Clinical Material Agreement

This Agreement is between Targeted Therapy Technologies, LLC—DBA: 3T Ophthalmics—("Company"), a corporation having a principal place of business at 16 Technology Drive, Suite 134, Irvine CA 92618,The Hospital for Sick Children (SickKids) with address at 555 University Avenue, Toronto, Ontario M5G 1X8 Canada, and Dr. Brenda Gallie, a physician with a professional affiliation with SickKids (“Principal Investigator”).

The authorized party representatives execute this Agreement as of the last date below, including all its terms and conditions.

The Hospital for Sick Children

Signature: DocuSigned by: Ramune Pleinys C7ED713F64374E6...
Name: Ramune Pleinys
Title: Executive Director, Research Operations
Date: 4/15/2020 | 1:02 PM PDT

PRINCIPAL INVESTIGATOR
Signature: DocuSigned by: Brenda Gallie E3AC3FB6DD65485...
Name: Brenda Gallie, MD
Title: Head, Retinoblastoma Programs, Hospital for Sick Children
Date: 4/15/2020 | 10:05 AM PDT

COMPANY

Signature: DocuSigned by: David Carpi 64D6171396C14E3...
Name: David Carpi, MSc
Title: Chief Operating Officer
Date: 4/6/2020 | 2:46 PM PDT

WHEREAS:

The protocol entitled "**PHASE I SUSTAINED-RELEASE TOPOTECAN EPISCLERAL PLAQUE (CHEMOPLAQUE) for RETINOBLASTOMA: STEP-RB**", a copy of which is attached hereto as Appendix A and, together with its amendments, incorporated herein by reference (the "Protocol") was developed in collaboration by Dr. Brenda Gallie, the Principal Investigator and Targeted Therapy Technologies LLC ("3T") encompassing among other material confidential 3T IND-enabling safety and pharmacokinetic data.

the Company wishes to provide the Company Product to support SickKids and the Principal Investigator in the conduct of clinical research to be carried out in accordance with the Protocol (the "Study"), and the Institution and Principal Investigator desires to accept this support for the conduct of the Study

Therefore, in consideration of the mutual covenants herein, and for other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, the parties hereto agree as follows:

1. Investigators and Research Staff

1.1 Principal Investigator. The Study will be conducted at SickKids under the supervision and direction of the Principal Investigator.

1.2 The Principal Investigator may, with the agreement of Company, recruit secondary sites as sub-investigators (Secondary Site). In the event that a Secondary Site is recruited to participate in the Study the Principal Investigator, as the holder of the IND, undertakes to ensure that the Secondary Site adheres to Good Clinical Practice with respect to execution of the Study and reporting of adverse events.

2. Protocol

2.1 Amendments. If Principal Investigator modifies the Protocol in any way that significantly affects the administration or use of Company's drug/device (e.g., dosage, duration of treatment), the objectives of the Study, or potential risks to Study subjects, Principal Investigator will promptly inform Company in writing. Nothing herein shall be construed as a right for the Company to prevent any modifications to the Protocol deemed necessary by the Principal Investigator, Institution, or the appropriate research ethics board ("REB"). In addition to any approvals, both parties shall agree on the final version of the Protocol and any amendments (other than those necessary to protect patient safety in the reasonable judgement of the Principal Investigator) prior to implementing the Protocol and any amendments.

3. Study Conduct

3.1 Sponsorship. SickKids, not Company, is the sponsor of the Study. Principal Investigator will not represent to any third party, including Study subjects, that Company is a sponsor.

3.2 REB Approval. Principal Investigator will ensure that the Study is approved by the REB.

3.3 Informed Consent. Principal Investigator shall ensure that all potential participants in the Study ("Subjects") are fully informed of all information necessary and sufficient to obtain informed consent and approval from the REB and the details of the Study. Thereafter, the Principal Investigator shall obtain an executed consent in a form approved by the Principal Investigator, REB and SickKids from each Subject.

3.4 Duration of Study. Principal Investigator expects to complete Study conduct (enrollment of all Study subjects and completion of all protocol requirements by each subject) by December 2022. The Principal Investigator agrees to notify the Company if this date changes and for greater clarity, this date is for reference only and shall not be construed as the termination date of the Study for the purposes of this Agreement.

3.5 Compliance. The Company, Principal Investigator and SickKids, shall conduct the Study and perform its/his/her obligations under this Agreement in accordance with all applicable laws, government regulations and guidelines including but not limited to the Canada Food and Drugs Act and all regulations made pursuant thereto, Health Canada's Therapeutic Products Directorate Guidelines, ICH Harmonised Tripartite Good Clinical Practice Consolidated Guideline ("ICH/GCP Guideline") to the extent applicable, the Tri-Council Policy Statement, "Ethical Conduct for Research Involving Humans", published by the Canadian Institutes of

Health Research, the Natural Sciences and Engineering Research Council of Canada and the Social Science and Humanities Research Council of Canada dated December, 2010, as amended from time to time, and the Declaration of Helsinki and in accordance with generally accepted clinical practices.

Company, Principal Investigator, and SickKids each represent and warrant that they will comply with all applicable federal, provincial and local laws and regulations pertaining to confidentiality, use and disclosure of patient health information and personal information ("PHI"). Without in any way limiting the foregoing, this obligation includes all requirements set forth in Ontario's *Personal Health Information Protection Act* (PHIPA) and Canada's *Personal Information Protection and Electronic Documents Act* (PIPEDA) and regulations issued pursuant thereto. In the event that any PHI about a Study subject is transferred by SickKids or Principal Investigator to Company or its employees or agents, Company and its employees and agents shall not use or disclose such information except with the knowledge and consent of the Subject as set out in the patient informed consent form, or as required by law. Such information shall be destroyed, erased or made anonymous, and Company shall take appropriate care in the disposal or destruction of the information to prevent unauthorized parties from gaining access to it. Company shall make its employees and agents aware of the importance of maintaining the confidentiality of transferred PHI.

Reporting: Principal Investigator will provide necessary reports pertaining the Protocol and/or Study for Governmental and Regulatory Agencies within twenty (20) days of written request by Company.

3.6 Confidentiality. During the course of the Study and during the term of this Agreement, Confidential Information may be disclosed by one party to another for the purpose of fulfilling the obligations of this Agreement or conducting the Study. Confidential Information as used herein is defined as all proprietary, commercial and technical information related to the Study disclosed by SickKids and/or the Principal Investigator to Company, and includes, without limitation, the Study protocol, Study Data, and Study Reports. Each party shall hold in confidence, to the same extent that it holds its own information of a similar nature in confidence, and not disclose or use for any purpose other than for the performance of this Agreement, the Confidential Information disclosed to it.

The obligations of Section 3.6 shall not apply to Confidential Information which,

i. can be shown to have been in a receiving party's possession before disclosure by;

ii. at the time of disclosure is, or thereafter becomes, through no breach of this Agreement, part of the public domain by publication or otherwise;

iii. is furnished to a receiving party by a third party;

iv. is developed by a receiving party independently of the disclosure and without use or access to the disclosing party's Confidential Information;

v. is required by statute or judicial process to be disclosed;

vi. published in accordance with Section 8 of this Agreement;

vii. must reasonably be disclosed to potential Subjects during the recruitment process, and Subjects who are or were enrolled in the Study, or to any of their lawful representatives, in order to obtain and maintain informed consent or as the information relates to their health, safety or diagnosis; or

viii. must reasonably be disclosed to regulatory authorities or the REB;

3.7 Notwithstanding the foregoing, the Parties agree that the Protocol may be shared with third parties who are bound to terms of confidentiality and non-use. Notwithstanding the foregoing, the Parties agree that the Protocol, Study Data, and Study Reports maybe shared with Government Agencies, Regulatory Agencies, REBs, IRBs as necessary.

3.8 All obligations of confidentiality and non-use created under this Agreement shall terminate ten (10) years from the completion or termination of this Agreement. Upon written request of the disclosing party, the receiving party agree to return all copies of Confidential Information to the disclosing party; provided, however, that the receiving party shall be entitled to retain archival copies of all Confidential Information solely to ensure compliance with their rights and obligations hereunder.

4. Product Grant. Company will provide at no cost to SickKids and Secondary Site (if any) the Company Product to be used in the Study (see Section 5, Company Product).

4.1 Basis of Support. This Agreement is not conditioned on any pre-existing or future business relationship between the Principal Investigator and Company, SickKids and Company or Secondary Site and Company. It is also not conditioned on any business or other decisions the Principal Investigator, SickKids or Secondary Site has made, or may make, relating to Company or Company's products.

5. Company Product. Company will provide sufficient supplies of the Company product—**(LISTED IN APPENDIX)**—("Company Product") to conduct the Study at SickKids and any Secondary Site(s). Company agrees to provide Company Product that: (1) has been manufactured, packaged and labeled in compliance with current good manufacturing practice (cGMP, Title 21 CFR Part 211) and the Canadian equivalent, including without limitation the requirements of Health Canada for use in the Study; and (2) free of defects and of merchantable quality. Company will maintain a valid US Investigational New Drug (IND) application as required by Applicable Law and Regulation to enable testing of the Company Product in humans. Company agrees to provide reasonable assistance to SickKids to obtain approval for the Study from Health Canada upon written request, this may include requesting Company to submit a Master File to Health Canada regarding the Company Product. If Company cannot for any reason provide the requested assistance, Company agrees to promptly notify SickKids and Principal Investigator and cooperate with SickKids and Principal Investigator in good faith to obtain approval. Company shall promptly report to Principal Investigator any significant developments relating to Company Product, including but not limited to adverse events that may impact the treatment of subjects who either are participating or have participated in the Study. Company shall provide to Principal Investigator an Investigator Brochure (IB) that reviews the safety and proper handling, and storage of Company Product as well as all relevant published information on the Company Product and all other information necessary and sufficient to obtain informed consent from all Subjects and approval from the REB.

