAE causally related with the Investigational Device is expected or unexpected to fulfill their reporting obligations regarding UADEs towards their IRB on Record (see **Figure 13.2**).

13.2.5.4. Obligations of the Sponsor

spmd, on behalf of SBI ALApharma Canada Inc., will be responsible for reviewing all SAE reports regarding the PI's determination of the expectedness of the event and determining the expectedness.

The Sponsor will also be responsible for determining whether and SAE is expected or unexpected.

13.2.6. Unanticipated Problem

The PI will be responsible for determining whether events (SAEs and non-AEs) meet the criteria of an unanticipated problem (UP) as defined in **Section 13.1.5**.

In the event that the PI's classification of the SAE is not an UP, however, SBI ALApharma Canada Inc. subsequently determines it is, SBI ALApharma Canada Inc. will report this determination to the PI and the PI will submit such reports to their REB/IRB of record.

Sites will maintain a log of all Ups that to not meet the criteria of an (S)AE; this log will be filed in the TMF.

13.2.7. Investigational Product Deficiencies

An investigational product (drug or device) deficiency is defined as an 'inadequacy of an investigational product with respect to its identity, quality, durability, reliability, usability, safety or performance including malfunction, use errors or inadequacy of supplied information or labelling'.

13.3. Time Periods and Frequency for Event Assessment and Follow-Up

The occurrence of an (S)AE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured as described in **Sections 13.2** and **13.4.2**.

Although the neurological AEs observed in the clinical trials of ALA HCl used for the visualization of glioma during resection surgery may be attributable to the greater amount of tissue resected in patients in the ALA arm as compared to control, Investigators are asked to assess for potential neurological AEs, in addition to other AEs, at each AE assessment time point.

The PI will record all reportable events with start dates occurring any time after the participant has signed the informed consent form until the Week 2 Visit. If an (S)AE is recorded at the Week 2

Visit the participant will continue to be assessed for an additional 7 (for non-serious AEs) or at least 30 calendar days (for SAEs) after the Week 2 visit. If liver enzymes are elevated at the Week 2 visit (as defined in **Section 12.7**), the patient will be followed until such time that levels return to baseline. At each visit, the ***surgeon*** investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information (**Section 13.2.4**). SAEs will be followed until resolution or stabilization. Clinical laboratory tests (e.g. blood panels) and other relevant medical tests (e.g. ECG) may be ordered to investigate a (S)AE if clinically warranted. Events occurring after the Week 2 Visit will not be recorded or reported as part of the study protocol.

13.4. Reporting Procedures

This section and subsequent sub-sections describe:

1. Documentation Procedures and Reporting Obligations to the Sponsor;
2. Regulatory Reporting Obligations to the Competent Authorities (Health Canada & FDA) and the Ethics Committees (REBs & IRBs)

13.4.1. Documentation Procedures and Reporting Obligations to the Sponsor

13.4.1.1. Adverse Events

The Investigator must document all AEs that occur during the observation period set in this protocol (**Section 13.3**) on the pages provided in the eCRF. Additional specific instructions may be provided in the investigator file and in the case report form itself.

All AEs (whether serious or not) must be documented on the "Adverse Event" page of the Case Report Form (CRF). All AEs will be described using the sign, symptom, or medical diagnosis on the AE ICRF in standard medical terminology in order to avoid the use of vague, ambiguous, or colloquial expressions. Each AE will be defined as serious or non-serious according to the definitions in **Section 13.1.2**. The investigator will evaluate the severity of each AE and causal relationship of the event to the Investigational Device (Eagle V1.2 Imaging System)/ Investigational Drug (PD G 506 A)/Surgical Procedure/ Other study-specific procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study beginning after the study patient has signed the informed consent form must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution, as defined by the participant's treating ***surgeon***.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

<u>Adverse Events exempted from reporting:</u>

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's baseline condition deteriorates during the study any time after administration of the investigational drug, it will be recorded as an AE. SAEs and Ups will be recorded in the safety data collection system throughout the study.

13.4.1.2. Serious Adverse Event Reporting (Eagle V1.2 and PD G 506 A)

Aes considered by the participant's treating ***surgeon*** to be a SAE as defined in **Section 13.1.2** (regardless of relatedness) will be reported via the SAE Report Form within 24 hours of awareness to:

spmd – safety strategies for health, Inc.
50 Dunham Rd, Suite 3200
Beverly, MA 01915
Email: SBI-ALApharma-PhV@spmd-safety.com
Fax: +1 978 338 0668

13.4.1.3. Other Events to be reported within the same timelines as SAEs (PD G 506 A only)

13.4.1.3.1. Overdose, Abuse, Misuse, Medication Errors, Occupational Exposure and other uses outside what is foreseen in the protocol

Definition overdose: Administration of a quantity of an investigational medicinal product given per administration or cumulatively which is above the maximum recommended dose according to the protocol dosing instructions . Clinical judgement should always be applied.

Definition abuse: Persistent or sporadic, intentional excessive use of an investigational medicinal product, which is accompanied by harmful physical or psychological effects.

Definition misuse: Situations where the investigational medicinal product is intentionally and inappropriately used not in accordance with the protocol dosing instructions.

Definition medication error: Unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Definition occupational exposure: The exposure to an investigational medicinal product, as a result of one's professional or non-professional occupation.

Drug overdose, drug abuse, drug misuse, medication errors, occupational exposure and other uses outside what is foreseen in the protocol should be reported in the same format (i.e. on SAE Report Form) and within the same timelines as a SAE, even if they may not result in an adverse outcome.

13.4.1.3.2. Reporting of Pregnancy

If a participant becomes aware that they are pregnant following consenting to participate and prior to receiving the investigational drug, their participation in the study will be terminated immediately. If a participant becomes aware that they are pregnant following administration of the investigational drug but prior to completing the study, they will complete the study according to the protocol. The PI will be responsible for reporting such an event within 24h of becoming aware that the participant is pregnant to:

spmd – safety strategies for health, Inc.
50 Dunham Rd, Suite 3200
Beverly, MA 01915
Email: SBI-ALApharma-PhV@spmd-safety.com
Fax: +1 978 338 0668

via the SAE Report Form.

The PI will request written permission to follow-up with the participant to pregnancy outcome. See **Appendix 5** for more detailed information.

Spmd on behalf of SBI ALApharma Canada Inc. will identify missing information and requests for follow-up will be sent directly to the Investigator. Spmd will inquire follow-up information in regular intervals form the investigators until all queries are resolved or not further information can be reasonably expected.

All responses to queries and supply of additional information by the investigator should follow the same reporting route and timelines as the initial report.

13.4.1.4. Investigational Product Complaints

Investigators are responsible for reporting any investigation drug and investigational device deficiency encountered. Reporting of such deficiencies are required even when they do not directly or indirectly contribute or potentially could have contributed to a reportable AE. Reporting of deficiencies that meet the criteria of an (S)AE must be reported according to **Sections 13.4.1 and 13.4.2)**. The PI will be responsible for reporting all other deficiencies in a timely manner, and no later than 15 calendar days after becoming aware of the deficiency to:

spmd – safety strategies for health, Inc.

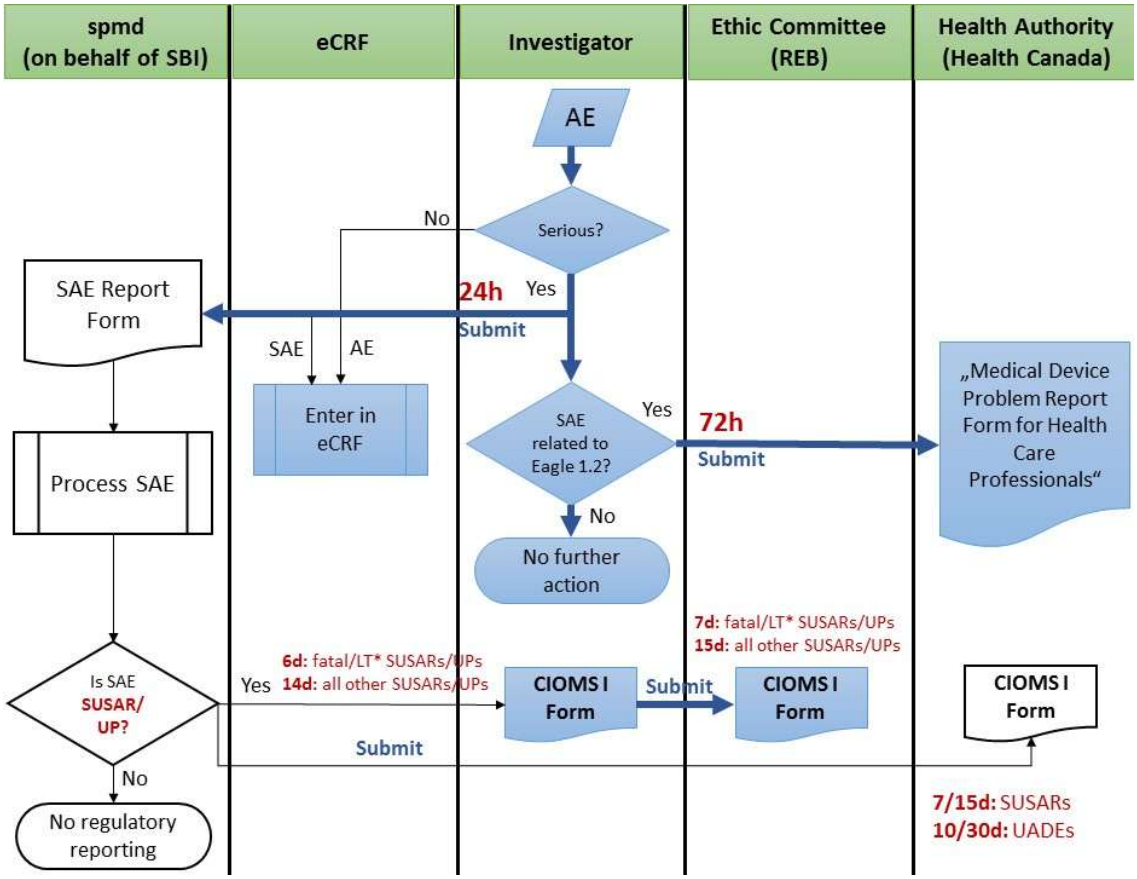
50 Dunham Rd, Suite 3200
Beverly, MA 01915
Email: SBI-ALApharma-PhV@spmd-safety.com
Fax: +1 978 338 0668

spmd will report all non-AE deficiencies to SBI ALApharma Canada Inc., who will investigate the deficiency and take corrective and preventative actions if warranted in accordance with GMP to protect the safety of participants, users, and other persons.

13.4.2. Regulatory Reporting of Adverse Events to Competent Authorities (Health Canada & FDA) and Ethic Committees (REBs & IRBs)

13.4.2.1. Summary of Regulatory Reporting Obligations

13.4.2.1.1. Canada



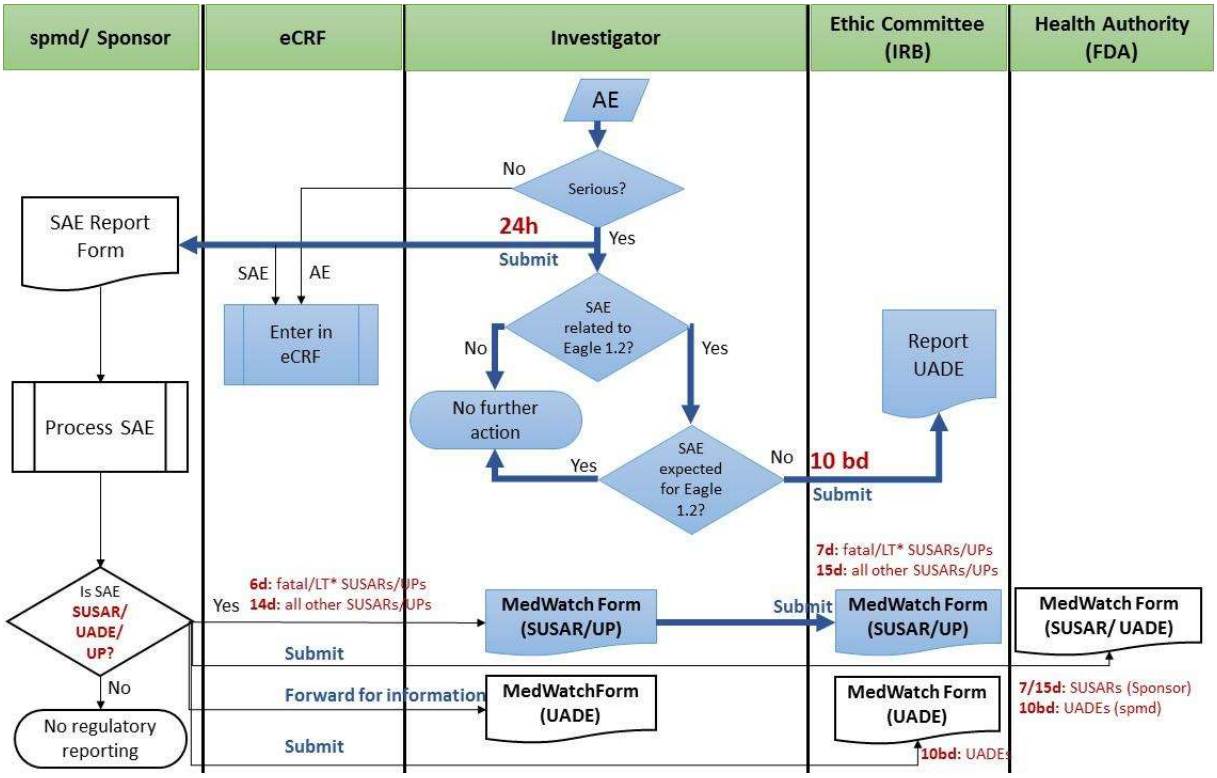
Q1: Is the AE serious?
A: No → document in eCRF → no further actions required.
B: Yes → document on SAE Report Form & send to spmd within 24h → document in eCRF → continue with Q2

Q2: Is the event related to the Investigational Device (Eagle V1.2)?
A: No → no further actions required

B: Yes → fill out "Medical Device Problem Report Form for Health Care Professionals" and send to Health Canada within 72h

Figure 13.1: (S)AE Reporting Algorithm for Canada (LT= life threatening)

13.4.2.1.2. USA



Q1: Is the AE serious?
A: No → document in eCRF → no further actions required.
B: Yes → document on SAE Report Form & send to spmd within 24h → document in eCRF → continue with Q2

Q2: Is the event related to the Investigational Device (Eagle V1.2)?
A: No → no further actions required
B: Yes → continue with Q3

Q3: Is the event expected for the Investigational Device (Eagle V1.2)?
A: No, event is unexpected → report event as UADE to IRB within 10 working days
B: Yes, event is expected → not further actions

Figure 13.2: (S)AE Reporting Algorithm for USA (LT= life-threatening; bd= business days)

13.4.2.2. PD G 506 A: SUSAR Reporting

spmd, on behalf of SBI ALApharma Canada Inc. will be responsible for reporting all serious and unexpected adverse events, which are judged as having a reasonable suspected causal relationship to the Investigation Drug PD G 506 A (Suspected Unexpected Serious Adverse Reaction – SUSAR) to the Food and Drug Administration and Health Canada.