5.1 Custody and Dispensing. The Principal Investigator or Secondary Site will maintain appropriate control of supplies of Company Product and shall be responsible for dispensing the Company Product.

5.2 Return of Company Product and Supplies. Unless otherwise instructed by Company in writing, SickKids or Secondary Site will return to Company any supplies of Company Product that expire during the term of this Agreement, as well as all supplies that remain unused or removed from patient eyes at the termination of this Agreement, at the expense of the Company.

5.3 Ownership and Use. Except as specified in the Protocol, Company grants Principal Investigator, SickKids, or Secondary Site no express or implied intellectual property rights in Company Product or in any methods of making or using Company Product. Principal Investigator, SickKids, and Secondary Site acknowledge they will have no rights to any past, current, or future intellectual property relating to Company Product. Principal Investigator or Secondary Site will use Company Product only as specified in the Protocol.

5.4 No Charge to Subjects. Principal Investigator, SickKids, or Secondary Site will not charge Study subjects or their insurers for Company Product.

6. Study Data. Principal Investigator and SickKids are free to publish the results of the Study, subject to the provisions of Section 8 (Publications), and to use data generated from the Study for their own research and educational purposes and programs, subject to compliance with applicable law. All patient medical records and proprietary confidential documentation and medical records of SickKids ("Institutional Records") are the property of SickKids. Study-related data generated during the course of the Study (the "Study Data") and contained in Institutional Records is the property of SickKids. Study Data (including study data generated by any Secondary Site) contained in Institutional Records shall be provided to Company by SickKids as necessary for the performance and analyses of the Study and Company regulatory submissions, consistent with the approved informed consent documents and applicable law. Institutional Records shall be retained by SickKids for such period of time as required by applicable law and the Protocol, whichever is longer. Study Data may be provided to the Company in accordance with Subject informed consent and REB approval and the Company shall be permitted to use Study Data in accordance with the terms of the informed consent, REB approval and Applicable Law. Data analysis performed by Company on Study Data will be shared with Principal Investigator for research and educational purposes and programs, subject to applicable law.

7. Study Report. Within three months after completion of Study conduct or termination of this Agreement, whichever occurs first, Principal Investigator will provide Company with a written report of the Study results ("Study Report"). Study Report shall constitute SickKids Confidential Information. The Study Report may take the form of a manuscript for publication (see Section 8, Publications). If the Agreement is terminated early, the Study Report will include, at minimum, the results of the Study up to the date of termination. SickKids hereby grants to the Company a non-exclusive, perpetual, royalty-free, worldwide license to use the Study Reports for internal research purposes, subject to the obligations of confidentiality set forth in this Agreement. Company will have right to use Study Report and related data for any and all governmental and regulatory submissions on a worldwide basis, provided that Company shall ensure Study Report and related data is not made public until SickKids and/or the Principal

Investigator publishes, advises the Company no publication will take place, or eighteen (18) months following the completion of the Study, whichever occurs first.

8. Publications. As a matter of basic academic policy, SickKids retains the right at its discretion to publish freely the results of the Study subject to the following:

8.1 Pre-Publication Review. SickKids will provide Company with a copy of any manuscript or other publication at least thirty (30) days prior to submission for publication:
(A) To ascertain whether Company's Confidential Information would be disclosed by the publication;
(B) To identify potentially patentable Technology so that appropriate steps may be taken to protect the Technology; and
(C) To confirm that the privacy rights of individuals are adequately protected.

Company shall complete its review within thirty (30) days after receipt of the publication. If the Company believes that any publication contains any information relating to any patentable Technology, the disclosure of such publication shall be delayed for up to sixty (60) days from the date of receipt of the publication to permit the filing of a patent application or taking of other actions deemed necessary by Company. If Company believes that any publication contains Confidential Information, Company shall so notify SickKids and it shall remove any such Confidential Information prior to publication or presentation; provided that the Company shall not request and SickKids and Principal Investigator shall not be required to delete Study Data or information relating to research methods used in the Study. However, Company will not otherwise exercise editorial control over the proposed publication, the final analysis and interpretation of the Study Data by the Principal Investigator and SickKids in the performance of this Study remains with the Principal Investigator.

8.2 Disclosure of Support. Principal Investigator will disclose Company support of the Study in all publications of Study results, including any resulting manuscript, study report, presentation, poster, or abstract submission to a scientific or medical congress.

9. Intellectual Property/Proprietary Rights/Use of Study Material;

i. Use of Company Product:
SickKids agrees that use of Company Product provided under this Agreement for any purpose outside of Study is prohibited. If SickKids uses Company Product provided under this agreement for any purpose outside of this Study, all data, conclusions, observations, results, inventions, discoveries, ideas, procedures, know-how, advancements and the like, whether patentable or not, shall be treated in all respects as Intellectual Property in accordance with this agreement and shall be the sole property of Company.

ii. Ownership:
SickKids agrees that all discoveries, information, inventions, know-how, and improvements resulting from the Company Product including but not limited to material that maybe subject to patent, trademark, or copyright protection (“Intellectual Property”) shall promptly be made known to Company and be the sole property of Company. SickKids represents and warrants that it has secured from Principal Investigator and Institution Personnel any and all transferable rights to intellectual property. Institution hereby transfers and assigns to Company, SickKids’s full right and title to all intellectual property and agrees to undertake such reasonable actions requested

by Company to give effect to such ownership. Company shall be free to use the Intellectual Property. Neither Company nor SickKids transfers to the other by operation of this agreement any patent right, copyright right or other proprietary right of any party, accept as may be described in this agreement.

10. Indemnification and Insurance.

10.1 Company shall indemnify and hold harmless SickKids, and the Principal Investigator, and their trustees, directors, employees, agents, volunteers, subcontractors, Secondary Site, and students ("Site Indemnitees") from any liability, damage, loss, or expense (including reasonable attorneys' fees and expenses of litigation) incurred by or imposed upon the Site Indemnitees or any one of them in connection with claims, suits, actions, demands, or judgments arising out of or connected with (i) the performance of the Study by SickKids in accordance with the Protocol or the Company's written instructions; (ii) Company's failure to manufacture, package or label the Company Product in accordance with cGMP specifications; (iii) any use of Study Data and Study Reports by Company; and/or (iv) Company's negligent acts or willful omissions ("Claims"), provided, however, that:

a. Company shall not indemnify and hold harmless the Site Indemnitees to the extent arising out of, in whole or in part: (i) the gross negligence, willful misconduct or wrongful acts of the Site Indemnitees.

SickKids shall ensure:

i. Company is promptly, and in any event within thirty (30) days after the Site Indemnitees' receipt of notice of any complaint, damage, loss, claim or injury relating to any loss subject to this indemnification, notified in writing of any such complaint, claim or injury;
ii. Company has sole control over the defense and settlement of any such claim or suit, including the right to select defense counsel and to direct the defense or settlement of any such claim or suit, provided that Company shall not compromise or settle any such claim or action without the prior written approval of SickKids and shall provide a diligent defense whether the claim or suit is rightfully or wrongfully brought; and
iii. The Site Indemnitees reasonably cooperate with Company and its legal representatives in the investigation and defense of any claims or suits covered under this Section. In the event that a conflict arises in the context of such an investigation or defense, SickKids shall have the right at its own expense to select and obtain representation by separate legal counsel.

c. SickKids shall, to the extent authorized by law, indemnify, defend and hold harmless Company, its agents, representatives and employees from any Claims to the extent resulting from the (i) improper or negligent administration of the Company Product; (ii) gross negligence or wrongful acts of SickKids, their agents, Secondary Site or employees pertaining to the activities of this Study and/or this Agreement; or (iii) failure to comply with the terms of the Protocol, provided, however, that: SickKids shall not indemnify, defend and hold harmless Company, its agents and employees from Claims to the extent arising out of the gross negligence, willful misconduct or wrongful acts of Company, its agents and employees;

d. Company shall ensure that:

i. SickKids is promptly, and in any event within thirty (30) days after Company, its agents or employees' receipt of notice of any complaint, claim or injury relating to any loss subject to this indemnification, notified in writing of any such complaint, claim or injury;

ii. SickKids has sole control over the defense and settlement of any such claim or suit, including the right to select defense counsel and to direct the defense or settlement of any such claim or suit, provided that SickKids shall not compromise or settle any such claim or action without the prior written approval of Company and shall provide a diligent defense whether the claim or suit is rightfully or wrongfully brought; and

iii. Company, its agents and employees reasonably cooperate with SickKids and its legal representatives in the investigation and defense of any claims or suits covered under this Section. In the event that a conflict arises in the context of such an investigation or defense, Company, its agents and employees shall have the right at their own expense to select and obtain representation by separate legal counsel.

The indemnity shall apply separately to each Indemnitee in such manner and to the same extent as though a separate indemnity had been given to each.

10.2 The Principal Investigator shall maintain his/her membership in the Canadian Medical Protective Association, and shall provide evidence of such membership upon request.

10.3 Prior to the first patient being enrolled, the Company and SickKids shall obtain appropriate and sufficient liability protection in respect to their respective obligations under this Agreement in amounts of at minimum 5 million dollars Canadian per occurrence and 10 million dollars Canadian per annual aggregate, and shall maintain in full force and effect such insurance to cover their respective obligations under this Agreement. The policy shall clearly apply to claims brought in Canada. SickKids and Company will provide evidence of such insurance upon written request of the other party and will provide thirty (30) days prior written notice of cancellation or non-renewal of its coverage.

11. Subject Injury. Company agrees to maintain insurance to reimburse SickKids for the cost of reasonable and customary medical treatment of any injury sustained by a Subject as a direct result of improper manufacturing, or defect in the Company Product.

12. Disclaimer of Warranty. Except as explicitly stated in this agreement, Company makes no warranties, express or implied, including any warranty of merchantability or fitness of the Company product for use in accordance with the protocol.

12.1 Disclaimer by SickKids. SickKids and Principal Investigator shall carry out the Study in accordance with the Study protocol but does not promise success in achieving any particular result. Except as expressly provided in this Agreement, SickKids and Principal Investigator, including its/her directors, officers, trustees, employees, fellows, medical and professional staff, appointees, students, trainees, contractors, agents, servants, successors, heirs and assigns, makes no covenants, representations or warranties, express or implied, as to any matter whatsoever, including, without limitation the Study Data and Intellectual Property developed under this Study; or the ownership, merchantability, or fitness for a particular purpose of the Study Data and Intellectual Property developed under this Study.

12.2 Limitation of Liability. Neither SickKids nor Principal Investigator shall be liable for any direct, indirect, consequential, or other damages suffered by Company or any third party

resulting from the use of the Study Data developed under this Study, except to the extent such damages arise from the gross negligence or willful misconduct of SickKids.

13. Obligation of SickKids when Participating Sites are Involved. In the event that SickKids utilizes any other site (including all employees, agents, investigators and other representatives of such site performing the Study, each a “Participating Site”) for the performance of the Study, SickKids agrees that:

(a) Prior to utilizing such Participating Site, Site shall enter into a written agreement with such Participating Site, the terms of which shall be substantially similar to the terms of this Agreement, including without limitation, compliance with obligations regarding applicable laws, safety, publication, intellectual property, indemnification, liability insurance, and data protection; and

(b) SickKids shall be responsible for the management and coordination of the performance of all such Participating Sites.

14. Termination. This Agreement will terminate upon the earlier of any of the following events:

14.1 Study Completion. For purposes of this Agreement, "Study Completion" is defined as completion of all Protocol-required activities for all enrolled subjects and receipt, by Company, of a final Study Report.

14.2 Early Termination. Either party may terminate the Agreement upon thirty (30) days written notice.

14.3 Subject Safety. Either Party may terminate this Agreement immediately if Subject safety is a concern or if regulatory or REB approval is not obtained, not reasonably obtainable, or withdrawn.

14.4 Change in Principal Investigator. SickKids shall have the right to terminate this Agreement if the Principal Investigator becomes incapacitated or no longer has privileges with SickKids and a suitable replacement is not found.

14.5 Effect of Termination. In the event of termination of the Agreement for any reason, Company shall continue to supply sufficient quantities of the Company Product as required to allow SickKids to safely terminate the participation of the Subjects in the Study. In addition, in the event of termination of the Agreement for reasons other than Subject safety, Company agrees that, subject to any necessary regulatory approvals being granted, SickKids shall be permitted to continue to treat Subjects with the Company Product through to completion of the schedule set out in the Protocol at the sole discretion of the Subject(s) and the Study principal investigator, and pursuant to accepted medical practice, and Company shall continue to supply the Company Product to the completion of the Protocol in quantities sufficient to treat such Subject(s). As the protocol delineates a single treatment for clarity the Company will not be required or be obligated to offer additional treatments for any patient.

14.6. Safety Reporting. After expiration or earlier termination of this Agreement, if information becomes available to Company which places the safety or efficacy of the Company Product in doubt, Company will give immediate written notice to SickKids.

14.7 Survival. The rights and obligations by their meaning or operation intended to survive shall survive the expiration or earlier termination of this Agreement. Termination of this Agreement shall not relieve any party of any obligation accrued prior thereto.

15. Entire Agreement. This Agreement and Appendix A constitute the entire agreement between the parties with respect to this subject matter.

16. Choice of Law. This Agreement is governed by the laws of the Province of Ontario and the federal laws of Canada applicable therein, without regard to its or any other jurisdiction's conflict of laws doctrine. Any legal action involving this Agreement will be adjudicated in the Province of Ontario.

[Signatures are on Page 1.]

Appendix A – Protocol

SickKids
THE HOSPITAL FOR SICK CHILDREN

PHASE I SUSTAINED-RELEASE TOPOTECAN EPISCLERAL PLAQUE (CHEMOPLAQUE) for RETINOBLASTOMA

STEP-RB

REB Number: 1000064742

Principal Investigator: Brenda L. Gallie, MD, FRCSC

Co-investigators: Furqan Shaikh, MD, FRCPC; Daniel A. Morgenstern, MB BChir, PhD; Ashwin Mallipatna, MBBS, MS, DNB

Sponsor: Dr. Brenda Gallie, The Hospital for Sick Children

Version 1.0, 4 February 2020

TABLE OF CONTENTS

1 STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with this protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable regulatory requirements. The Principal Investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Research Ethics Board (REB), except where necessary to eliminate (an) immediate hazard(s) to the trial participants.

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

Name of Principal Investigator (Print): Brenda L. Gallie

Signature of Principal Investigator: _____ Date: _____

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	PHASE I SUSTAINED-RELEASE TOPOTECAN EPISCLERAL PLAQUE (CHEMOPLAQUE) for RETINOBLASTOMA (STEP-RB)
Study Description:	We hypothesize that treatment of intraocular retinoblastoma will be improved by Topotecan delivered over 42 days by diffusion from a Chemoplaque glued to the sclera with minimal toxicity. This Phase I study will establish Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D) with a Rolling 6 design and 4 dose levels
Objectives:	Primary Objectives: • To determine the safety and tolerability of the Chemoplaque in patients with retinoblastoma. Safety Objectives: • To define and describe toxicities of sustained Topotecan to the eye via the Chemoplaque • To define and describe systemic toxicities of sustained Topotecan to the eye via the Chemoplaque Secondary Objectives: • To describe the anti-tumour efficacy of the Chemoplaque as secondary therapy in eye(s) with active retinoblastoma after completion of primary standard of care treatment Exploratory Objectives: • To measure impact of the Chemoplaque on number and invasiveness of subsequent therapies required to achieve Complete Remission.
Endpoints:	Study period: 9 weeks Primary Endpoints: • To estimate the MTD or RP2D of topotecan hydrochloride administered as a Chemoplaque to pediatric patients with active Retinoblastoma. • To define and describe the toxicities of the Chemoplaque administered on this schedule. • Toxicity will be scored by CTCAE version 5.0 Secondary Endpoints: • Tumour evaluation scored with standard terminology at each EUA, estimating tumour response by number of tumour sites and appearance (primarily based on Ret Cam imaging), and

	tumour size (based on relevant imaging tools) in standard monitoring for intraocular retinoblastoma: o **Complete Response (CR):** Decrease in tumour activity 100% from baseline. o **Very good partial response (VGPR):** Decrease in tumour activity greater than or equal to 80% and less than 100% from baseline. o **Partial response (PR):** Decrease in tumour activity greater than or equal to 20% and less than 80% from baseline. o **Stable disease (SD):** Less than 20% decrease in tumour activity from baseline. o **Progressive disease (PD):** Increase in tumour activity greater than or equal to 20% from baseline or development of new tumours requiring more than minimal focal therapy. • **Eye salvage rate (ESR)**, defined as the percentage of eyes that remained with a functional vision at the end of the study period. • **Overall eye salvage rate (OESR),** based on survival curve (Kaplan-Meyer) for eye preservation beyond study period (off-study at 6, 12, 24, 36 months). • **Associated treatment burden (ATB),** defined as the frequency of additional (co-adjuvant) treatments and its associated-morbidity to control disease in the study period (3 months). • **Overall associated treatment burden (OATB),** defined as the frequency of additional (co-adjuvant) treatments and its associated-morbidity to control disease beyond the study period. • **Overall survival curve (OS),** defined as the time to death from the date of initial Chemoplaque (regardless of the cause of death). • **Progression-free survival (PFS)**, defined as the time from initial Chemoplaque insertion to the occurrence of tumour recurrence beyond the study period. • **Post-intervention treatments for study eye** (patients will be off-study and Chemoplaque removed): 0 Number and Type: Chemotherapy (systemic and/or intra-arterial); focal laser, cryotherapy; intra-vitreal chemotherapy; external beam radiotherapy; brachytherapy; and other(s) as medically indicated in the standard of care. 0 Number of EUAs: total, for eye evaluation, MRI, other procedures. Exploratory Endpoints: • Identification of demographic (e.g., SES, gender, age at study treatment).

	• Impact of initial disease extent (e.g., TNMH staging). • Impact of all prior treatments • Impact of all post-Chemoplaque treatments
Study Population:	A minimum of four (4) (if two DLTs at both starting and reduced dose levels), and a maximum of 24 children of any gender or demographic with active intraocular retinoblastoma and good general health otherwise, from birth to 18 years. A minimum of 14 patients are required to examine four dose levels with no DLTs.
Phase:	1
Description of Study Intervention:	The Intervention is a device containing chemotherapy formulated to diffuse through sclera into the eye. • Available in 0.6 mg and 0.9 mg of Topotecan HCl formulation. • Attached to sclera by glue under conjunctiva and Tenon's capsule. • Applied 1 or 2 per eye, to deliver 4 escalating doses: 0.6, 0.9, 1.2 [2x0.6], 1.5 [0.6 + 0.9] or 1.8 [2x0.9] mg. Route: Continuous exposure via diffusion from the Chemoplaque
Study Duration:	• Up to 3 years to complete accrual, based on historical data indicating 25 eligible patients at SickKids from May 2015 to October 2018 • 5 years follow-up per patient
Participant Duration in the Study and Off-study Data Collection:	Each participant included in the study will be treated with the Chemoplaque for 6 weeks; evaluation continues for toxicity and tumour activity for 3 weeks following the removal of the Chemoplaque. Total study period: 9 weeks. Off-study evaluations will be standard of care for 5 years. When not feasible to conduct off-study visits directly, observations and data collection will utilize surrogate centers and/or censoring techniques.