Spmd, on behalf of SBI ALApharma Canada Inc. will be responsible for providing the CIOMS I Form (Canada) MedWatch Form (USA) for all SUSARs to the PI for reporting to their REB/IRB of Record according to local requirements.

The PI will report:

- All fatal/ life-threatening SUSARs within 7 calendar days; and
- All other SUSARs within 15 calendar days;

to their REB/IRB on Record according to local requirements.

13.4.2.3. Eagle V1.2 Imaging System: SAR/ UADE Reporting

spmd, on behalf of SBI ALApharma Canada Inc. will be responsible for reporting all serious adverse events, which are judged as having a reasonable suspected causal relationship to the Investigational Device Eagle V1.2 Imaging System (Serious Adverse Reaction – SAR) to Health Canada.

Spmd, on behalf of SBI ALApharma Canada Inc. will be responsible for reporting all serious and unexpected adverse events, which are judged as having a reasonable suspected causal relationship to the Investigational Device Eagle V1.2 Imaging System (Unanticipated Adverse Device Effect – UADE) to the Food and Drug Administration.

The Canadian PI will report:

- All SARs within 72 hours to Health Canada using the "Medical Device Problem Report Form for Health Care Professionals"; and
- All fatal/ life-threatening UPs/UADEs within 7 calendar days to their REB on Record according to local requirements
- All other UPs/UADEs within 15 calendar days to their REB on Record according to local requirements.

Spmd, on behalf of SBI ALApharma Canada Inc. will be responsible for providing the CIOMS I Form (Canada) for all UADEs to the PI for reporting to their REB of Record according to local requirements.

The US PI will report:

- All UADEs within 10 business days to their IRB of Record according to local requirements.

13.4.2.4. Unanticipated Problem (UP) Reporting

UPs that do not meet the criteria of an AE (e.g. events that place the participant or others at a greater risk of physical or psychological harm than was previously anticipated, or have implications for the conduct of the study or the integrity of research data) will be reported by the PI to their REB/IRB of Record as well as spmd at:

spmd – safety strategies for health, Inc.
50 Dunham Rd, Suite 3200
Beverly, MA 01915
Email: SBI-ALApharma-PhV@spmd-safety.com
Fax: +1 978 338 0668

The following are examples of non-AE Ups which would require reporting the REB/IRB:

- An increase in the rate of occurrence of an expected SAE that is judged by the PI or sponsor to be clinically important
- A major safety finding from a newly completed animal study that indicated significant risk to human participants or the specific population being studied
- Breaches of privacy or confidentiality

13.5. Study Pausing Rules

Administration of investigational drug within the study will be paused when three grade 3 AEs determined to be "probably" or "definitely" related (as determined by the Investigator) to the investigational drug or three grade 3 AEs determined to be "probably" or "definitely" related to the investigational device are reported in the clinical database. SBI ALApharma Canada Inc. and spmd will receive an automatic notification from the clinical database indicating the 3rd such AE has been recorded. Spmd will inform investigators within 1 business day of the third grade 3 "possibly" or "definitely" related event being reported, and administration of study drug and enrolment of new study patients will be stopped. In parallel, spmd will inform the DSMB and CATO-SMS that the study has been paused. Within 1 business day of being notified that the study has been paused, CATO-SMS will provide the DSMB and spmd with AE listing reports. The DSMB will provide recommendations to SBI ALApharma Canada Inc. and spmd for proceeding with the study, including a recommendation for future suspension of enrolment and study drug administration if additional drug- or device-related ("probably" or "definitely") AEs are reported. Spmd will inform the Investigators on the decision of the DSMB. SBI ALApharma Canada Inc. will inform the appropriate regulatory authorities of the temporary pause and the disposition of the study.

Administration of the investigational drug within the study will also be suspended if any drug- or device-related ("possibly", "probably" and "definitely"; as determined by the Investigator or Sponsor) SAE is reported to spmd. Spmd will notify SBI ALApharma Canada Inc. and investigators within 1 business day of this SAE being reported. Enrolment of new study patients and administration of study drug will be stopped. In parallel, spmd will inform the DSMB and will provide the DSMB with the SAE report. The DSMB will provide recommendations for proceeding with the study to SBI ALApharma Canada Inc. and spmd. Spmd will inform the Investigators on the decision of the DSMB. ALApharma Canada Inc. will inform the appropriate regulatory authorities of the temporary pause and the disposition of the study.

Part A is an open-label training phase of the study to refine workflow and provide training. SBI ALApharma Canada Inc., the Study Steering Committee and the DSMB will be closely monitoring the workflow issues as patients are enrolled and will determine when this process has been optimized. It is anticipated that no more than 75 subjects will be required for Part A. If necessary, enrollment may be temporarily suspended after completion of the first 30 patients in Part A prior to initiating Part B so that sample size estimation can be confirmed and any other necessary amendments can be incorporated into the protocol.

13.6. Safety Oversight

Safety oversight will be under the direction of the DSMB composed of individuals with the appropriate expertise, such as but not limited to:

- Medical Oncology, Solid Tumor
- Surgical Oncology
- Radiation Oncology
- Clinical Research Nursing
- Biostatistics

The DSMB will meet at least semi-annually to assess safety data. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. Each data element that the DSMB needs to assess will be clearly defined at the 1st DSMB meeting. The DSMB will provide its input, in the form of recommendations directly to SBI ALApharma Canada Inc. and site PIs.

14. Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

The study monitor, in accordance with the sponsor's requirements, will ensure that the study is conducted and documented properly by carrying out the activities outlined in International Council for Harmonisation E6, Section 5.18.4 and as detailed in the study Monitoring Plan.

Types of monitoring will include:

- On-site and/or monitoring
- Centralized monitoring, including:
    - targeted data verification
    - confirmation of completion of eCRFs
    - query resolution
    - eligibility criteria review
    - adverse event and concomitant medication review
    - screening/enrolment data

- review of anonymized FL imaging data for the purposes of identifying sites requiring re-training
- statistical monitoring to identify missing or invalid data and unusual data patterns which may indicate additional on-site monitoring and/or additional training is required

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. Independent audits may be performed as required by the sponsor.

15. Statistical Considerations

15.1. General Considerations

Descriptive summaries of variables will be provided where appropriate. For continuous variables, the number of non-missing values (n) and the median, mean, standard deviation, minimum, and maximum will be tabulated. For categorical variables, the counts and proportions of each value will be tabulated. Confidence intervals will also be provided as appropriate. All statistical tests will be performed at the 0.05 level.

Further details on all analyses will be provided in the statistical analysis plan (SAP).

15.2. Sample Size Estimation

The sample size of Part A has been chosen on pragmatic grounds to be approximately 75 study patients. The number of patients ultimately included in Part A will be decided by the Steering Committee and the Sponsor based on the perceived understanding of the protocol by clinical sites and the feedback obtained during the Part A training phase. Part A will not be randomized; all study patients in Part A will receive PD G 506 A. Data acquired from Part A will be used to confirm the Investigators' understanding of fluorescence guided resection (FGR) procedures in the protocol and to confirm the sample size for Part B. Only data from participants in Part B will be used for the analyses of primary and secondary efficacy. Data from all patients in both Part A and Part B will be used for the evaluation of safety and analyses will include assessments of data from Part A and Part B separately, as well as all study patients (Part A and Part B together).

P(1.1) Conversion Rate among all patients =

$$\frac{\text{\# patients with at least one histopathology-positive margin following SoC and histopathology negative final margins after FGR}}{\text{All patients imaged (Arm 2)}}$$

The sample size in Part B of the study is only driven by the primary endpoint P(1.1). The primary endpoint is intended to determine the percentage of patients with at least one histopathology-positive margin after SoC who then have all histopathology-negative margins after FGR (conversion rate among all patients in Arm 2). To demonstrate benefit, the point estimate P(1.1) must be statistically significantly greater than 1%. By meeting this primary endpoint, we will demonstrate that FGR adds clinical benefit above and beyond what is achieved with SoC.

Based on the expected 3% conversion rate estimate for P(1.1), a total of 500 patients will be required in Part B of the study to demonstrate statistical significance at a Type 1 error level of 0.05 with 90% power using a 2-sided Z test for a binomial proportion assuming a null hypothesis proportion of 1%.

Using a randomization ratio of 1:6 (Arm 1-SoC; Arm 2: PD G 506 A), a total sample size of 525 patients (Arm 1: N=72; Arm 2: N=428) would be required, accounting for a 5% loss to follow-up. The primary efficacy analysis will be based on the mITT (modified intention-to-treat population), which includes all Part B patients randomized to Arm 2 who undergo surgery and have recorded surgical histopathology data.

15.3. Definitions of Units of Analysis

The definitions of TP, TN, FP, and FN at the units of analysis of orientation, patient and primary specimen are provided in Table 15.1.

Table 15.1: Levels of Analysis and Diagnostic Performance Definitions

Diagnostic Performance Parameter	Orientation Level Analysis	Patient Level Analysis	Primary Specimen Level Analysis
Level of Analysis Definition	An orientation-level analysis evaluates each orientation as a single data point with a total of at least 5 orientations per patient (in cases where an area of skin is removed with the lump, there may be n = 5 data points per patient). Orientation-level analyses evaluate efficacy based on the performance characteristics in each anatomical location of the entire surgical cavity. An orientation is comprised of two contiguous tissue surfaces that have been separated by a scalpel (or other surgical tool e.g., electrocautery) during tissue resection. The tissue surfaces are from the primary specimen, cavity shave specimens, and the final cavity surface. An orientation is described based on the anatomical location of the contiguous tissues (e.g. S, M, P, L, I, A).	A patient-level analysis evaluates each patient as a single data point.	A primary specimen level analysis evaluates each biopsy from the bisected primary specimen (i.e., primary tumor mass) as a single data point. At most, there will be one FL-positive and one FL-negative biopsy per patient included in the analysis.
True Positive	Orientation that is fluorescence positive and histopathology positive.	Patient has at least one TP orientation without any FN orientations	Fluorescence is observed in the primary specimen biopsy that is histopathology-positive for carcinoma
True Negative	FL-negative orientation with final margin for that orientation from cavity shave specimens or primary specimen (if no shaves taken) negative on histopathology	Patient has all TN orientations	No fluorescence is observed in the primary specimen biopsy that is histopathology-negative for carcinoma

Diagnostic Performance Parameter	Orientation Level Analysis	Patient Level Analysis	Primary Specimen Level Analysis
False Positive	FL-positive orientation with final margin for that orientation from cavity shave specimens or primary specimen (if no shaves taken) negative on histopathology	Patient has at least one FP orientation without any FN or TP orientations	Fluorescence is observed in the primary specimen biopsy that is histopathology-negative for carcinoma
False Negative	FL-negative orientation with final margin for that orientation from cavity shave specimens or primary specimen (if no shaves taken) positive on histopathology	Patient has at least one FN orientation has at least	No fluorescence is observed in the primary specimen biopsy and the biopsy is histopathology-positive for carcinoma

15.4. Analysis Populations

The analysis populations and timepoints are described below.

15.4.1. mITT Analysis Population

The mITT population includes all subjects who are randomized (Arm 1 and Arm 2), dosed (Arm 2 only), have the fluorescence imaging performed (Arm 2 only) and have recorded surgical pathology data. The mITT will be used for all ***patient-level*** and ***orientation-level*** analyses. Missing data will be imputed, and full detail will be provided in the Statistical Analysis Plan.

15.4.2. Safety Population

The safety population includes all subjects who are randomized (Arm 1 and Arm 2) and receive PD G 506 A (Arm 2 only); this population will be used for all safety analyses.