1.2 SCHEDULE OF ACTIVITIES (SOA)

	Study Visit									Follow-up[a]	
										Over 1 year	Over 5 years
Day (+/-7 day window)	-21 to -1	0	7	14	21	28	35	42	63		
WEEK	-1	0	1	2	3	4	5	6	9	q4-12 weeks	q3-6 months
Administrative procedures											
Informed consent	X										
Demographics	X										
Medical history	X										
Concomitant medications	X	X	X	X	X	X	X	X	X		
Treatment											
Administer Chemoplaque		X									
Scheduled removal of Chemoplaque								X			
Clinical assessments											
Height/weight	X	X		X		X		X	X		
Physical exam	X	X		X		X		X	X	X	X
Vital signs	X	X		X		X		X	X		
Performance status[b]	X	X	X	X		X		X	X	X	X
AE and SAE evaluation					continuously						
Examination under anaesthesia		X		X		X		X	X	X	X
Rb activity clinical evaluation		X		X		X		X	X	X	X
Visual acuity testing	X			X		X		X	X	X	X
Clinical laboratory tests											
CBC with differential and platelets	X	X		X		X		X	X		
Serum chemistry[c]	X	X		X		X		X	X		
Serum pregnancy test[d]	X										

a. Follow-up assessments will be according to standard of care and specific protocol visits are not mandated per protocol.

b. Performance status includes parent report of child activity, pain, behavior changes, and functional vision.

c. Serum chemistry: sodium, potassium, creatinine, urea, ALT, unconjugated/ conjugated bilirubin, albumin, calcium, phosphate, magnesium.

d. Females of reproductive potential will have a serum pregnancy test.

2 INTRODUCTION

2.1 STUDY RATIONALE

2.1.1 PATHOGENESIS OF RETINOBLASTOMA

Retinoblastoma is the most common pediatric malignant intraocular tumour and originates from the retina (the light-sensitive innermost layer of the ocular wall).[1,2] Retinoblastoma arises when both copies the retinoblastoma tumour suppressor gene, RB1, are pathogenic (non-functional) in a developing retinal cell. It affects one or both eyes, depending on the developmental timing of the first RB1 pathogenic variant: if RB1 is damaged in all cells of the person, both eyes are usually independently affected by retinoblastoma when the second RB1 gene is damaged in a specific susceptible developing retinal cell. If both RB1 genes are damaged only in the developing retinal cell that becomes a tumour, only one tumour is formed, affecting one eye.

The primary goal of therapy is prevention of tumour spread outside the eye to save the child's life. If the tumour is advanced (with a potential to spread outside the eye), removal of the eye (enucleation) is the safest option. However, if the tumour is less advanced and the optic nerve is visible, vision and eye salvage become the priorities.

In unilaterally affected children with poor visual potential, treatment burden is weighed against potential outcomes in an informed discussion with the parents. For advanced, high risk disease, enucleation is a good choice that avoids invasive procedures that might not control disease but consume a large part of the child's early life experience. However, since bilateral disease threatens both eyes and blindness, efforts to save the worst eye may be more extensive, still recognizing that life is most important.

2.1.2 CANCER STAGING

Staging at initial diagnosis determines treatment and prognosis. Two staging schemes to predict eye salvage have caused significant confusion in the literature, preventing proper comparison between studies.[1,3] The International Intraocular Retinoblastoma Classification (IIRC) staged eyes as Group A (very low risk) through E (very high risk).[4] A subsequent modification of this classification[5] resulted in severely advanced eyes being classified with less-affected eyes, so that "Group E" did not equate to risk of extraocular disease.[1,6,7] The 2017 American Joint Committee on Cancer (AJCC) 8th edition TNMH (tumour, node, metastasis, heritable trait) clinical and pathological staging system is the first evidence-based system for retinoblastoma to predict prognosis of both eye(s) and patients, and to include heritability as a prognostic factor.[3] Patients carrying a pathogenic variation of the *RB1* gene are labelled "H1". The TNMH is informed by an international survey of 1728 eyes with retinoblastoma comparing all the previous classifications and best separates features of eye disease predictive of the likelihood to save the eye without use of external beam irradiation.

2.1.3 POPULATION

SickKids patients with from birth to 18 years with active retinoblastoma following completion of first-line therapy (chemotherapy, IAC, brachytherapy), regardless of gender, race, ethnicity, or other demographic factor, may be screened for trial participation.

2.1.4 CURRENT STANDARD OF CARE FOR RETINOBLASTOMA

2.1.4.1 BASELINE CHEMOTHERAPY

Following recognition that radiation of H1 patients significantly increased life-long risk for second cancers,[8,9] systemic chemotherapy with carboplatin, etoposide and vincristine became the primary therapy to control intraocular retinoblastoma.[10-15] Following use of intra-arterial chemotherapy (IAC) in Japan,[16] this approach to intraocular retinoblastoma has been widely promoted without systematic clinical research.[17-28] Either form of chemotherapy to the eye requires multiple subsequent therapies (local, systemic) to consolidate the initial response and achieve complete remission.[29]

2.1.4.2 BRACHYTHERAPY

Brachytherapy with Iodine125, ruthenium, palladium is used for isolated primary or refractory tumours. Brachytherapy does not increase risk of second cancers and when accurately designed to deliver the treatment dose to the specific tumour can be a definitive therapy.

2.1.4.3 RADIOTHERAPY

The prevalence of second malignancies in retinoblastoma patients carrying a pathogenic variant of *RB1* (AJCC Cancer Staging H1) remains high, especially following external beam radiation therapy.[8,9] Therefore radiotherapy is now only used if all other eye salvage options have failed for the last eye of a H1 retinoblastoma patient. At the cost of doubling the second cancer risk, radiotherapy has potential to save the eye with useful vision.

2.1.4.4 CONSOLIDATION WITH FOCAL LASER PHOTOCOAGULATION OR CRYOTHERAPY

Focal therapy is effective for cT1a (Group A) eyes with small tumour(s) not threatening macula or optic nerve. Consolidation with laser photocoagulation or cryotherapy following chemotherapy (systemic or IAC) is effective for cT1b (Group B) eyes with intraretinal disease.[29] For cT2b (Groups C-D) eyes (tumour invasion out of the retina into vitreous and/or subretinal space) focal consolidation contributes to salvage of eyes.[30]

2.1.4.5 PERIOCULAR CHEMOTHERAPY

Chemotherapy has been delivered locally to the eye. Direct injection of carboplatin into the subconjunctival or subtenon space was associated with complications including optic atrophy with profound vision loss,[34] ocular motility problems,[35] and periorbital cellulitis.

A single arm trial of systemic and subtenon carboplatin for Groups C and D retinoblastoma (ClinicalTrials.gov Identifier: NCT00072384) had slower enrollment than expected and was terminated with inadequate recruitment,[31] in part because of acute inflammatory response and complications of rectus muscle fibrosis causing restrictive strabismus.[32]

Subtenon injections of Topotecan in fibrin sealant reduced small volume intraocular retinoblastoma when combined with focal therapy.[33] Doses ranged from 2.01–4.62 mg/m^2. Ocular toxicity was minimal and no motility restriction was observed. Systemic effects included CTCAE grade 1-4 hematologic toxicity that improved after one week and did not require intervention.

Small molecules delivered by periocular injection are rapidly cleared into systemic circulation through exposure of the agent to the conjunctival and surrounding orbital tissues in a pre-clinical model.[34]

2.1.4.6 INTRA-VITREAL INJECTION OF CHEMOTHERAPY

Vitreous seeds are generally resistant to systemic and intra-arterial chemotherapy. Intravitreal chemotherapy (IVitC) (melphalan and/or topotecan) now has good impact on the most difficult form of intraocular retinoblastoma to cure.[35] IVitC is commonly repeated monthly depending on clinical response. The main complications include vitreous hemorrhage, retinal tears/detachment, damage to the lens leading to cataract, endophthalmitis and direct retinal toxicity when the drug is not well dispersed through the vitreous.[36,37] A recent retrospective study of intravitreal chemotherapy injections in 10 retinoblastoma treatment centers worldwide found no extraocular extension of tumour when used with the described precautions, including selection of eyes where the source of seeds is controlled, preinjection lowering of intraocular pressure, and post-injection cryotherapy to the needle and injection site.[35,38]

2.1.4.7 ONCOLYTIC VIRUS THERAPY

One recent publication[39] describes the basic science of engineering an oncolytic virus that targets cancer cells that have lost *RB1*, demonstrated to target *RB1*-deficient cells. Two patients were treated with intravitreal injections: both eyes showed very significant inflammation; one eye was enucleated with remaining active tumour on pathology.

2.2 CHALLENGES IN MEASURING RESPONSE IN RETINOBLASTOMA

There are several challenges to objectively measuring tumour response in retinoblastoma, and no previous retinoblastoma trial has described tumour responses quantitatively.

There are several reasons for this limitation. First, there is no single objective method to measure tumour dimensions due to the complexity of multiple tumours in both eyes and largely subjective “expert” interpretation of “active” vs “quiescent” tumour mass vs scar remnant. Second, retinoblastoma target lesions can include the primary tumour(s) and vitreous/subretinal seeds. Third, there are no established criteria for retinoblastoma that describe the response of the entire eye inclusive of all target lesions and seeds. Unlike most other solid tumours that can only be visualized by radiologic imaging with no estimate of “viable” disease, viable vs non-viable areas of retinoblastoma tumours are judged when directly visualized by the treating ophthalmologist during EUAs and captured with photography, optical coherence tomography (OCT)[40] and best summarized in the standard retinal drawing. Since the 1950s innovation of the indirect ophthalmoscope facilitated a wide field of view of the whole retina, the standardized retinal drawing with an internationally endorsed color code (for example, active retinoblastoma is drawn in yellow) has been a key part of management of retinoblastoma. In this clinical trial we will use standard of care consensus of the care team, to evaluate tumour activity at various time points.