15.4.3. Primary Specimen Biopsy Population

The primary specimen biopsy population includes all tissue samples where collection of biopsies from the primary specimen is performed in accordance with the primary specimen biopsy collection algorithm (**Table 12.1**). The Point-level Population will be used for the exploratory analyses.

15.4.4. Timepoints of Efficacy Analyses

15.4.4.1. Fluorescence Assessment at the End of SoC

Efficacy endpoints that evaluate diagnostic performance of PD G 506 A at the "initial fluorescence assessment at end of SoC" include fluorescence assessments of the ***outside surface(s)*** of the last resected ***SoC-driven cavity shave specimens*** (or the ***outside surface*** of the ***primary specimen*** if no cavity shave specimens are obtained) and fluorescence assessments of the ***final cavity after SoC.***

Histopathology assessments for presence or absence of carcinoma are obtained from the ***outside surface(s)*** of the last resected ***SoC driven cavity specimen(s)*** removed (or the ***outside surface*** of the ***primary specimen*** if no cavity shave specimens are obtained) and the ***inside surface(s)*** of the first (innermost) ***FL-driven cavity shave specimen(s)***, if collected (**Figure 15.1**).

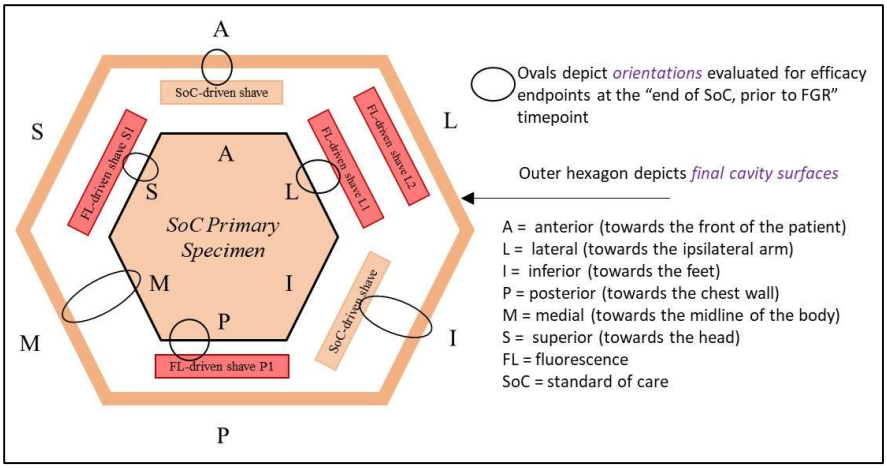


Figure 15.1. Orientations Included in "Initial Fluorescence Assessment at the End of SoC" Endpoints and Analyses

15.4.4.2. Fluorescence Assessment During Fluorescence Guided Resection (FGR)

Efficacy endpoints that evaluate diagnostic performance of PD G 506 A "after SoC" include fluorescence assessments of the ***outside surface(s)*** of the last resected ***SoC-driven cavity shave specimens*** (or the ***outside surface*** of the ***primary specimen*** if no cavity shave specimens are obtained) fluorescence assessments of the ***inside surface(s)*** and ***outside surface(s)*** of all ***FL-guided cavity shave specimens,*** and fluorescence assessment of the ***final cavity*** after FGR. Histopathology assessments for presence or absence of carcinoma are obtained from the ***outside surface(s)*** of the last resected ***FL-guided cavity shave specimen(s) removed*** (***Error! Reference source not found.***).

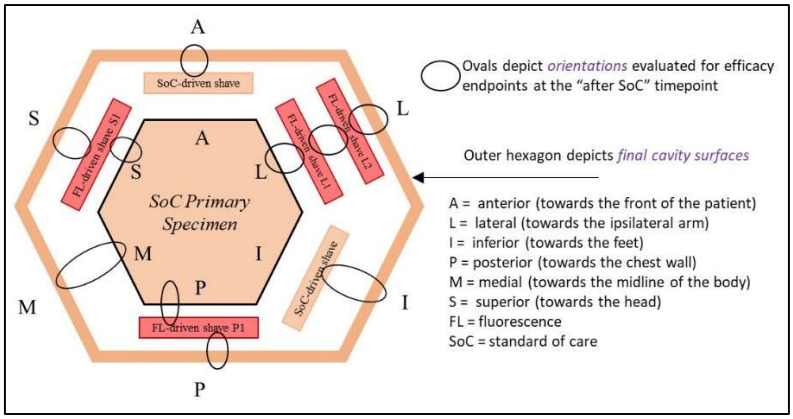


Figure 15.2. Orientations Included in "Fluorescence Assessment during Fluorescence Guided Resection (FGR)" Endpoints and Analyses

Completion of FGR and BCS SurgeryEfficacy endpoints that evaluate the diagnostic performance of PD G 506 A at the "completion of FGR and BCS surgery " include fluorescence assessment of the ***final cavity*** and the ***outside surface(s)*** of the last resected ***FL-driven cavity shave specimens***, the ***outside surface(s)*** of the last resected ***SoC-driven cavity shave specimens*** (if no ***FL-driven cavity shave specimens*** are taken for the particular orientation), and the ***outside surface(s)*** of the ***primary specimen*** (if no cavity shave specimens are obtained for the particular orientation) (**Figure 15.2**). Histopathology assessments for presence or absence of carcinoma are obtained from the ***outside surface(s)*** of the last resected ***specimen(s)*** removed.

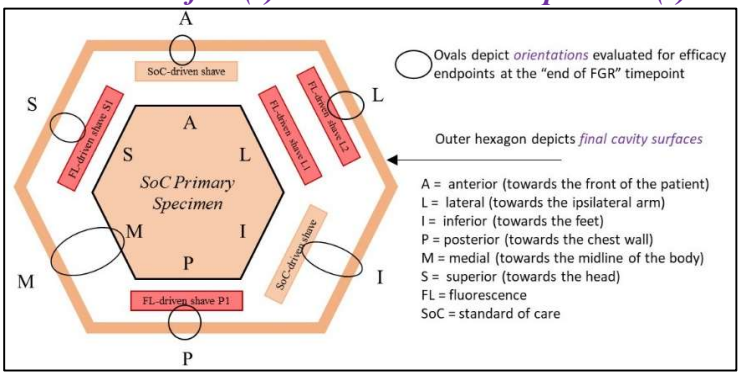


Figure 15.2: Orientations Included in "Completion of FGR and BCS" Endpoints and Analyses

15.4.4.3. Entire Resection

Efficacy endpoints that evaluate diagnostic performance of PD G 506 A over the entire resection, incorporate fluorescence assessments of all ***specimen surfaces*** and the ***final cavity***. Histopathology assessments for presence or absence of carcinoma are obtained from the ***outside surface(s)*** of the ***primary specimen***, and both inside and outside surfaces of ***cavity shave specimens*** (**Figure 15.3**).

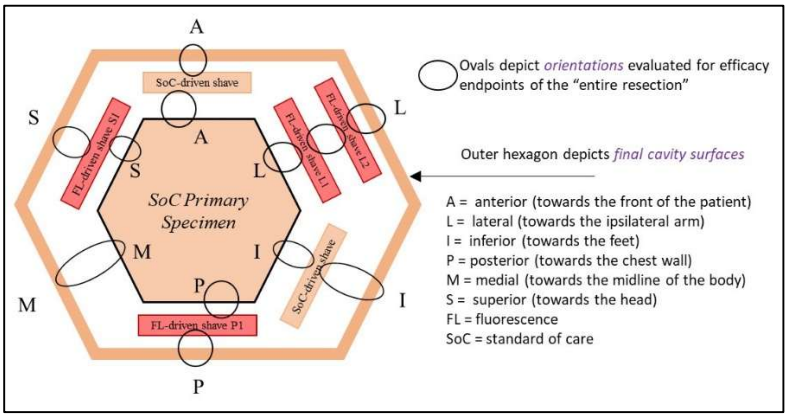


Figure 15.3. Orientations Included in "Entire Resection" Endpoints and Analyses

15.5. Formulas

Detailed formulas for the primary, secondary, and exploratory endpoints can be found in **Section 7**.

15.6. Primary and Key Secondary Endpoint Analyses

There is one primary endpoint and three co-key secondary endpoints for this study: P(1.1), P(2.1), P(2.2) and P(2.3) See **Section 7** for the formulas used. These four endpoints will each be tested at the 0.05 level. Only the primary efficacy endpoint test must be significant for the study to be considered positive. Information on the analyses and hypotheses are provided below.

15.6.1. Primary Endpoint:

1. P(1.1): Conversion Rate Among All Patients

The primary endpoint, P(1.1), is the percentage of participants with negative-margins following FGR among all patients following SoC. Participants that are converted from margin-positive after SoC to margin-negative after FGR will be considered a 'clinical success' and will be counted towards the numerator of the primary endpoint. If at the completion of Eagle V1.2 Imaging System assessment red PpIX FL is still observed on the ***final margins after FGR*** and/or in the ***surgical cavity*** and no further resection is performed, the anatomical surface(s) of residual fluorescence (i.e., S, M, P, L, I, A) and the reason for not performing further ***FGR*** is recorded. In such cases, orientation(s) involving FL observed in the ***final margin after FGR*** and/or in the ***surgical cavity*** will *not* contribute to the determination of a histopathologically-negative final margin for this primary endpoint.

Participants that are margin-positive after SoC and remain margin-positive after FGR will be considered a 'clinical failure' and will be counted towards the denominator of the primary endpoint proportion. See **Section 7.1** for the formula.

The number and percentage of patients with negative-margins following FGR among patients with positive margins following SoC will be provided along with a two-sided 95% confidence interval calculated using the Wilson (score) method. The analysis will be performed using the mITT population.

The statistical hypothesis is as follows: H_o : P(1.1) ≤ 1% vs H_a = P(1.1) > 1%

If the lower bound of the Wilson (score) confidence interval is above 1%, the endpoint will be assumed to be statistically significant. The result is expected to be >3%.

15.6.2. Key Secondary Endpoints:

The secondary endpoints will be tested sequentially at the 0.05 level.

2. P(2.1) Conversion Rate among SoC margin-positive patients

The secondary endpoint, P(2.1), is the percentage of participants with negative-margins following FGR among patients with positive margins following SoC. Participants that are converted from margin-positive after SoC to margin-negative after FGR will be considered a 'clinical success' and will be counted towards the numerator and the denominator of this secondary endpoint. If at the completion of Eagle V1.2 Imaging System assessment, red PpIX FL is still observed on the ***final margins after FGR*** and/or in the ***surgical cavity*** and no further resection is performed, the anatomical surface(s) of residual fluorescence (i.e., S, M, P, L, I, A) and the reason for not performing further ***FGR*** is recorded. In such cases, orientation(s) involving FL observed in the ***final margin after FGR*** and/or in the ***surgical cavity*** will *not* contribute to the determination of a histopathologically-negative final margin for this primary endpoint.

Participants who are margin-positive after SoC and remain margin-positive after FGR will be considered a 'clinical failure' and will be counted towards the denominator of the primary endpoint proportion. See **Section 7.1** for the formula.

The number and percentage of patients with negative-margins following FGR among patients with positive margins following SoC will be provided along with a two-sided 95% confidence interval calculated using the Wilson (score) method. The analysis will be performed using the mITT population.

The statistical hypothesis is as follows: H_o: P(2.1) ≤ 3% vs H_a = P(2.1) > 3%.
If the lower bound of the Wilson (score) confidence interval is above 3%, the endpoint will be assumed to be statistically significant. The result is expected to be >15%.

3. P(2.2): Patient-level Specificity

P(2.2) will be calculated on a patient-level using the mITT Population.

P(2.2) will be calculated as follows: Specificity = 100% x ($TN_{patient}$ / ($TN_{patient}$ + $FP_{patient}$))

The patient-level specificity estimate along with a two-sided 95% confidence interval calculated using the Wilson (score) method will be provided.

The statistical hypothesis is as follows: H_o: P(2.2) ≤ 70% vs H_a: P(2.2) > 70%

If the lower bound of the confidence interval is above 70%, the endpoint will be assumed to be statistically significant. The patient-level specificity is expected to be >80%.

4. **P(2.3): Patient-level Sensitivity**

P(2.3) will be calculated on a patient-level using the mITT Population.

P(2.3) will be calculated as follows: Sensitivity = 100% x ($TP_{patient}$ / ($TP_{patient}$ + $FN_{patient}$))

The patient-level sensitivity estimate along with a two-sided 95% confidence interval calculated using the Wilson (score) method will be provided.

The statistical hypothesis is as follows: H_o: P(2.3) ≤ 50% vs H_a: P(2.3) > 50%

If the lower bound of the confidence interval is above 50%, the endpoint will be assumed to be statistically significant. The patient-level sensitivity is expected to be >70%.

15.7. Secondary and Exploratory Endpoint Analysis

Secondary and exploratory endpoints based on ***patient-level*** data will be analyzed using similar methods to the primary and key secondary endpoints, using Wilson (score) confidence intervals. Re-operation rates will be compared between treatments using Fisher's exact tests.

Secondary and exploratory endpoints based on ***orientation-level, primary specimen-level, and point-level*** data will be analyzed using a weighted estimator, proposed by Lee and Dubin (Lee and Dubin, 1994), which takes into account the correlation (clustering) of the margins within a patient. This method will be used to calculate the estimates and two-sided 95% confidence intervals.

Descriptive statistics will be used to summarize the weight of resected tissue specimens (SoC specimens *vs.* FGR specimens). Mean total tissue weight (Arm 1 *vs.* Arm 2) will be compared using a two-sample t-test.

Breast-Q survey results will be summarized using actual values and change from baseline values using descriptive statistics. The difference in change scores between Arm 1 and Arm 2 will be summarized descriptively and presented along with a 95% confidence interval on the difference in means. For the Breast-Q survey results at 3 months, if the lower bound of this confidence interval is ≥ - 10 then non-inferiority will be claimed. Results at 6 months and 1 year will be described with summary statistics. For the analysis of Breast-Q survey results, the previously defined minimal important difference as the reference point for what patients consider a meaningful change in Breast-Q scores. The minimal important difference is defined as: "The smallest difference in score in a domain of interest that patients perceive as beneficial and which would mandate, in the

absence of troublesome side effects and excessive cost, a change in the patient's (health care) management"[70]. While patients in Arm 2 are anticipated to have marginally more tissue removed as a result of ***FGR*** as compared to SoC [analyzed in secondary endpoint P(2.16)], it is not anticipated that resection of this additional tissue will negatively affect the patient's satisfaction with the appearance of their breasts as compared to patients in Arm 1. For secondary endpoint 18 [P(2.18a) & P(2.18b)] we have defined a mean difference in change score ≤ -10 (Arm 1 – Arm 2) as meeting our criterion for non-inferiority. Previous studies have reported a minimal important difference in Breast-Q scores of 7-8[71] for the breast satisfaction subscale in breast reconstruction patients. To date there are no known publications addressing the minimal important difference using the Breast Conserving Therapy module of the Breast-Q survey. While a change score of ≥ -10 would represent a negative change in breast satisfaction, this risk may still be considered acceptable to patients if the intervention is associated with improved clinical outcomes (e.g. decreased probability of having positive margins).

Depth of tumor analyses of tissue specimens identified by FL imaging will be summarized using descriptive statistics.

Exploratory subgroup analyses will be performed on key efficacy endpoints. Subgroups will include patients who underwent sentinel node mapping with blue dye injection vs. those who did not, and patients who underwent comprehensive circumferential shaves during surgery vs. those who had selective shaves during BCS.

15.8. Safety Analysis

The safety of the procedure and device will be assessed for both Arm 1 and Arm 2. The rates of procedure-related WHO grade 3-5 adverse events, drug-related WHO grade 3-5 adverse events, and device-related WHO grade 3-5 adverse events will be summarized descriptively by treatment arm. Additional summaries may be performed. Full details will be provided in the SAP.

16. Data Management

Data management will be performed according to the Data Management Plan to ensure the accuracy, quality and integrity of the data.

eCRFs will be used to capture study assessments and data. The study coordinator or other delegated study staff will enter data from source documents into the eCRFs. Training will be provided for the electronic data capture (EDC) system. All study staff using the EDC system must have the necessary education, training, and experience or any combination of these. The investigator will be responsible for documenting employee education, training, and previous experience that pertain to the EDC system for all site staff using the EDC system. The investigator must maintain adequate security of the EDC system, including documentation that all users have been trained and a list of authorized users. To ensure all data entries can be tracked, all personnel responsible for data entry

must obtain a unique user identification (user ID) and password before any data can be entered in the eCRFs. Authorized study staff will be assigned a unique user ID only after receiving training.

The investigator must make study data accessible to the site monitor, other authorized representatives of the sponsor, and the appropriate regulatory authority inspectors. The eCRF for each subject will be checked against source documents at the site by the site monitor, and a final copy of the eCRF will be signed by the investigator with an electronic signature. A copy of the final eCRFs will be provided to the investigator in PDF after study closure to be kept in the investigator's study files. See the Data Management Plan for additional details.

17. Deviation from the Clinical Investigation Plan

17.1. Procedures for Reporting Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Study Manual of Procedures requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation. All deviations must be addressed in study source documents and reported to SBI ALApharma Canada Inc.. Should any deviations from the protocol occur, these will be reviewed by SBI ALApharma Canada Inc. for their clinical significance. Protocol deviations must be sent to the local REB/IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their REB/IRB requirements.

18. Amendments to the Clinical Investigation Plan

18.1. Procedures for Reporting Amendments

No changes to the protocol or Study Manual of Procedures will be permitted (except when specific to the protection of the life or physical well-being of a subject in an emergency) without the written approval from SBI ALApharma Canada Inc. and the governing REB/IRB. If the event is performed without written approval from all parties, the investigator may be terminated from the study.

The investigator will be responsible for submitting sponsor-approved amendments in a timely fashion to the REB/IRB. SBI ALApharma Canada Inc. will be responsible for notifying/seeking approval for any amendments requiring notification of or approval from the governing regulatory authority (e.g. Health Canada and/or FDA). SBI ALApharma Sites will notify sites if recruitment should be put on hold while an amendment is being reviewed.

19. Data Handling and Record Keeping

19.1. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Paper source documents include:

- Signed informed consent forms
- Study data collection tools (e.g. Pathology Data Collection Tool), may also be electronic
- Participant's medical files (if maintained in paper format)
- Investigational product accountability records

Electronic source documents include:

- Participant's medical files (if maintained in electronic format; e.g. clinic notes, surgical notes, surgical pathology report, etc.)
- Study data collection tools (e.g. Intraoperative Data Collection Tool, Pathology Data Collection Tool), may also be paper if electronic is not available
- Eagle V1.2 Imaging System data

Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official study record.

Clinical data will be entered into the EDC system by sites. The EDC system used for this study will be IBM Clinical Development, a 21 CFR Part 11-compliant data capture system. CATO SMS will be responsible for data management activities. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents (participant medical files).

Imaging data (including video and image files) will be uploaded into an electronic image database by sites. BioTel Research will be responsible for developing and managing the image database.

19.2. Study Records Retention

In Canada, essential study documents will be maintained for a period of 25 years, in accordance with section C.05.012 of Canada's Food and Drug Regulations - Division 5 "Drugs for clinical trials involving human subjects".

In the USA, all study documents are required to be retained for a minimum of 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing

applications or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational device and/or agent in accordance with 21 CFR Parts 312 and 812. To meet this requirement essential study documents will be maintained for a period of at least 7 years from the date that the study is closed. No records will be destroyed without the written consent of SBI ALApharma Canada Inc. It is the responsibility of SBI ALApharma Canada Inc. to inform the investigator when these documents no longer need to be retained.

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21. Appendices

Appendix 1. Synopsis

Protocol Title: A prospective multi-center clinical study evaluating the use of PD G 506 A and the Eagle V1.2 Imaging System for the visualization of carcinoma during breast conserving surgery

Short Title: Fluorescence imaging of carcinoma during breast conserving surgery

Rationale: Breast conserving surgery (BCS) is performed on patients with breast cancer to resect and completely remove carcinoma while conserving as much of the surrounding healthy tissue as possible. Current methods do not allow surgeons to determine the adequacy of surgical resection in real-time during the ***index surgical procedure***. This often results in the need for a second surgical procedure (re-excision), or in some cases more than two surgical procedures in order to establish appropriate surgical margins after histopathological examination is complete, which typically takes approximately two weeks from the time of the ***index surgery***.

Re-excisions increase poor cosmesis, complications, discomfort, stress, adjuvant delay, medical costs and risk of local recurrence[4, 8, 10-18, 72, 73]. Reducing positive margin rates can be achieved through optimizing surgical procedures[19]. Thus, it is desirable for surgeons to have new methods to visualize carcinoma in real-time during surgery in order to assess the surgical cavity and margins of excised specimen(s) during the ***index*** BCS procedure.

5-aminolevulinic acid hydrochloride (ALA HCl) is a prodrug that is metabolized intracellularly to form the fluorescent molecule protoporphyrin IX (PpIX). The exogenous application of ALA HCl leads to a highly selective accumulation of PpIX in malignant tissues. Visualization of breast carcinoma based on the imaging of ALA HCl-induced PpIX fluorescence has been demonstrated in an investigator-initiated trial in Canada, using a prototype handheld fluorescence imaging device called PRODIGI (Phase 2 Study #10-0633; clinicaltrials.gov identifier: NCT01837225). Protocol SBI-CIP 20-002 is a pivotal Phase 3 trial designed to evaluate the efficacy and safety of PD G 506 A to aid in the visualization of carcinoma during BCS. The Eagle V1.2 Imaging System will be used in this trial to visualize red PpIX fluorescence.

Objectives: This Phase 3 study will evaluate the safety and ***patient-level*** clinical usefulness, as well as ***patient*** and ***orientation-level*** diagnostic performance of PD G 506 A (ALA HCl granules for oral solution)-induced fluorescence for the real-time detection of carcinoma during standard of care (SoC) BCS. ***Orientation-level*** analyses are based on the fluorescence and carcinoma status of the ***primary specimen***, ***cavity shave specimens*** removed during resection, and the fluorescence status of the ***final cavity after FGR*****.**

Overall Design: Protocol SBI-CIP 20-002 is a 2-part, double -blind [pathologist(s) & patients - blinded] randomized placebo-controlled trial (Arm 1: SoC BCS, Arm 2: SoC BCS + Eagle V1.2 Imaging System + PD G 506 A) to evaluate the safety and ***patient-level*** clinical usefulness, as well as ***patient-*** and ***orientation-level*** diagnostic performance of PD G 506 A-induced fluorescence for the real-time visualization of malignant tissue(s) during SoC lumpectomy for breast cancer. Part A is an open-label training phase of the study to optimize workflow and Part B of the study is randomized and double-blind and will serve as the pivotal portion of the study.
The Eagle V1.2 Imaging System will be used for the visualization of fluorescence. Data from the SoC arm will not be used for statistical analysis of the primary and key secondary efficacy endpoints. The purpose of the SoC arm is to compare patient reported cosmetic outcomes between study arms as well as to minimize bias introduced into the SoC procedure if the study ***surgeon*** is aware that they have an opportunity to revise the margins further after SoC is completed.

Number of Patients: The sample size of Part A has been chosen on pragmatic grounds to be approximately 75 patients. Part A will include 75 patients assigned to receive PD G 506 A and undergo SoC BCS followed by FGR. The sample size for Part B will be determined based on the results of the first 30 Part A patients' data.

In Part B of the study, patients will be randomized in a ratio of 1:6 (Arm 1: N=72; Arm 2: N=428) in up to 20 sites in Canada and the United States. A total of 525 patients would be required, accounting for a 5% loss to follow-up. The primary efficacy analysis will be based on the mITT population, which includes all Part B patients randomized to Arm 2 who undergo surgery and have recorded surgical histopathology data.

Treatment Groups and Duration:
Part A will include up to 75 subjects and will not be randomized; all patients in Part A will receive PD G 506 A.

In Part B, study patients will be randomized 1:6 to:

- Arm 1 (SoC): placebo + conventional BCS (data from this arm will not be analyzed for the primary or secondary efficacy endpoints)
- Arm 2 (experimental): PD G 506 A (20 mg/kg) + conventional BCS + Eagle V1.2 Imaging System intraoperative assessment

Patients in both arms will be enrolled at the time their index BCS procedure is scheduled and followed until the first post-operative follow-up, approximately 2 weeks (10 - 14 days) after their surgical procedure. A 3-month, 6-month and 1-year follow-up will also be performed.

Investigational Drug: PD G 506 A for oral solution (aminolevulinic acid [ALA] hydrochloride [HCl] granules for oral solution) will be administered as a single dose (20 mg/kg body weight)

approximately 3 hours (min 2 hours, max 4 hours) prior to anesthesia. PD G 506 A is an optical imaging agent for real-time visualization of carcinoma.

Investigational Device: The Eagle V1.2 Imaging System consists of a handheld, wireless, battery-powered, imaging camera (Handheld Fluorescence Camera) and related accessories. The Handheld Fluorescence Camera has 405 nm and white light illumination light sources and dual imaging sensors with optical filters for imaging of PD G 506 A-induced red PpIX fluorescence and standard full spectrum visible light, respectively.

Study Population: Study patients will be adult female surgical patients with breast cancer undergoing breast conserving surgery.