2.3 IMPORTANCE OF THIS TRIAL

For retinoblastoma patients, this innovative approach to deliver chemotherapy locally to the eye over a prolonged time, with minimal systemic exposure, is important to achieve salvage for more eyes. This trial acknowledges that multiple treatments are necessary to salvage eyes. The Chemoplaque has potential to control intraocular retinoblastoma with low toxicity and reduce the number of highly invasive therapies with serious side effects needed, thus reducing treatment burden and cost.

2.4 BACKGROUND

2.4.1 *PRECLINICAL STUDIES*

2.4.1.1 *ANIMAL STUDIES*

Purpose: To determine the safety, tolerability, and the pharmacokinetics (ocular and plasma) of various dosages of topotecan hydrochloride (TPT) formulated in the Targeted Transscleral Delivery Systems (TTDS) designed as Episcleral Chemoplaques (Episcleral Topotecan) and implanted onto the sclera of New Zealand White rabbits.[41]

Methods: Female rabbits (n=87) assigned to toxicity (n=5 per dose group) or pharmacokinetics (n=3 per time point) groups, were implanted in the right eye with the test article TTDS Episcleral Implant containing doses ranging from 0.3 mg to 0.9 mg topotecan HCl. For the pharmacokinetic arm of the study, rabbits were euthanized after 24 hours, 48 hours, and 7, 14, 21, 28, 42, and 56 days (n=3 per time point). Plasma, ocular tissues (that were divided into distal and proximal sections relative to the implant site), and the test articles were collected from each animal during necropsy.

Ocular tolerability and toxicity were assessed by ocular examination (slit lamp biomicroscopy and indirect ophthalmoscopy), applanation tonometry (pneumatonometer), and electroretinography (ERG). Retinal findings were documented by fundus photography. Systemic tolerability was assessed by weight progression and observations for signs of toxicity.

Topotecan was assayed in the plasma and ocular tissue samples using a validated high-pressure liquid chromatography (HPLC) method for the detection and quantification of total topotecan and its lactone isoform (LLOQ = 1 ng/ml or ng/gram). Drug distribution is reported as C_{max} (maximum concentration), T_{max} (time when it reached maximum concentration), T_{LC90} (time above topotecan LC_{90} in retinoblastoma cell lines, 5 ng/ml or gram) and AUC (area under the time concentration curve).

Results: All studied doses of Chemoplaque Topotecan were well tolerated systemically. No measurable concentrations of topotecan—either total topotecan or its lactone isoform—were found in the plasma after implantation of any dose of Chemoplaque Topotecan. All rabbits gained weight during the study period of 84 days. There was no evidence of a systemic response to topotecan treatment in the body weight data or daily health observations.

Tissue distribution of topotecan is shown in Table 1. After implantation with Chemoplaque Topotecan 0.3 mg (containing 0.3 mg topotecan HCl), the proximal ocular tissues with therapeutically relevant exposure to topotecan's active (lactone) isoform (C_{max}, T_{max}, T_{LC90}) were: Choroid (2.7 µg/g, day 2, 14 days), sclera (1.3 µg/g, day 2, 21 days), retina (0.86 µg/g, day 2, 14 days). Topotecan (lactone isoform) also reached therapeutic concentrations in the distal sclera on days 2 and 14.

After implantation with Chemoplaque Topotecan 0.6 mg (containing 0.6 mg topotecan HCl), the proximal ocular tissues with therapeutically relevant exposure to topotecan's active (lactone) isoform (C_{max}, T_{max}, T_{LC90}) were: Choroid (10.6 ug/g, day 2, 21 days), retina (1.1 ug/g, day 1, 21 days), sclera

(1 ug/g, day 21), and vitreous humor (8.2 ng/ml, day 21). In addition, topotecan lactone isoform was also detected at relevant concentrations in the distal tissues—sclera (126.3 ng/g on day 21), retina (50 ng/g on day 2), and vitreous (30 ng/ml on day 2).

After implantation with Chemoplaque Topotecan 0.9 mg (containing 0.9 mg topotecan HCl), the proximal ocular tissues with therapeutically relevant exposure to topotecan's active (lactone) isoform (C_{max}, T_{max}, T_{LC90}) were: Choroid (21.6 ug/g, day 2, 21 days), retina (2 ug/g, day 1, 28 days), sclera (6.9 ug/g, day 2, 21 days), and vitreous humor (10.21 ng/ml, day 21). In the distal tissues relevant distribution of topotecan lactone was found in the sclera (36.71 ng/g, day 14, 21 days), choroid (166.23 ng/g, day 7, 21 days), retina (87.32 ng/g, day 7, 21 days) and vitreous (5.72 ng/ml on day 21).

2.4.1.2 OCULAR TOXICITY

Between days 1 and 7 after the implantation of any dose of Chemoplaque Topotecan (0.3, 0.6 and 0.9 mg of Topotecan HCl) a mild discharge, congestion and swelling of the conjunctiva, predominantly near the implantation site, was observed. Between days 1 and 14, peaking on day 7, some degree of hyperemia of the choroid was noticed in all the eyes exposed to Chemoplaque Topotecan. It was predominantly mild (decrease of the white reflex between the mid-to-large choroidal vessels), but appeared to increase in extension and slightly in intensity from mild to moderate (blurred delineation of the mid-to-large choroidal vasculature) as a function of the dose.
Serous exudative retinal detachment was observed in eyes exposed to any dose of Episcleral Topotecan starting on day 7 and subsiding before day 21—mostly between days 7 and 14. Spontaneous and complete resolution occurred before day 28 in all cases. It was mostly located in the quadrant directly exposed to the test article, superior-temporal, but it was also sporadically found in the adjacent inferior quadrant (inferior-temporal) in the 0.6-mg and 0.9-mg dose groups.

Tissue	Location	AUC (ng*day/mL)	Cmax (ng/mL)	Tmax (days)	AUC (ng*day/mL)	Cmax (ng/mL)	Tmax (days)
		0.3 mg Total Topotecan HCl			0.3 mg Lactone Topotecan		
Plasma	N/A	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ
Aqueous	N/A	62.73	20.91	2	11.1	3.7	2
Sclera*	Distal	1253.75	214.13	2	205.99	26.29	2
	Proximal	29647.65	3563.05	2	8432.57	1304.18	2
Choroid*	Distal	243.42	81.14	2	< LLOQ	< LLOQ	< LLOQ
	Proximal	55170.19	8436.24	2	14787.6	2667.81	2
Retina*	Distal	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ
	Proximal	9688.91	2322.07	2	3178.36	858.41	2
Vitreous	Distal	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ
	Proximal	14.04	2.34	7	< LLOQ	< LLOQ	< LLOQ
		0.6 mg Total Topotecan HCl			0.6 mg Lactone Topotecan		
Plasma	N/A	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ

Aqueous	N/A	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ
Sclera*	Distal	4903.13	532.55	21	1351.65	126.35	21
	Proximal	19447.84	2068	21	8375.94	974.2	21
Choroid*	Distal	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ
	Proximal	117736.91	20489.06	2	47986.32	10578.64	2
Retina*	Distal	150.18	50.06	2	150.03	50.01	2
	Proximal	25749.42	1597.09	1	10976.41	1075.62	1
Vitreous	Distal	266.35	80.85	2	90.15	30.05	2
	Proximal	218.5	19.9	21	71.18	8.22	21
		0.9 mg Total Topotecan HCl			0.9 mg Lactone Topotecan		
Plasma	N/A	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ
Aqueous	N/A	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ	< LLOQ
Sclera*	Distal	3478.14	214.28	21	690.355	36.71	14
	Proximal	183221.3	19750.57	2	59133.35	6899.66	2
Choroid*	Distal	3682.85	283.19	7	1560.79	166.23	7
	Proximal	275148.59	39784.82	2	109849.45	21555.99	2
Retina*	Distal	2585.04	159.28	14	865.38	87.32	7
	Proximal	44149	2583.86	1	26170.91	2012.95	1
Vitreous	Distal	94.64	9.16	14	66.92	5.72	21
	Proximal	764.82	51.64	21	153.77	10.21	21

Table 1. Pharmacokinetics of topotecan (total and lactone) after implantation of Topotecan Chemoplaques containing 0.3, 0.6 or 0.9 mg of topotecan HCl: Area under the time-curve (AUC), maximum concentration (C_{max}) and time to maximum concentration (T_{max}) (*ng/g).

Atrophy of the choroid was observed as mild starting at day 21 and it evolved up to day 42 to moderate (grade II) in dose groups 0.3-mg and 0.6-mg, or to severe (grade III) in dose group 0.9-mg. It invariably stabilized between days 56 and 83. The presence of atrophy in the adjacent inferior-temporal quadrant was more frequent in eyes exposed to higher doses.

In animals implanted with Chemoplaque Topotecan 0.3 mg, there was no substantial difference in the intraocular pressure between the right eye (implanted) and the left eyes (controls) during the follow-up period (Figure 1). After Chemoplaque Topotecan 0.6 mg implantation, implanted eyes demonstrated a significant decrease in the intraocular pressure on days 7 (9 mmHg, CI 95% 2.4-15.6) and 14 (7.6

mmHg, CI 95% 2.2-13) compared to the control eyes. In the Chemoplaque Topotecan 0.9 mg group, the average decrease in the IOP in tested vs. control eyes was also significant on day 7 (10.6 mmHg, CI 95% 2.17 to 19.03).

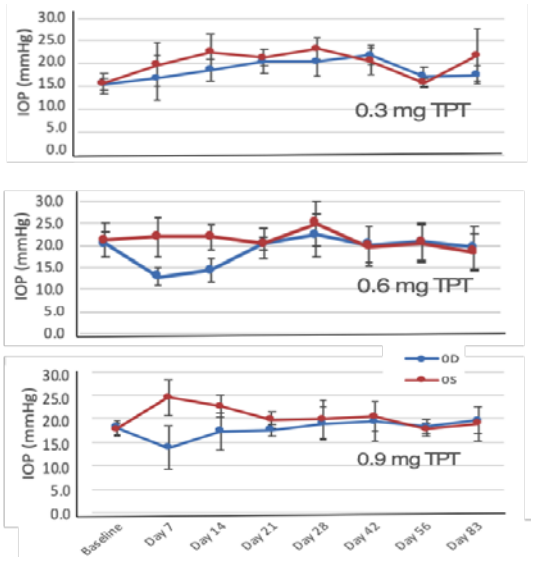


Figure 1. Intraocular pressure (IOP) progression before and after implantation of Chemoplaque Topotecan containing 0.3, 0.6, or 0.9 mg of topotecan HCl. Tested eye: OD. Control eye: OS.

After implantation of 0.3-mg, 0.6-mg or 0.9-mg Chemoplaque Topotecan, due to the large variability inherent to the measured ERG responses in normal and control eyes, mostly non-significant changes were detected in either the amplitude or the implicit time of the studied parameters under the different stimuli conditions (Figure 2). On day 84, although mostly within the 95% confidence intervals of the control eye ERG readouts, a trend in the implanted eyes was observed towards a decrease of approximately 20 to 40% in the amplitude of a and b waves in scotopic and photopic conditions.

Non-significant decrease (within 95% confidence intervals of the ERG responses between tested and control eyes) were seen in both directions and mostly within the 95% confidence intervals. Significant but sporadic findings included changes after exposure to doses of topotecan at 0.3 mg in b-wave amplitude (scotopic 10 on day 84), and at 0.6 mg in the b-wave implicit time (photopic 3000 on day 14). Significant and consistent differences across different stimuli parameters were seen after 0.9 mg of topotecan on day 84, in the a-wave amplitude (scotopic 10000) and the b wave amplitude (scotopic 10 and 10000, and photopic 3000).

Explanted Chemoplaques were completely depleted of topotecan at day 28 in all dose groups. Assay of the implant content of the 0.3 and 0.9 mg doses collected at necropsy on Day 21 showed that the content of the implant had decreased by 100%. The 0.6 mg dose decreased by 97% on day 21 and 100% by Day 28.

In general the Chemoplaques were well tolerated. Both globes, the implant site, bulbar conjunctiva, both eyelids and the lacrimal glands were examined histopathologically. There was a small amount of chronic inflammation and mineralization in the wall of the implant pocket in some animals in all groups. Similarly, there was mild subacute inflammation in the bulbar conjunctiva in the right eye of some animals in all groups, probably nonspecific and secondary to the surgical and handling procedures. There was no meaningful difference between the three treatment groups. The left eye was normal in all animals.

Figure 2. Electroretinography implicit time and amplitude 84 days after implantation of Chemoplaques containing 0.6 or 0. 9 mg topotecan HCl (TPT). Tested eye: OD (right), Control eye: OS (left).

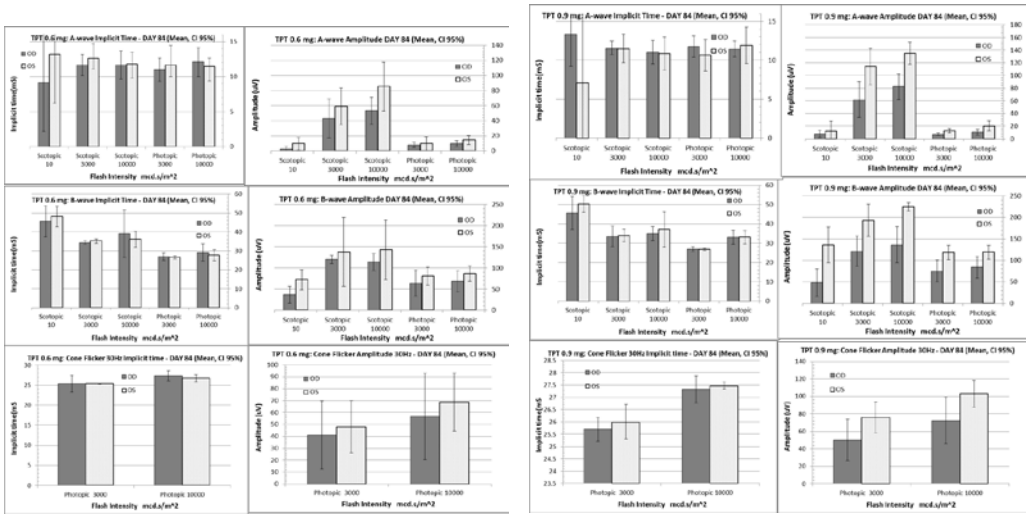
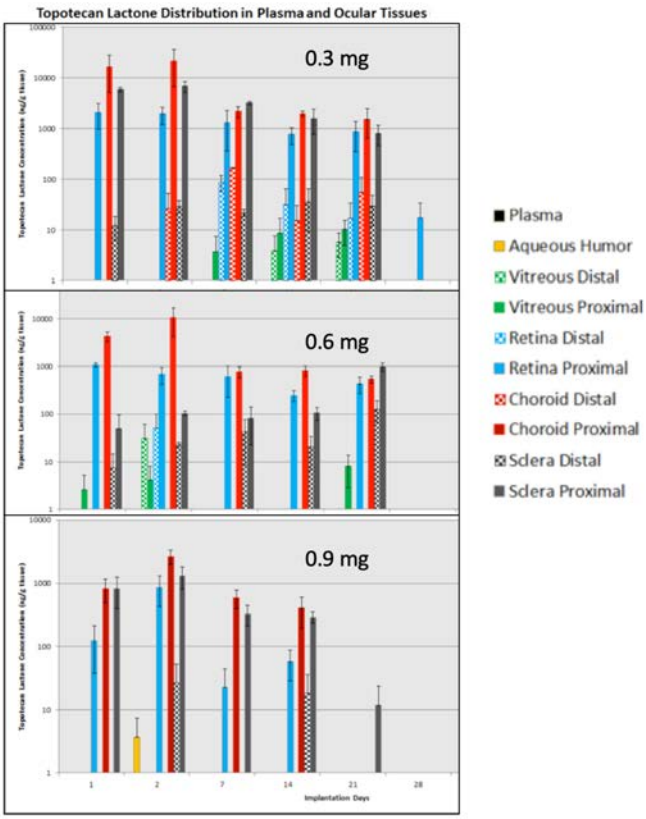


Figure 3. Ocular and plasma distribution of topotecan lactone after implantation of Chemoplaques containing 0.3, 0.6, or 0.9 mg of topotecan HCl. Plasma concentrations < LLOQ. LLOQ for plasma and ocular tissues: 1 ng/ml or 1 ng/gram.



2.4.2 PILOT COMPASSIONATE USE

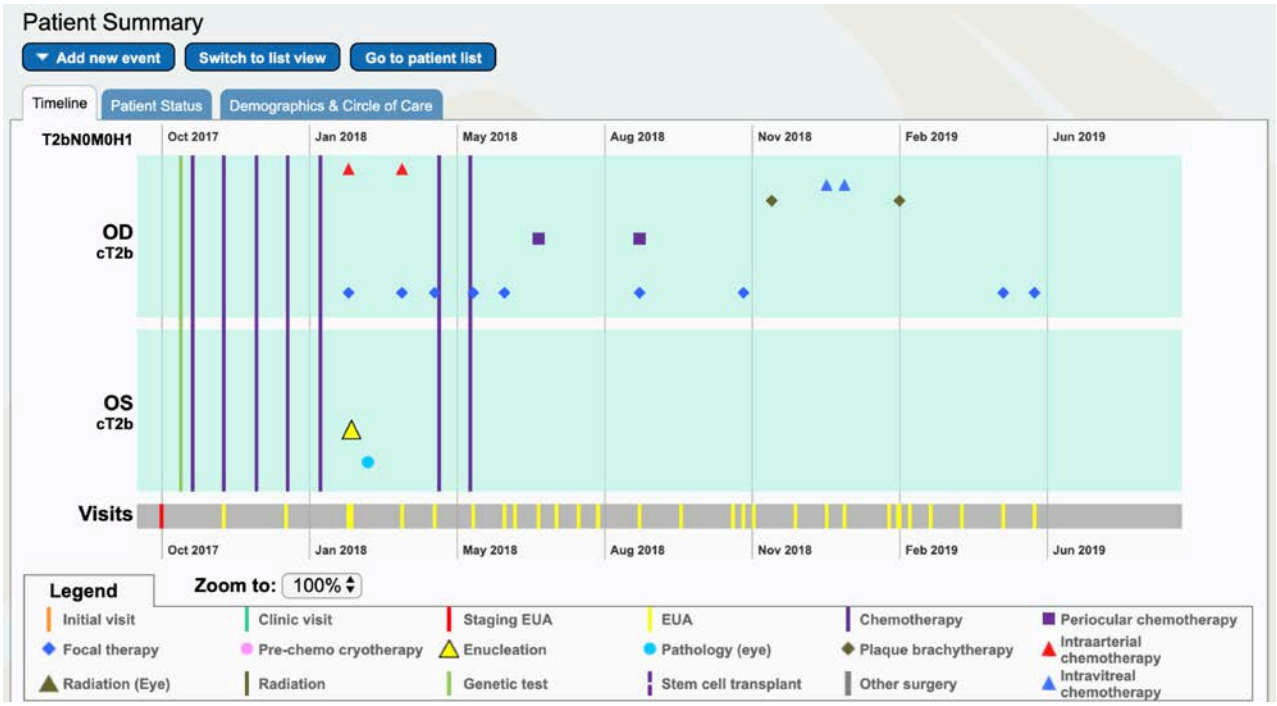
Three patients have been treated with Chemoplaque Topotecan under the jurisdiction of Health Canada's Special Access Program. Two patients were close to losing their last eye to retinoblastoma and the remaining treatment options were judged to be dangerous to vision or to have serious lifelong implications of increasing second cancer risk to close to 50%. These inevitable risks were greater than the theoretical risks of the "never before in Human" Chemoplaque. The third patient would be eligible for the STEP-RB Protocol, if it were opened, but risk losing the eye due to refractory recurrence after chemotherapy. Each patient experienced neither eye nor systemic toxicity. The first two had a rapid regression of small volume disease. Patient One (SAP #107477) had further treatments for recurrence of the large volume tumour at Day 135 that was controlled by standard therapies and is in Complete Remission at 1 year with no toxicity. Patient Two (SAP #111735) had further therapy at Day 110 to repair ocular complications from treatments preceding the Chemoplaque. Recurrence of disease was managed by removal of the eye, considering that the child had extensive previous treatments collectively increasing risk of extraocular disease. Patient Three (SAP #127728) is too recent to report efficacy.