Inclusion criteria

1. Female, 18 years or older
2. Histologically or cytologically confirmed primary breast cancer (includes invasive lobular carcinoma, invasive ductal carcinoma, inflammatory breast cancer, papillary breast cancer, adenoid cystic carcinoma of the breast, mucinous breast cancer, metaplastic breast cancer, cribriform carcinoma and ductal carcinoma *in situ,* alone or in combination with invasive disease)
3. Scheduled for a lumpectomy (including bilateral lumpectomy) of a breast malignancy [eligibility for breast conserving surgery/partial mastectomy based on clinical staging using TNM staging system (AJCC Cancer Staging Manual: Breast Cancer, 8th Edition[67])].
4. Patient must have normal organ and bone marrow function and be an appropriate surgical candidate per site standard of care
5. Women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) starting the day entering the study, and for the duration of the study period (until the Week 2 visit)

Subject exclusion criteria

Disease and SoC treatment:

1. Currently on (neo)adjuvant therapy to treat another cancer
2. Receiving or intended to receive neoadjuvant therapy to treat the primary breast cancer (including chemotherapy, endocrine therapy and radiotherapy)
3. Stage 4 cancer, inclusive of metastatic disease
4. Non-invasive diseases of the breast (includes phyllodes, Paget's disease of the breast, lobular carcinoma *in situ*)
5. Patients who have had the following procedures performed on the involved breast:
    a. Surgery for a benign lesion(s) within 1 year of the BCS date
    b. Breast implants inserted within 1 year of the BCS date

c. Breast reduction, surgery for malignant disease or mastectomy (at any time prior to the BCS date)
d. Surgery for a benign lesion(s) or insertion of implants >1 year prior to the BCS date and who have signs of ongoing inflammation, active tissue healing and/or extensive scarring
e. Radiation at anytime prior to the BCS date and who have signs of ongoing inflammation, active tissue healing and/or extensive scarring

6. Patients for whom intraoperative frozen section analysis is planned

Concomitant diseases:

7. Patients who have not recovered from adverse events due to an investigational pharmaceutical or diagnostic agents administered more than 30 days prior to their scheduled surgical procedure
8. History of hypersensitivity to ALA HCl or porphyrins
9. Known or documented personal or family history of porphyria
10. Patient has a recording of any parameter as defined below:
    Bilirubin: Above upper limit of normal
    AST (SGOT): > 2.5 X institutional upper limit of normal
    ALT (SGPT): > 2.5 X institutional upper limit of normal
11. Patient has an estimated glomerular filtration rate (eGFR) < 60 mL/min, calculated using the MDRD (Modification of Diet in Renal Disease Study) equation for estimating GFR.
12. Uncontrolled concurrent illness that in the opinion of the Investigator would prevent the patient from participation in the study, including but not limited to:
    a. Ongoing or active infection;
    b. Cardiovascular disease (e.g. symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia).
13. Patients who have the following collagen vascular diseases:
    a. Lupus
    b. Scleroderma
    c. Sjogren's Syndrome

Concomitant medications:

14. Use of an investigational drug within 30 days of their scheduled surgical procedure
15. Simultaneous use of other potentially phototoxic substances (such as St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones and tetracyclines), and topical preparations containing ALA for 24 hours during the perioperative period.

Consent/compliance/other:

16. Social or medical situations including uncontrolled psychiatric illnesses that would in the opinion of the Investigator limit compliance with study requirements (e.g. ability to travel for follow-up)
17. Patients who are pregnant or become pregnant (it is unknown if ALA HCl is teratogenic or has abortifacient effects)
18. Patients who are breastfeeding (there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ALA HCl, breastfeeding should be discontinued if the mother is treated with PD G 506 A)
19. Inability to consent

Appendix 2. Study Workflow

The following is a summary of steps to be performed as part of this clinical study. Refer to the referenced sections of the protocol for more details.

Step	Action
Baseline Procedures (Section 12.2 & 12.3)	
1	Pre-screen patient for eligibility
2	Perform informed consent procedure. If patient signs informed consent proceed to Step 3 If patient requires more time to consider participation provide her with the ICF to take home. If patient refuses participation, do not approach again.
3	Complete screening for eligibility Bloodwork must be performed ≤ 7 days prior to Day 1 (day of surgery) Diagnostic imaging may be performed ≤ 90 days prior to Day 1 (day of surgery) Diagnostic histopathology may be performed ≤ 90 days prior to Day 1 (day of surgery)
4	Enrol eligible participant once their surgery has been booked Note: Site must complete the Enrollment Form and submit to the sponsor a minimum of 2 business days prior to the planned breast conserving surgery.
5	Administer Breast-Q survey ≤ 30 days prior to Day 1 (day of surgery)
Day 1 Pre-operative Procedures (Section 12.4.1)	
6	Confirm participant weight and eligibility. Note: weight used for calculating the investigational drug administration volume (collected ≤ 7 days prior to surgery) must be provided to the 3rd party responsible for preparing and dispensing the investigational drug.
7	Measure baseline blood pressure and heart rate prior to administration.
8	Administer investigational drug (PD G 506 A) or placebo approximately 3 hours prior to anesthesia (min: 2 hours; max: 4 hours). Note: administration to be performed by a medically qualified individual (e.g. nurse) that is blinded to treatment allocation. Neither the ***surgeon*** nor ***surgeon's assistant*** can administer the investigational drug/placebo.
9	Monitor participant for acute AEs (for 30 minutes post-dosing).
10	Monitor and record blood pressure and heart rate immediately after dosing and 30 minutes post-dosing.

Step	Action
11	Monitor and record blood pressure and heart rate at least every hour following the initial 30-min observation period post-dosing. This should be done by appropriately trained medical staff (e.g. patient's nursing staff). NOTE: Patients must have an IV line in place prior to study drug administration NOTE: The patient should receive instructions on reporting symptoms of hypotension, (e.g. light headedness, blurry vision, nausea, dizziness, weakness, blurry vision, etc.) after receiving the study drug. NOTE: During this period of medical supervision from the time of P DG 506 A dosing until the initiation of anesthesia, trained medical personnel and applicable therapies should be immediately available for the treatment of hypotension or any other hypersensitive reactions during administration of PD G506A and the post-administration monitoring period.
12	Describe and provide participant with light-protection instructions (written) and list of other common photosensitizing medications which should be avoided **(Appendix 3)**.
Day 1 Intraoperative Procedures (**Sections 12.4.2** & **12.4.3**)	
13	***Surgeon*** performs SoC lumpectomy (as described in **Section 12.4.2**) up to the point of removing the ***primary specimen***. ***Primary specimen*** is placed inside a black or opaque container and moved to the DIB NOTE 1: do not send the specimen out of the operating room and/or perform any SoC intraoperative imaging at this stage. NOTE 2: the ***primary specimen*** must be marked (e.g. sutured) for identification of the anatomical surfaces as per SoC; specimen inking cannot be performed at this stage
14	***Surgeon's assistant*** places the excised ***primary specimen*** collected in Step 13 inside the DIB and acquires FL-video and FL-images of the 6 surfaces NOTE 1: In cases where a given anatomical surface of the excised tissue does not fit inside the field of view of the camera, multiple still images of each anatomical surface will be acquired to capture all anatomical surfaces of all margins NOTE 2: WL imaging of a particular surface is recommended when positive red PpIX fluorescence is observed. NOTE 3: if specimen inking is performed intraoperatively, it must be performed after FL-imaging of the ***primary specimen*** is complete.
15a	***Surgeon*** performs ***SoC margin assessment*** including white light visualization and palpation and/or intraoperative ultrasound and/or specimen radiography.
15b	If applicable, radiologist reports findings of specimen imaging to ***surgeon.***
16	***Surgeon*** verbalizes response to

Step	Action
	"Do you intend to revise a margin based on ***SoC margin assessment***?" If 'Yes' – verbalize which margin(s) will be revised and which ***SoC margin assessment*** technique informed that decision, proceed to Step 17 If 'No' – proceed to Step 21 Record response on Intraoperative Data Collection Tool.
17	***Surgeon*** revises margin(s) identified in Step 15a. ***SoC-driven cavity shave specimen(s)*** is placed in a black/opaque container and moved to the DIB. Note 1: all ***cavity shave specimens*** must be marked (e.g. sutured) for orientation purposes as per SoC. Note 2: all ***cavity shave specimens*** must be assigned an identifier that indicates from which margin they were resected and whether they are the 1st, 2nd, 3rd, etc. shave resected from that margin. The identifier should not indicate whether the shave specimen was SoC-driven or FL-driven.
18	***Surgeon's assistant*** acquires FL-video and FL-images of the ***outside surface and inside*** of all (if any) ***SoC-driven cavity shave specimens*** collected in Step 15a using the DIB. NOTE 1: In cases where a >1 ***SoC-driven cavity shave specimen*** is resected for a given anatomical surface (e.g. two lateral SoC-driven cavity shave specimens) FL-video and FL-images of both the ***inside*** and ***outside surface*** of all shaves for that orientation must be collected.
19	***Surgeon*** verbalizes completion of the SoC lumpectomy procedure *procedures unrelated to the resection of the primary tumor need not be completed at this stage. Record time of completion of SoC lumpectomy in the Intraoperative Data Collection Tool.
20	If Part A – Proceed to Step 21 If Part B, open randomization envelope: Arm 1 (SoC): proceed to Step 29 Arm 2 (SoC + PD G 506 A + Eagle V1.2 Imaging System): proceed to Step 21 Record the time at which the envelope was opened on the Intraoperative Data Collection Tool.
21	***Surgeon*** acquires FL-video and FL-images of all applicable surfaces of the ***final cavity***

Step	Action
22	The ***surgeon*** reviews all FL-video and FL-images acquired and assigns a FL-status to all tissue surfaces imaged, including the ***primary specimen*** (all anatomical surfaces), all ***SoC-driven cavity shave specimens*** (inside and outside surfaces), and the ***final cavity after SoC***. The ***surgeon*** will verbalize their responses to the questions below and the ***surgeon's assistant*** (or designated individual) will record the data in the Intraoperative Data Collection Tool. For the ***primary specimen,*** the ***surgeon*** verbalizes their response to: i. "While using the Eagle V1.2 Imaging System, do you (surgeon) see red fluorescence on the [insert specific anatomical location e.g. posterior] surface of the ***primary specimen*** If 'Yes' – the (posterior) margin of the ***primary specimen*** is classified as FL-positive If 'No'– the final (posterior) margin of the ***primary specimen*** is classified as FL-negative Repeat for all surfaces (i.e., S, M, P, L, I, A) of the ***primary specimen.*** If ***SoC-driven cavity shave specimens*** were collected, the ***surgeon*** verbalizes their response to: ii. "While using the Eagle V1.2 Imaging System, do you (surgeon) see red fluorescence on the inside surface of the [insert specific anatomical location e.g. posterior] ***SoC-driven cavity shave specimen***? If 'Yes' – the inside surface of the (posterior) ***SoC-driven cavity shave specimen*** of is classified as FL-positive If 'No'– the inside surface of the (posterior) ***SoC-driven cavity shave specimen*** of is classified as FL-negative iii. While using the Eagle V1.2 Imaging System, do you (surgeon) see red fluorescence on the outside surface of the [insert specific anatomical location e.g. posterior] ***SoC-driven cavity shave specimen***? If 'Yes' – the outside surface of the (posterior) ***SoC-driven cavity shave specimen*** is classified as FL-positive

Step	Action
	If 'No'– the outside surface of the (posterior) ***SoC-driven cavity shave specimen*** is classified as FL-negative Repeat for all ***SoC-driven cavity shave specimen*** resected. iv. "While using the Eagle V1.2 Imaging System, do you (surgeon) see red fluorescence on the [insert specific anatomical location] surface of the ***final cavity after SoC***? If 'Yes' – the (posterior) surface of the ***final cavity after SoC*** is classified as FL-positive If 'No'– the (posterior) surface of the ***final cavity after SoC*** is classified as FL-negative Repeat for all surfaces of the ***final cavity after SoC***.
23	The surgeon resects ***FL-driven cavity shave specimens*** based on the FL-status of the surfaces of the ***final cavity after SoC*** and ***final margins after SoC.*** Based on the FL status of the [insert specific anatomical location e.g. posterior] of the ***final cavity after SoC*** and ***final margin after SoC***, perform the following: Cavity FL-positive/ Specimen FL-positive: resect a ***FL-guided cavity shave specimen*** of the (posterior) surface of the cavity, Cavity FL-positive/ Specimen FL-negative: resect a ***FL-guided cavity shave specimen*** the (posterior) surface of the cavity Cavity FL-negative/ Specimen FL-positive: resect a ***FL-guided cavity shave specimen*** of the (posterior) surface of the cavity Cavity FL-negative/ Specimen FL-negative: no ***cavity shave specimen*** NOTE 1: if it is not possible to resect a ***cavity shave specimen*** (e.g. the posterior margin is at the chest wall) the FL status of the specimen must will be noted, however no additional tissue resection is required. NOTE 2: all ***cavity shave specimens*** must be marked (e.g. sutured) for orientation purposes as per SoC. NOTE 3: all ***cavity shave specimens*** must be assigned an identifier that indicates from which margin they were resected and whether they are the 1st, 2nd, 3rd, etc. shave resected from that margin (e.g., 1st lateral shave, 2nd lateral shave). The identifier should not indicate whether the shave was SoC-driven or FL-driven.
24	Repeat Steps 22-23 until all 6 anatomical ***orientations*** have been evaluated.

Step	Action
	If no ***FL-guided cavity shave specimens*** are resected, proceed to Step 29. If ≥1 ***FL-guided cavity shave specimen*** is resected, proceed to Step 25.
25	***Surgeon*** performs FL imaging of the outside and inside surface of all ***FL-driven cavity shave specimens*** resected in Step 23 and the corresponding surfaces of the ***surgical cavity*** . Record response to the following, for each anatomical location (i.e., S, M, P, L, I, A) where a ***FL-driven cavity shave specimen*** was collected: i. "While using the Eagle V1.2 Imaging System, do you (surgeon) see red fluorescence on the outside surface of the ***FL-driven cavity shave specimen***? If 'Yes' – the outside margin of the ***FL-driven cavity shave specimen*** is classified as FL-positive. If 'No'– the outside margin of the ***FL-driven cavity shave specimen*** is classified as FL-negative ii. "While using the Eagle V1.2 Imaging System, do you (surgeon) see red fluorescence on the ***cavity surface*** corresponding to the location where the ***FL-driven cavity shave specimen*** was resected? If 'Yes' – the ***cavity surface*** is classified as FL-positive If 'No'– the ***cavity surface*** is classified as FL-negative Record the FL-status of the outside surface of the ***FL-driven cavity shave specimen(s)*** and corresponding ***cavity surface(s)*** on the Intraoperative Data Collection Tool.
26	Based on the FL status of the outside surface of the ***FL-driven cavity shave specimen(s)*** and ***cavity surface*** determined in Step 25, ***surgeon*** performs the following, for each anatomical location (i.e., S, M, P, L, I, A): Cavity FL-positive/ Shave FL-positive: resect a ***FL-guided cavity shave specimen*** Cavity FL-positive/ Shave FL-negative: resect a ***FL-guided cavity shave specimen*** Cavity FL-negative/ Shave FL-positive: resect a ***FL-guided cavity shave specimen*** Cavity FL-negative/ Shave FL-negative: no cavity shave specimen
27	Repeat Steps 25-26 until no additional red PpIX fluorescence is observed on the outside surface of the last round of ***FL-driven cavity specimen(s)*** AND ***surgical cavity***, or until no further tissue can be resected based on the ***surgeon's*** best clinical judgement.