These children were treated with the Chemoplaque as salvage therapy for eyes with retinoblastoma refractory to conventional therapies, vision potential and no clinical features suggestive of high risk of extraocular extension.

2.4.2.1 *PATIENT ONE*

A child with a constitutional *RB1* gene pathogenic variant was diagnosed with both eyes stage [3] cT2b (Group D Murphree classification[4] retinoblastoma. After 4 months treatment (Figure 4a) with systemic chemotherapy his left eye was removed because extensive refractory retinoblastoma threatened the optic nerve and choroidal invasion.

***Figure 4a**. DEPICT HEALTH graphic display of treatments since diagnosis of retinoblastoma in Patient One.*



The child's right eye received systemic chemotherapy (2 different regimens, 8 total cycles, partial response, then recurrence) and intra-arterial chemotherapy (2 cycles, no response). After 8 months, there was still refractory multiply recurrent extensive disease (Figure 4a). The large nasal tumour (partially calcified, 6.5 mm elevation adjacent but not contiguous to the optic disc) showed growth of the main tumour in every direction with adjacent "greasy" vitreous seeds. Throughout the retina were ~30 laser- and chemo-resistant tumours. The fovea was intact (excellent visual potential) but detached by new serous retinal detachment related to the active large nasal tumour. The only remaining conventional treatments were external beam irradiation or removal of his only eye.

Health Canada authorized the first human application compassionate use of Chemoplaque Topotecan. The Target tumours were (i) the 30+ small volume tumours for 360o near the ora serrata, (ii) the partially calcified tumour nasal to the optic nerve.

On Day 0 the 0.6 mg Topotecan Chemoplaque was glued to sclera under conjunctiva (Figure 4b). Blood tests and pain scores were normal (no pain). No ocular or systemic toxicities were observed.

(i) Small volume tumours (>30, diffuse)
Day 12: Very Good Partial Response (VGPR) (A decrease in tumour parameter greater than or equal to 20% and less than 90% from baseline.) Vision improved by Day 12 (fovea center of vision reattached).
Day 28: Complete Response (CR) (decrease in tumour parameter by 100% from baseline, or no viable residual disease by imaging including OCT, ultrasound and ultrasound biomicroscopy.) CR has been durable for 1 year.

(ii) Partially calcified nasal tumour
Day 28: Partial Response (PR) (A decrease in tumour parameter greater than or equal to 20% and less than 90% from baseline.)
Day 156: Progressive Disease (PD) (Increase in tumour parameter by greater than or equal to 30% from baseline or development of new tumours requiring more than minimal focal therapy.) The PD in the large tumour required multiple interventions to the nasal tumour, made feasible by the CR in the multiple small volume tumours.

At year 1.5 after insertion of the Chemoplaque there has been no Chemoplaque-related toxicity. The CR in the multiple small-volume resistant tumours has been durable. Vision is 20/100. External beam radiation and enucleation have been avoided.

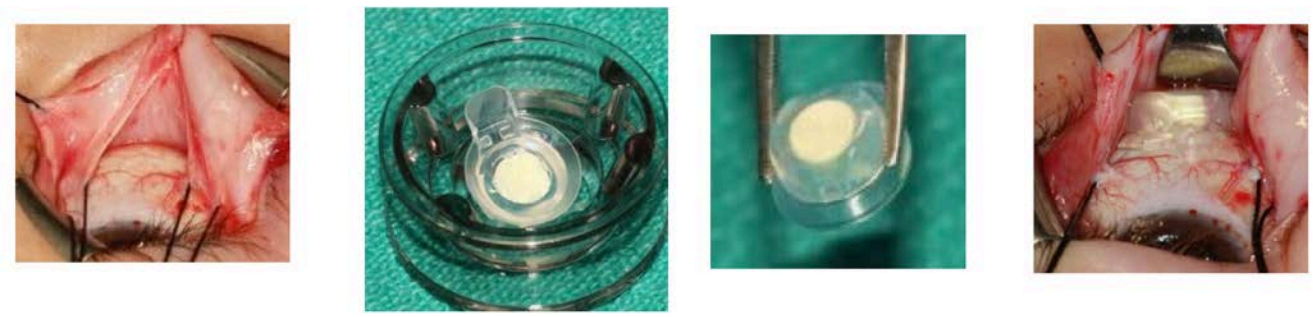


***Figure 4b**: Placement of the Chemoplaque on dry sclera under Tenon's Capsule under general anaesthetic.*

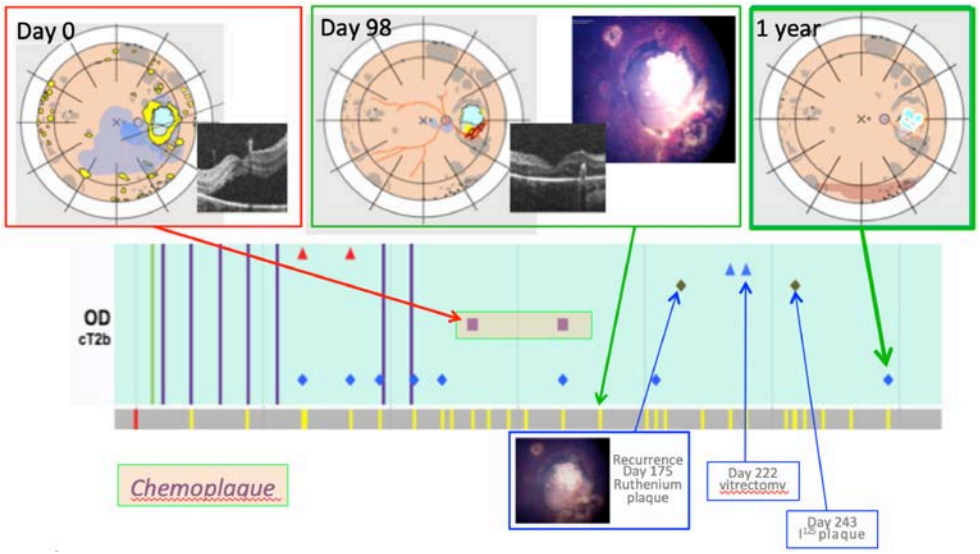


***Figure 4c**: Retinoblastoma in right eye from Day 0 (Chemoplaque insertion), Day 98, and follow-up treatments (ruthenium plaque, vitrectomy, I^{125} plaque) for the Day 156 recurrence in calcified nasal tumour. No recurrence in the 30 distributed small volume tumours at Day 365 (1 year); 20/100 last vision.*

2.4.2.2 *PATIENT TWO*

This child had bilateral retinoblastoma, both eyes treated with systemic chemotherapy (2 different regimens, 10 total cycles, partial responses), IAC (2 cycles, non-responsive) and external beam irradiation therapy over one year (Figure 5a). Four months later there was massive recurrence in both eyes. The right eye was removed.

The left eye had dispersed tumour recurrences with vitreous seeding and vitreoretinal fibrous proliferation. The fovea was detached with a serous retinal detachment. The tractional retinal detachment was covered with highly active retinoblastoma (Figure 5b). There were no more conventional options except removal of the child's last eye. Health Canada authorized compassionate use of the 0.6 mg Topotecan Chemoplaque.

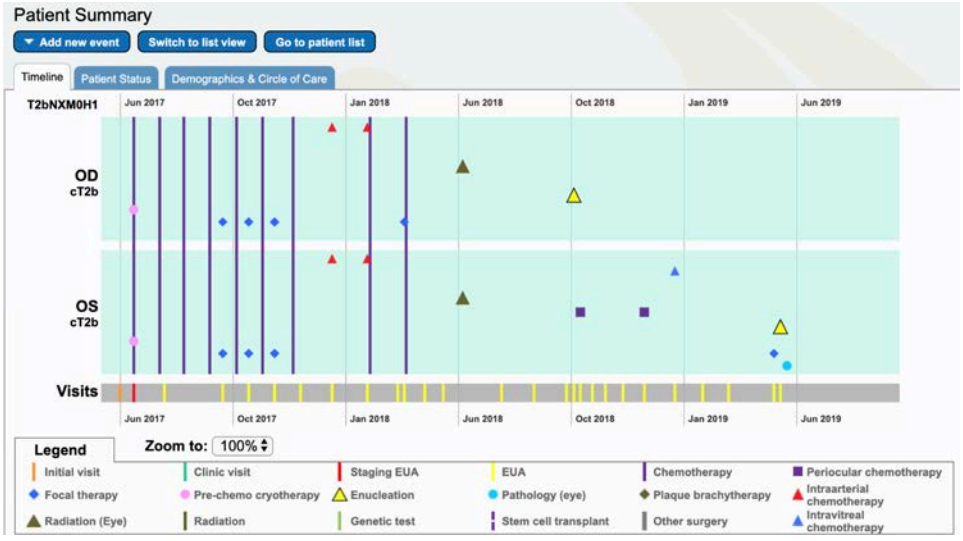


Figure 5a: DEPICT HEALTH graphic display of treatments since diagnosis Patient Two.