Step	Action
28	***Surgeon*** verbalises completion of Eagle V1.2 Imaging System assessment. If either the ***surgical cavity*** or ***final margin after FGR*** remain FL-positive and no further resection is performed, record the anatomical location(s) of residual fluorescence (i.e., S, M, P, L, I, A) and the reason for not performing further ***FGR***.
29	***Surgeon*** completes surgical procedure as per SoC (e.g., performs sentinel node procedure, if indicated, closes surgical cavity as per SoC) and all samples are sent to pathology.
Peri-operative Procedures (Specimen Biopsy Collection Section 12.4.4.1; conducted in a subset of clinical sites)	
30	Bisect or serially section the primary specimen through the centre of the primary mass and place the sectioned specimen on the DIS with the tumor cross-section facing up. NOTE 1: this step may be performed at any time after completion of SoC lumpectomy procedure and Eagle V1.2 Imaging System assessment of the primary specimen NOTE 2: the tissue may be sectioned by any qualified individual (e.g. surgeon, surgeon's assistant, pathologist, pathologist's assistant) however interpretation of the fluorescence images must be performed by the ***surgeon or surgeon's assistant***. The individual grossing the specimen (e.g. pathologist's assistant) must remain blind to the fluorescence imaging results collected by the ***surgeon*** and/or ***surgeon's assistant***. NOTE 3: the weight of all specimens must be recorded during grossing (as described in Steps 39-40), and should be performed prior to biopsy collection.
31	Capture FL and WL image(s) of the entire surface of the inside of the sectioned specimen:
32	***Surgeon*** or ***surgeon's assistant*** makes determination of where red PpIX fluorescence (if any) is observed inside the sectioned specimen. Ink the area(s) where biopsies will be collected. Collect tissue biopsies while recording a fluorescence video in order to document the locations where biopsies were collected. • If both positive and negative fluorescence are observed, collect 1 fluorescence-positive and 1 fluorescence-negative biopsy • If only positive fluorescence is observed, collect 1 fluorescence-positive biopsies • If only negative fluorescence is observed, collect 1 fluorescence-negative biopsies

Step	Action
	Biopsies should be identified with an identifier that does not indicate the fluorescence status of the tissue. Record the fluorescence status of each of the collected biopsies in the Intraoperative Data Collection Tool. Note 1: the location of collected biopsies should adhere to the procedure described in **Section 12.4.4.1**
Day 1 Peri-operative Procedures (Specimen Grossing, **Section 12.4.4.2**)	
33	Receive research samples in clinical pathology laboratory for grossing and formalin fixation.
34	Weigh each individual tissue specimen (excluding biopsies) and record the mass on the Pathology Data Collection Tool.
35	Perform specimen grossing and inking as per standard of care.
36	Fix tissue samples as per standard clinical pathology laboratory protocols.
Day 1 Post-operative Procedures (**Section 12.4.5**)	
37	Prior to discharge, collect and record participant's blood pressure and heart rate as well as evaluate and record any adverse events and provide participants with sunscreen to take home.
Post-operative Pathology Procedures (**Section 12.6**)	
38	Block the ***primary specimen*** according to standard procedures. Block all ***cavity shave specimens*** in total. Block biopsies individually. Note 1: ***cavity shave specimens*** must be oriented such that histological sections can be made perpendicularly to the ***inked inside*** and ***outside surfaces*** Note 2: biopsies must be oriented such that histological sections can be made perpendicularly to the ***inked surface*** (i.e., imaged surface) Record the tissue block ID in the Pathology Data Collection Tool.
39	Pathologist evaluates the ***primary specimen*** as per SoC. Record the status of all ***primary specimen*** anatomical surfaces (i.e., S, M, P, L, I, A) on the Pathology Data Collection Tool: i. Presence/absence of carcinoma at each inked surface ii. Presence/absence of carcinoma below each inked surface iii. Presence/absence of non-malignant abnormal cells (e.g. hyperplastic, dysplastic) at or below each inked surface

Step	Action
	If carcinoma is present, record the following additional information of the Pathology Data Collection Tool: i. Type(s) of carcinoma (e.g. IDC, ILC, DCIS, if other specify) ii. Shortest distance from the ***inked surface*** to carcinoma If non-malignant abnormal cells are present, record the following additional information: i. Type(s) of abnormal cells (e.g. hyperplastic, dysplastic)
40	Pathologist evaluates all ***cavity shave specimens*** and records the following on the Pathology Data Collection Tool: i. Presence/absence of carcinoma at or below the ***inked outside surface*** of all ***cavity shave specimens*** ii. Presence/absence of carcinoma at or below the ***inked inside surface*** of all ***cavity shave specimens*** iii. Presence/absence of non-malignant abnormal cells (e.g. hyperplastic, dysplastic) at or below the ***inked inside surface*** of all ***cavity shave specimens*** If carcinoma is present, record the following additional information on the Pathology Data Collection Tool: i. Type(s) of carcinoma (e.g. IDC, ILC, DCIS, if other specify) ii. Shortest distance from each ***inked surface*** (i.e., inside and outside surfaces) to carcinoma If non-malignant abnormal cells are present, record the following additional information: i. Type(s) of abnormal cells (e.g. hyperplastic, dysplastic)
41	Pathologist evaluates all tissue biopsies and records the following on the Pathology Data Tool i. Presence/absence of carcinoma anywhere in a given biopsy ii. Presence/absence of non-malignant abnormal cells (e.g. hyperplastic, dysplastic) anywhere in a given biopsy If carcinoma is present, record the following additional information on the Pathology Data Collection Tool i. Type(s) of carcinoma (e.g. IDC, ILC, DCIS, if other specify) ii. Shortest distance from the inked surface to carcinoma If non-malignant abnormal cells are present, record the following additional information:

Step	Action
	i. Type(s) of abnormal cells (e.g. hyperplastic, dysplastic)
Follow-up Procedures (Sections 12.5 & 12.7)	
42	Perform Day 2 follow-up within 24 hours (+24 hours) of the surgery. If participant has been discharged, follow-up may be performed via the telephone. Record any AEs in the EDC.
43	Perform Week 2 follow-up within 14 days (-4 days) of the surgery, including administration of the post-operative Breast-Q survey. Record any AEs in the EDC If no unresolved AE(s), this is the last in-person study visit. If unresolved AE(s) is present, follow for additional 7 days. If unresolved SAE(s) is present, follow for additional 30 days. Record any (S)AE(s) and outcome in the EDC.
44	Perform 3-month follow-up within 80 – 90 days of the surgery, including administration of the post-operative Breast-Q survey. If the patient is schedule to received adjuvant radiation therapy prior to 80 days post procedure, perform the 3-month visit within 7 days prior to commencement of radiation therapy.

AE, adverse event; DCIS ductal carcinoma *in situ*; DIB, Dark Imaging Box; DIS, Dark Imaging Sheet; EDC, electronic data capture; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; SoC, standard of care

Appendix 3. Sun Protection Instructions and List of Other Common Photosensitizing Medications Which Should be Avoided

The following is an example of the information which should be provided to all study participants at the time of dosing. Formatting and non-critical information may be modified by sites to meet the requirements of their institution or REB/IRB of record. Modifications must be approved by the sponsor prior to implementation.

STUDY TITLE:
A prospective multi-center clinical study evaluating the use of PD G 506 A and the Eagle V1.2 Imaging System for the visualization of carcinoma during breast conserving surgery

SUN PROTECTION INSTRUCTIONS

As part of the clinical study, you received the contrast agent ALA. This substance will make you sensitive to light. It is very important that you follow these instructions for the **48 hour period** following surgery to avoid sunburn.

- Keep out of direct sunlight and all sources of bright indoor lights.
- When inside, draw curtains and dim lights to avoid exposure to sunlight and indoor lights
- If you will be exposed to any sunlight, please cover all body surfaces with appropriate clothing, wear a hat and sunglasses and apply sunscreen.
- Generously apply the sunscreen to any exposed areas of skin (for example, face, neck, décolleté, hands etc.) at least 30 minutes before intended exposure.

Please keep in mind that UV light can pass through some glass when you are sitting close to windows in the house or car. Use appropriate caution to minimize exposure to direct sunshine through windows. You will be provided with complementary SPF 60+ sunscreen by the study research group for your use. If at any time you experience an unexpected sunburn or other related skin reaction, please inform your clinical care or research study team.

If you have any questions or concerns, please contact:

[insert investigator contact information]

Study: _____ Date: _____

Patient: _____

Dear Doctor/Pharmacist,

Please note that the above patient is participating in a clinical trial at [insert study site] and may receive one dose of ALA HCl orally (aminolevulinic acid hydrochloride). ALA is a naturally occurring substance that when illuminated with violet-blue light, emits a visible red fluorescence. ALA may cause skin photosensitivity reactions. According to the investigator's brochure, enhanced photosensitivity due to the combination of ALA and another photosensitizing drug, although uncommon, cannot be excluded. Therefore while on this study, patients **should try to avoid exposure to other photosensitizing agents for up to 2 weeks after administration of ALA. If the patient cannot avoid photosensitizing agents, the patient should be informed about skin protection (wear sunscreen on exposed areas, sun-protective clothing and sunglasses and seeking shade when outdoors). A list of potential photosensitizing agents is provided below.**

Antimicrobials	***Psychiatric Medications***	***NSAIDs***	***Others***
Azole Antifungals • Itraconazole • voriconazole Ceftazidime Griseofulvin Quinolones • Ciprofloxacin • levofloxacin • Norfloxacin • Ofloxacin Sulfonamides Tetracyclines • Doxycycline • tetracycline Trimethoprim	Alprazolam chlordiazepoxide chlorpromazine desipramine Fluphenazine imipramine Perphenazine Prochlorperazine Trifluoperazine Tricyclic Antidepressants: • amitriptyline • clomipramine • desipramine • doxepin • imipramine • loxapine • nortriptyline	Celecoxib Diclofenac Ibuprofen Indomethacin Ketoprofen Meloxicam Naproxen Piroxicam Sulindac Tiaprofenic acid	Amiodarone Coal Tar derivatives, topical Diltiazem Methoxsalen Quinidine Quinine St. John's wort (Hypericin extracts) Sulfites Tolbutamine Verteporfin
Diuretics	***Retinoids, systemic***	***Retinoids, topical***	
Acetazolamide Chlorothiazide Chlorthalidone Furosemide Hydrochlorothiazide Methazolamide Metolazone	Acitretin Alitretinoin	Adapalene Tazarotene	

Medications that may cause phototoxic reactions Therapeutic Choices. Canadian Pharmacist Association, 2013

The above list is not exhaustive. If any of these drugs are required by a patient within two weeks after ALA administration, *or if the patient is starting any new medication*, please notify one of the following hospital staff:

During office hours: [insert investigator/study coordinator contact information]

For emergency contact outside of regular office hours please call: [insert emergency contact]

Appendix 4. Study Governance Considerations

Regulatory and Ethical Considerations

This trial will be conducted in compliance with the protocol, International Conference on Harmonization (IHC) of technical requirements for registration of pharmaceuticals for human use Good Clinical Research Practice (GCP) and all applicable regulatory requirement(s).

This may include an inspection by SBI ALApharma Canada Inc. representatives and/or Health Canada representatives at any time. The investigator must agree to the inspection of study-related records by the Health Canada/SBI ALApharma Canada Inc. representatives, and must allow direct access to source documents to the Health Canada/SBI ALApharma Canada Inc. representatives. Health Canada approvals/authorizations/notifications, where required, will also be in place and fully documented prior to study start.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB/IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the REB/IRB before the changes are implemented to the study. All changes to the consent form will be REB/IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

Financial Disclosures and Conflict of Interest

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Investigators, sub-investigators and study team members are required to declare in writing any actual, perceived or potential conflict of interest to SBI ALApharma Canada Inc. in advance of study start or their participation in the study (whichever comes first). Additionally, investigators, sub-investigators and study team members, will be required to comply with their institution's conflict of interest policy as related to the conduct of this trial.

Informed Consent Process

(a) Consent and Other Informational Documents Provided to Participants

Consent forms describing in detail the investigational drug, investigational device, study procedures, and risks are given to the participant and written documentation of informed consent

is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol:

- Study Flyer
- Informed Consent Form

(b) Consent Procedures and Documentation

Surgeon investigators will be responsible for confirming patient eligibility and a member of patient's circle of care will introduce the patient to the study. If the patient expresses interest in the study, the investigator or study personnel (e.g. study coordinator) will be responsible for discussing the study with the patient, answering any questions and obtaining informed consent. The rights and welfare of the patient will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. Patients will be provided information about the study and allowed appropriate time (minimum 24 hours if requested) to decide to volunteer for the study. Patients that request additional time to consider their participation may be provided a copy of the Informed Consent Form to take home and the research team will follow-up with them via telephone within 2-5 business days. All participants will be required to sign 2 copies of the Informed Consent Form, one of which they will keep and the other of which will be retained by the investigator.

Investigator will document the date and time that written consent was obtained as well as any questions/concerns discussed with the patient. Screening may not be performed in patients that have not provided written informed consent.

Data Protection

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and SBI ALApharma Canada Inc. and their agents. This confidentiality is extended to cover testing of biological samples and clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of SBI ALApharma Canada Inc..

The study monitor, other authorized representatives of SBI ALApharma Canada Inc., representatives of the IRB/REB, regulatory authorities, investigational drug manufacturer and device manufacturer may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the governing IRB/REB, institutional regulations or governing regulatory body.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in the clinical study database. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems will be secured and password protected. At the end of the study, all study databases will be de-identified, archived and retained by SBI ALApharma Canada Inc. (the sponsor).

Publication Policy

The results of this study may not be published or presented at medical or scientific meetings without the expressed written permission of the sponsor. The study investigator agrees to submit all manuscripts or abstracts to the sponsor for review before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. SBI ALApharma Canada Inc. will register the trial in public registries (e.g. clinicaltrials.gov, Health Canada Clinical Trial Registry). In accordance with standard editorial and ethical practices, the results of this multicenter study will be reported in its entirety and not as individual site data. A coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

The data generated by this study may be used for publication in peer-reviewed scientific journals, presented at conferences, used for commercial marketing, or submitted to regulatory authorities worldwide to support medical device and drug licenses.

Data Quality Assurance

- All participant data relating to the study will be recorded on an eCRF. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, REB/IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- Quality control procedures will be implemented beginning with the data entry system and data quality control checks, that will be run on the database, will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- The site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring and auditing by or on behalf of SBI ALApharma Canada Inc., and inspection by local and regulatory authorities.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- All possible effort will be taken to ensure that the protocol is performed as accurately as possible and with all possible care by the clinical and research staff. All deviations from the protocol will be appropriately documented and reported as described in **Section 17.1**

Source Documents

- Source documents are filed at the investigator's site.
- Data reported entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the Data Management Plan.

Study and Site Suspension and Closure

All study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed. Regulatory authorities will be notified of the completion of the study, as appropriate.

The sponsor reserves the right to temporarily suspend or prematurely close a study site or study at any time for any reason at the sole discretion of the sponsor. The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the suspension or premature closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the REB/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Data that are not sufficiently complete and/or evaluable

Written notification, documenting the reason for study suspension or early closure, will be provided by SBI ALApharma Canada Inc. to the investigators and regulatory authorities will be notified, as appropriate. If the study is prematurely terminated or suspended, the PI will promptly inform the governing IRB/REB and will provide the reason(s) for the termination or suspension.

If temporarily suspended, the study may resume once concerns about safety, protocol compliance and/or data quality are addressed and satisfy SBI ALApharma Canada Inc. and/or REB/IRB.

Circumstances that may warrant termination or suspension of the trial include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Discontinuation of further study treatment development

Written notification, documenting the reason for study site suspension or termination, will be provided by SBI ALApharma Canada Inc. to the investigator and regulatory authorities will be notified, as appropriate. If the study site is prematurely terminated or suspended, the PI will promptly inform the governing REB/IRB and will provide the reason(s) for the termination or suspension.

The study may resume at a suspended site once concerns about safety, protocol compliance and/or data quality are addressed and satisfy SBI ALApharma Canada Inc. and/or REB/IRB.

Appendix 5. Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in **Appendix 5 Table 5.1**.

Appendix 5 Table 5.1: Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation ● Oral ● Intravaginal ● Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation ● Oral ● Injectable
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation ● Intrauterine device (IUD) ● Intrauterine hormone-releasing system (IUS) Bilateral tubal occlusion
Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES: a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

Pregnancy Testing

Pregnancy testing will be performed locally at each site at baseline and on the Day 1 (prior to administration of the investigational agent) to confirm eligibility.

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive blood or urine pregnancy test.

Collection of Pregnancy Information

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form

and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The investigator will request written permission to follow the participant until the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor as described in **Section 13**. While the investigator is not obligated to actively seek this information in former study participants, they may learn of an SAE through spontaneous reporting.

Any participant that becomes pregnant following consenting to participate and prior to receiving the investigational drug, will be terminated immediately. If a participant becomes aware that they are pregnant following administration of the investigational drug but prior to completing the study, they will complete the study according to the protocol.

Appendix 6. Breast-Q Version 2.0 © - Breast Conserving Therapy Module

BREAST-Q™ - BREAST CANCER CORE SCALE (PREOPERATIVE) VERSION 2.0: SATISFACTION WITH BREASTS

With your breast area in mind, in the past week, how satisfied or dissatisfied have you been with:

	Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a. How you look in the mirror clothed?	**1**	**2**	**3**	**4**
b. How comfortably your bras fit?	**1**	**2**	**3**	**4**
c. Being able to wear clothing that is more fitted?	**1**	**2**	**3**	**4**
d. How you look in the mirror unclothed?	**1**	**2**	**3**	**4**

BREAST-Q™ – BCT MODULE (POSTOPERATIVE) VERSION 2.0: SATISFACTION WITH BREASTS

The following questions are about your breasts and your breast cancer treatment (by treatment, we mean lumpectomy with or without radiation). If you have had a lumpectomy and radiation of both breasts, answer these questions thinking of the breast on which the study procedure was performed. If you are unsure on which breast the study procedure was performed, ask your surgeon. With your breasts in mind, in the past week, how satisfied or dissatisfied have you been with:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	How you look in the mirror clothed?	**1**	**2**	**3**	**4**
b.	The shape of your lumpectomy breast when you are wearing a bra?	**1**	**2**	**3**	**4**
c.	How normal you feel in your clothes?	**1**	**2**	**3**	**4**
d.	Being able to wear clothing that is more fitted?	**1**	**2**	**3**	**4**
e.	How your lumpectomy breast sits/hangs?	**1**	**2**	**3**	**4**
f.	How smoothly shaped your lumpectomy breast looks?	**1**	**2**	**3**	**4**
g.	The contour (outline) of your lumpectomy breast?	**1**	**2**	**3**	**4**
h.	How equal in size your breasts are to each other?	**1**	**2**	**3**	**4**
i.	How normal your lumpectomy breast looks?	**1**	**2**	**3**	**4**
j.	How much your breasts look the same?	**1**	**2**	**3**	**4**
k.	How you look in the mirror unclothed?	**1**	**2**	**3**	**4**

Appendix 7. Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC). A history of all amendments will be provided below.

Amendment 7: (13-Nov-2023), Version 1.7

Overall Rationale for Amendment:
Inclusion of safety information as a response to review of SUSAR case 2023SBI00001 as per the Ad Hoc DSMB meeting on 26 Jul 2023. Patient to have IV in place prior to administration of study drug. Dosing to take place in a location where patient can remain under medical supervision from the time of drug administration to anesthesia. Add hourly monitoring of BP and HR after 30 minutes post-administration measurement (as is currently required per protocol); given 2-4 hour window between study drug administration and anesthesia this will add 1-2 additional BP and HR readings.

Inclusion of safety request from FDA in IND 147228 Sequence 0047 in regards to SUSAR case 2023SBI00001. Revision to include necessity of increased monitoring of study patients by medical personnel following administration of study drug

Summary of Changes

Section	Changes/rationale
3.4 Contract Research Organisation 3.8 Monitoring Information	Updated CRO information from: Name : CATO SMS Contact : Aleksandra Trajkovic to: Name : Allucent Contact : Andrew Daleus In order to account for CRO change in name, and Project Manager
4 Synopsis 8.1 Description of the Study Design 13.5 Study Pausing Rules 15.2 Sample Size Estimation	Modified the language regarding the patients from Part A of the trial that will be used to confirm sample size for Part B from: *The sample size for Part B will be determined based on the results of Part A patients' data, but is currently expected to be approximately 350 patients in approximately 20 different clinical sites in Canada and the USA* to: *The sample size for Part B will be determined based on the results of Part A patients' data, but is currently expected to be approximately 350 patients in approximately 20 different clinical sites in Canada and the USA. Sample size estimation for Part B will occur after TP residual FL is found in an orientation following SOC in at least 3 patients in Part A.*

	Additionally, all note of the total patients in Part A of the trial has been clarified to state: *Part A will include approximately 75 subjects*
5. Schedule of Activities (SOA)	Modified Baseline screening from: *≤ 30 to Day 0 before procedure* to: *≤ 90 to Day 0 before procedure* In order to account for the inclusion of Biopsy and Imaging done as SoC more than 30 days prior to surgery as part of screening for the trial, as noted in previous protocol amendment 1.6. Updated Figure 5.1 Schematic of Study Visits and Procedures through Week 2 Visit to note this change to -90 days for baseline screening.
12.1 Screening (Day -90 – Day 0)	Modified title of section 12.1 from: *Screening (Day -30 – Day 0)* to: *Screening (Day -90 – Day 0)* In order to account for the inclusion of Biopsy and Imaging done as SoC more than 30 days prior to surgery as part of screening for the trial, as noted in previous protocol amendment 1.6. Clarified language regarding the use of Standard Of Care blood and examination results within 7 days prior to signing of ICF as per NTF 007 released on 15-Jun-2023. The following language has been included: *Baseline blood work may be collected before obtaining informed consent if both of the following criteria are met:* *3. Baseline blood work required to confirm eligibility according to study protocol SBI-CIP 20-002 is performed as part of the site's standard of care for all patients undergoing breast conserving surgery.* *4. Standard of care baseline blood work is collected ≤ 7 days prior to surgery* *Baseline blood work **may NOT be collected before obtaining informed consent if the following criterion is met:*** *2. Baseline blood work required to confirm eligibility according to study protocol SBI-CIP 20-002 is NOT performed as part of the site's standard of care for all patients undergoing breast conserving surgery.*
12.2 Enrolment and Randomization	Added requirements for the patient to meet additional safety monitoring requirements for risk of hypotension as per NTF 008 released on 28-Jul-2023, and the Dear Doctor Letter released to sites on 23-Aug-2023 Following language included: *'Continued monitoring of the patient at hourly intervals following the initial 30-min observation post-administration of the study drug can be done by trained medical personnel (e.g. the patient's nursing staff).'*
12.3.1 Pre-operative Procedures	Updated language from:

	'Baseline heart rate and blood pressure will be collected prior to administration and post-administration heart rate and blood pressure will be monitored and recorded immediately after and 30 minutes after administration. *The participant will be observed for 30 minutes following administration for any acute (S)AE(s). (S)AE monitoring will continue for the duration of the study period (until the Week 2 visit) as described in **Section 13.3**.'* to: *'Patients must have an IV line in place prior to study drug administration, and must be under medical supervision from the time of dosing until the initiation of anesthesia. Baseline heart rate and blood pressure will be collected prior to administration and post-administration heart rate and blood pressure will be monitored and recorded immediately after and 30 minutes after administration. Post-administration heart rate and blood pressure will continue to be collected at least hourly following the measurement at 30-mins post dosing, until the initiation of anesthesia. The participant will be observed for 30 minutes following administration for any acute (S)AE(s). (S)AE monitoring will continue for the duration of the study period (until the Week 2 visit) as described in **Section 13.3**. Instructions will be provided to the patient to immediately report any possible symptoms of hypotension (e.g. light headedness, blurry vision, nausea, dizziness, weakness, blurry vision, etc.) after receiving the study drug.* *While the patient is under medical supervision from the time of P DG 506 A dosing until the initiation of anesthesia, trained medical personnel and applicable therapies should be immediately available for the treatment of hypotension or any other hypersensitive reactions during administration of PD G506A and the post-administration monitoring period.'*
Appendix 1. Study Workflow	Step 11 of the Study Workflow has been amended to include the following language: *'Monitor and record blood pressure and heart rate at least every hour following the initial 30-min observation period post-dosing. This should be done by appropriately trained medical staff (e.g. patient's nursing staff).* *NOTE: Patients must have an IV line in place prior to study drug administration* *NOTE: The patient should receive instructions on reporting symptoms of hypotension, (e.g. light headedness, blurry vision, nausea, dizziness, weakness, blurry vision, etc.) after receiving the study drug.* *NOTE: During this period of medical supervision from the time of P DG 506 A dosing until the initiation of anesthesia, trained medical personnel and applicable therapies should be immediately available for the treatment of hypotension or any other hypersensitive*

	reactions during administration of PD G506A and the post-administration monitoring period.' Numbering of steps following this included Step 11 has been updated accordingly.

Amendment 6: (04-Jan-2023), Version 1.6

Overall Rationale for Amendment:

Improve Day 1 logistics (in response to site feedback), define the scope of exclusion criteria 5 to align with rationale for excluding patients with prior surgery (i.e. to exclude patients with changes to the breast tissue that may affect efficacy of drug/device).

Summary of Changes

Section	Changes/rationale
5. Schedule of Activities	Modified to improve day 1 logistics: • Dosing to be based on weight of patient collected within 7 days prior to study drug administration Day of surgery weight will still be collected and recorded in EDC
4 Synopsis 9.3 Eligibility	Modified exclusion criterion 5 from: Patients who have had previous surgery on the involved breast including breast surgeries, mastectomies, breast reconstructions or implants to: Patients who have had the following procedures performed on the involved breast: a. Surgery for a benign lesion(s) within 1 year of the BCS date b. Breast implants inserted within 1 year of the BCS date c. Breast reduction, surgery for malignant disease or mastectomy (at any time prior to the BCS date) d. Surgery for a benign lesion(s) or insertion of implants >1 year prior to the BCS date who have signs of ongoing inflammation, active tissue healing and/or extensive scarring Radiation at any time prior to the BCS date and who have signs of ongoing inflammation, active tissue healing and/or extensive scarring
6.2.3 Residual device risk and mitigation	Added description of residual burn risk and mitigation to match Section 3.4 of Eagle V1.2 Imaging System Instructions for Use
19.1 Data Collection and Management Responsibilities	Updated source document description to specify data collection tools may exist in either electronic or paper format
n/a	Corrected spelling of sponsor name from SBI ALAphama Canada, Inc. to SBI ALApharma Canada Inc. Removed reference to Medical Monitoring contact details as pharmacovigilance, medical inquiries and medical review of eCRFs is performed by spmd, Inc.

Amendment 5: (24-Mar-2022), Version 1.5

Overall Rationale for Amendment:
To address non-clinical hold feedback FDA provided on 27 November 2021 and further clarify and/or modify imaging data collection, study specific procedures related to blinding, randomization, training, and SoA.

Summary of Changes

Section	Changes/rationale
5. Schedule of Activities	Modified to improve day 1 logistics: • Blood pregnancy test permitted within 7 days prior to surgery • Abbreviated physical examination permitted on Day 1 if full examination performed within 7 days prior to surgery Modified to allow patients with older diagnostic biopsies to participate: • Baseline diagnostic tissue sample collection permitted up to 90 days prior to surgery Figure 5 updated to include Part A and B design
7.1 Primary Objectives and Endpoints	Updated based on recommendation of FDA: • Abbreviated description of primary endpoint P(1.1) updated to differentiate from conversion rate among all patients endpoint • Changed primary endpoint P(1.3) from patient-level specificity "at the end of FGR" to "at the final assessment at the end of SoC" (specificity at the end of FGR moved to secondary endpoint 4)
7.2 Secondary Objectives and Endpoints	Updated based on recommendation of FDA: • Conversion rate among all patients elevated to secondary endpoint 1 [P(2.1)] • Orientation-level diagnostic performance of combined imaging (in vivo and ex vivo) at the end of FGR elevated from exploratory endpoint 20 to secondary endpoint 3 [P(2.3)] • Clarified terminology e.g. replaced "FL- orientations" with FL-negative orientation" • Updated abbreviated description of secondary endpoint 12: percentage of patients with true-negative fluorescence at the end of standard of care Updated to improve clarity • Added sequential numbers to all endpoints [e.g. P(2.17a)]
7.3 Exploratory Objectives and Endpoints	Updated based on recommendation of FDA: • Corrected the parameter description for exploratory endpoints 28 & 29 to include SoC-guided shaves • Removed exploratory endpoint 32 as it was a duplicate of exploratory endpoint 27 (diagnostic performance of PD G 506 A to detect cancer in the primary specimen)
8. Study Design	Updated to allow for all participating sites to have opportunity to perform first procedures under training conditions: • Added ~45 patients to Part A and description of training requirements for all surgeons and surgeon's assistant's participating in the trial
8.1 Description of the Study	Updated based on recommendation of FDA:

	• Added description of stratification at randomization and permuted block randomization
8.3 Minimizing Bias	Updated to improve clarity: • Clarified language to state that individual grossing the specimen (e.g. pathologist's assistant) must remain blind to the fluorescence imaging data collection of the serially sectioned specimen • Added that neither surgeon nor surgeon's assistant can dose patient due to risk of unblinding
10.1.2.4 Dosing and Administration	Updated to improve clarity: • Added that dosing container must be amber, as described in Pharmacy Manual
10.1.3 Investigational Medical Device	• Updated description of system components to match Eagle V1.2 Imaging System IFU (Rev 1.4)
10.1.3.1 Handling/Storage/Accountability	Updated to improve clarity: • Added details about use of Device Accountability Log and Device Return/Repair/Destruction Log
10.3 Blinding	Updated based on recommendation of FDA: • Added description of surgeon being blinded to fluorescence imaging data collected during SoC and requirement that surgeon refrain for viewing the specimen tagging procedure performed by the surgeon's assistant
12.2 Enrolment and Randomization	Updated based on recommendation of FDA: • Added description of preparation and dissemination of randomization envelope and unblinding of OR team after completion of SoC lumpectomy Updated to improve clarity: • Added description of Enrolment Form
12.3.3. Study-specific Procedures	Updated to improve clarity: • Added description of process in event of accidental unblinding in the operating room
12.3.3.1 Specimen Tagging	• Corrected error in flow chart regarding the number of sutures to be placed on a FL-driven shave specimen
12.3.4 Perioperative Procedures	Updated to improve perioperative logistics: • modified to permit surgeon's assistant (in addition to surgeon) to interpret fluorescence images collected of the serially sectioned specimen and direct location of biopsy collection Updated to improve clarity: • Language in Table 12.1 updated to reflect the similarities in requirements for collecting biopsies from specimens with a palpable vs. non-palpable mass
12.6 Week 2 Visit	Updated based on recommendation of FDA: • Definition of clinically significant elevation of liver enzymes added. Definition based on CTCAE v5.0 definition of a grade 2 event
15.2 Sample Size Estimation	Updated based on recommendation of FDA: • Null proportion for P(1.1) changed from 0 (0.01%) to 0.03 (3%) and updated sample size calculated using null variance (rather than sample variance) • P(1.2) updated to reflect change to endpoint in Section 7 • Updated overall sample size due to change threshold for P(1.1)

15.4.5.3 End of FGR	Updated based on recommendation of FDA: • definition corrected to include the outside surfaces of the last SOC-guided shave specimens (if no FL-guided shave specimens are taken for the particular orientation)
15.4 Analysis Populations	Updated based on recommendation of FDA: • Modified definition of mITT
Throughout protocol	Updated to improve clarity: • Other surgical tools (besides scalpel) can be used for SOC BCS procedure • Neither surgeon or surgeon's assistant can be responsible for dosing patient (due to risk of accidental unblinding) • Patient should be observe for 30 mins post dosing but blood pressure and heart are collected immediately after and 30 mins post dosing • Only outside surface of first SoC-driven shave specimen must be imaged; inside and outside surface of subsequent SoC shaves must be collected in FL-video and FL-images • WL imaging is recommended when PpIX fluorescence is observed on a tissue surface

Amendment 4: 01-Oct-2021:

Overall Rationale for the Amendment: To address feedback Health Canada provided during the CTA review process

Summary of Changes

Section # and Name	Description of Change	Brief Rationale
Synopsis & 9.3 Exclusion criteria, Exclusion criterion 11	Use eGRF as a method of measuring renal function instead of serum creatinine or creatinine clearance. Furthermore, the exclusion criterion applies to all patients, not just those whose creatinine levels exceed institutional normal.	Required as per Health Canada feedback
Synopsis & 9.3 Exclusion criteria, Exclusion criterion 13:	Add Sjogren's Syndrome to the list of collagen vascular diseases that are an exclusion criterion	Required as per Health Canada feedback

Amendment 3: 14-Apr-2021

Overall Rationale for the Amendment: Modifications to clarify the intraoperative data collected to ensure all data required for endpoint analysis is collected. Modifications to clarify communication between CATO-SMS (CRO) and spmd (PV) in relation to study pausing rule

Summary of Changes

Section # and Name	Description of Change	Brief Rationale
Section 12 Study Procedures & Appendix 1 Study Workflow	Updated to clarify FL-status for all tissue surfaces must be recorded	FL-status of all tissue surfaces required for analysis of diagnostic performance endpoints
Section 13.5 – Study Pausing Rules	Updated to clarify that CATO-SMS is responsible for providing AE listing to DSMB	Required to clarify responsibilities and channel of communication between CRO and PV vendors. New language aligns with DSMB Charter v1.1

Amendment 2: 28-Mar-2021

Overall Rationale for the Amendment: to address feedback from the FDA provided during the IND review

Section # and Name	Description of Change	Brief Rationale
Section 5 SoA; Section 12.6 Week 2 Visit; Section 13.3 Time Periods and Frequency for Event Assessment and Follow-up	Added language stipulating if liver enzymes are elevated at the week 2 visit, participant must be followed until levels return to baseline	Required as per FDA safety feedback
Section 5 SoA; Section 13.3 Time Periods and Frequency for Event Assessment and Follow-up	Added assessment for neurological adverse events (AEs) at each AE assessment time point	Required as per FDA safety feedback

Section 10.5 Concomitant Therapy; Section 10.6 Prophylactic Medications Treatments and Procedures; Section 10.7 Warnings and Precautions	Changed duration of sun protection from 24 to 48 hours after PD G 506 A	Required as per FDA safety feedback
Section 5 SoA & 12.6 Week 2 Visit	Added assessment of phototoxic reactions to physical exam at 2 week visit	Required as per FDA safety feedback
Section 13.5 Study Pausing Rules	Added rule to suspend enrollment for safety review after any SAE; revised communication between sponsor and contract research organization and pharmacovigilance vendors (spmd and CATO)	Required as per FDA safety feedback
Entire protocol; Section 12 Study Procedures and Schedule	Altered study design to include a 2-part design where Part A is an open-label training phase of the study to optimize workflow and Part B of the study is randomized and single-blind and will serve as the pivotal portion of the study	To formalize the plan for a what was previously identified as the "roll-in" phase of the study and what is now called Part A of the 2 part study.
Section 2 Definitions	Definitions have been revised and new definitions are provided	Updated to use FDA terminology (e.g. orientation) per FDA clinical feedback
Section 7 Endpoints	This section has been entirely replaced from version 1.1. Endpoints have been revised in accordance with advice and recommendations received by FDA	Updated study endpoints per FDA clinical feedback
Section 15 Statistical Considerations	Section has been entirely replaced from the previous version. Efficacy endpoints have been revised in accordance with advice	Updated to reflect new study endpoints per FDA clinical feedback

	and recommendations received by FDA and analyses are updated accordingly	
Section 12 Study Procedures and Schedule and Appendix 1 Study Workflow	Updates have been made to clarify the pathology data collection requirements in accordance with the new efficacy endpoints (e.g., distance to presence of cancer in each specimen)	Updated to reflect new study endpoints per FDA clinical feedback.

Amendment 1: 6-Jan-2021

Overall Rationale for the Amendment: to fulfill requirements of Advarra central IRB review

Section # and Name	Description of Change	Brief Rationale
Entire protocol	Clarification throughout protocol that the study is placebo controlled	Requested by Advarra IRB
Section 4 Synopsis; Section 9.2 Inclusions Criteria	Added clinical staging criteria using current tumor, nodes, metastases (TNM) staging system to assess eligible patients	Clarification requested by Advarra IRB
Section 12.6 Week 2 Visit (Day 10 - 14)	Clarification that final pathological tumor staging, pathological tumor features/characteristics and nodal involvement will be collected from the surgical pathology report	Clarification requested by Advarra IRB
Section 12.8 Extension Phase	Added 3- and 6-month follow-up to match V1.1 of the template Informed Consent Form	Updated as requested by Advarra IRB

Country or site-specific amendments will be numbered as follows:

Example of Numbering a country-specific Protocol Amendment

Type of Protocol Amendment	*Numbering*	*Type of changes*
Country-specific	*Amendment 3/USA-2*	*Same changes specific to USA added to global Amendment 3 (no new changes for Canada)*

Global	*Amendment 3*	*New changes for all*
Country-specific	*Amendment 2/CAD-2*	*Additional changes specific to Canada added to global Amendment 2*
Country-specific	*Amendment 2/CAD-1*	*Same changes specific to Canada added to global Amendment 2 (no new changes for Canada)*
Global	*Amendment 2*	*New changes for all*
Country-specific	*Amendment 1/USA-1*	*Same changes specific to USA added to global Amendment 1 (no new changes for USA)*
Global	*Amendment 1*	*New changes for all*
Country-specific	*Amendment USA-1*	*Changes specific to USA added to original protocol*

Example of Numbering a Site-specific Protocol Amendment

Type of Protocol Amendment	*Numbering*	*Type of changes*
Site-specific	*Amendment 2/SS-1 <<Insert Site Number(s)>>*	*Same changes specific to site(s) added to global Amendment 2 (no new changes for site[s])*
Global	*Amendment 2*	*New changes for all*
Site-specific	*Amendment 1/SS-1 <<Insert Site Number(s)>>*	*Changes specific to site(s) added to global amendment*
Global	*Amendment 1*	*New changes for all*

Global, country- or site-specific amendments will be tracked in Document History Tables as follows:

Example of Document History Table for Global and Country-specific Protocol Amendments

DOCUMENT HISTORY	
Document	*Date of Issue*
Amendment 2/USA-1	*1-Feb-2016*
Amendment 2	*1-Feb-2016*
Amendment 1/USA-1	*1-Jan-2015*
Amendment 1	*01-Dec-2015*
Original Protocol	*01-Oct-2015*

Example of Document History Table for Site-specific Amendments to a Global Amendment

DOCUMENT HISTORY	
Document	*Date of Issue*
Amendment 2/SS-1	*1-Feb-2016*
Amendment 2	*1-Feb-2016*
Amendment 1/SS-1	*1-Jan-2015*
Amendment 1	*01-Dec-2015*
Original Protocol	*01-Oct-2015*