Health Canada authorized the Second human compassionate use of the Chemoplaque. The Target tumours were the small volume primary original tumour and the dispersed active tumour attached to vitreous traction lines and floating vitreous seed.

On Day 0 the Chemoplaque was glued to sclera under conjunctiva. Blood tests and pain scores were normal (no pain). No ocular or systemic toxicities were observed.

Day 28 PR: Decrease in tumour parameter greater than or equal to 20% and less than 90% from baseline.)

Day 110 VGPR: the residual tumour was only detected by vitrectomy to release the retinal traction.

Day 209 PD: definitive recurrence was treated by enucleation. Pathology showed pT1, active tumour recurrence with no risk of spread outside the eye.

Dispersed small tumours showed 50% reduction and marked reduction of vitreous seeds Day 28 (Figure 5b). No active-appearing tumours or seeds were visible by Day 48 and the fovea had re-attached. No signs of local or systemic toxicity were observed. Minimal superficial vitreous hemorrhage was seen over of the shrinking masses of tumour that disappeared by Day 48, perhaps related to tumour necrosis rather than Chemoplaque toxicity. The Chemoplaque was removed at Day 77. Although no active tumour was visible, the cytology from the vitrectomy fluid showed active retinoblastoma tumour clumps. At Day 132 there was no active tumour detected by visual examination and OCT which showed only scarring in the vitreous traction. However, at Day 209, intra-retinal recurrences inferiorly were noted and confirmed on OCT. The family elected enucleation. Pathology of the enucleated eye was pT1 (residual focal active retinoblastoma, no features suggestive of risk for extraocular spread).

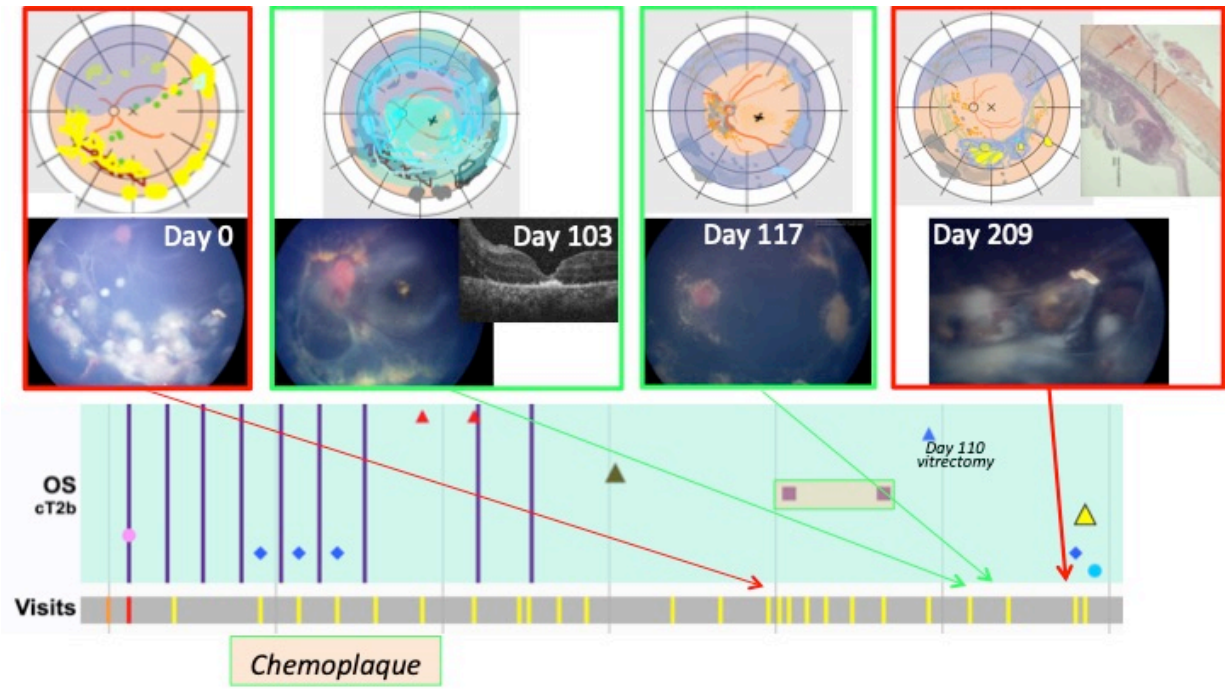


Figure 5b: Graphic display in DEPICT HEALTH including images of the left eye of SAP Patient Two.

2.5 RISK/BENEFIT ASSESSMENT

The episcleral implant delivers the drug to the eye in a sustained controlled manner providing therapeutic concentrations in the eye tissues, while minimizing unnecessary systemic absorption, but effectively controlling tumour growth.

The Chemoplaque consists of three elements which all have extensive use in humans with no risks at the small doses of this device. The drug is topotecan hydrochloride (0.6–0.9 mg) formulated in Poly Lactic-co-Glycolic Acid (PLGA), a standard matrix polymer/drug formulation, contained within a silicone Episcleral Implant designed for sealed attachment to the episclera. These ingredients have all been used in human in different contexts and higher doses. In rabbits, the only toxicity was Grade 1 serous subretinal fluid opposite the location of the Chemoplaque between days 7 and 21 that resolved completely (See Investigator's Brochure). Local serous detachment was not observed in the two human SAP cases.

The two SAP children showed no significant toxicity of the Chemoplaque over 70 days. SAP Child One had Grade 1 hemorrhage local to the main calcified tumour, which is expected when retinoblastoma tumours are treated and start to regress, and which resolved quickly. No systemic toxicity was observed.

Theoretical risks include: infection, unexpected local or systemic toxicity, lack of efficacy to block tumour growth, disappointment that the study therapy did not cause the hoped-for tumour control.

Theoretical benefits are: enhanced control of intraocular retinoblastoma, reduction in need for more toxic therapies (some with lifelong risks such as second cancers), more rapid control of intraocular tumour with reduced number of anesthetics, and salvage of eyes otherwise might be removed because of risk of extraocular extension of disease.

The potential benefits are highly significant for patient welfare, while the risks, based on two SAP children treated with minimal toxicity, are consistent with the non-toxic nature of the three ingredients in the Chemoplaque.

Known risks include:

Grade 3 conjunctival toxicity in quadrant containing the Chemoplaque.

3 OBJECTIVES AND ENDPOINTS

Primary Objectives	Primary Endpoints	Justification for Endpoints
To determine the safety and tolerability of the Chemoplaque in patients with retinoblastoma.	• To estimate the MTD or RP2D of topotecan hydrochloride administered as a Chemoplaque to pediatric patients with active Retinoblastoma. • To define and describe the toxicities of the Chemoplaque administered on this schedule. • Toxicity (both eye and heme/onc) will be assessed by CTCAE v5.0	When the target doses are determined with acceptable toxicities, Phase 2 studies can be planned.
Secondary Objective	**Secondary Endpoints**	**Rationale of Secondary Endpoints**
To describe the anti-tumour efficacy of the Chemoplaque as secondary therapy in eye(s) with active retinoblastoma after completion of primary standard of care treatment.	Efficacy of the Chemoplaque to control residual retinoblastoma after primary standard care, scored for standard measures of CR, VGPR, PR, SD, or PD. Overall survival (OS), defined as the time from the date of initial Chemoplaque insertion to the date of death regardless of the cause of death. • Overall eye salvage (ES), defined as the time from the date of initial Chemoplaque insertion to the date of eye removal (enucleation) regardless of the reason for enucleation. • Progression-free survival (PFS), defined as the time from initial Chemoplaque insertion to the occurrence of DP or death from any cause. PFS will be assessed at 6 months, 12 months, 2 years and 5 years. • Number of Post-intervention treatments for study eye including: o Chemotherapy (systemic and/or intra-arterial); focal laser, cryotherapy; brachytherapy; intra-vitreal chemotherapy; external beam radiotherapy; other; o Number of EUAs: total, and for eye evaluation, MRI, other procedures.	The secondary endpoints determine the degree to which the Chemoplaque is likely to improve on the standard of care, setting the stage for a Phase 2 study.

Exploratory Objectives	Exploratory Endpoints	Rationale
To evaluate the potential role of the Chemoplaque in the treatment of retinoblastoma.	Identification of demographic (e.g., SES, gender, age at study treatment). • Impact of initial disease extent (e.g., TNMH staging). • Impact of all prior treatments (exploratory data in DEPICT HEALTH). • Impact of all post-Chemoplaque treatments (potential future RAI study) in DEPICT HEALTH. • Validity of the RAI in determining tumour response (CR, VGPR, PR, SD, PD)	The SAP pilot patients indicate the potential for the Chemoplaque to reduce intensity and toxicity of current standard of care therefore we will explore these impacts.

4 STUDY DESIGN

4.1 HYPOTHESES

Primary Hypothesis:

The delivery of topotecan via an episcleral implant will be safe and well tolerated.

Secondary Hypothesis:

Topotecan delivered via episcleral implant will demonstrate anti-tumour activity.

STEP-RB is a single site, single-arm, non-randomized, dose escalation phase I toxicity clinical trial. The Chemoplaque intervention will last 63 days unless an adverse event requires earlier removal. Toxicity will be assessed until 21 days following plaque removal. The study intervention involves the insertion and removal of the Chemoplaque, examinations under anaesthesia (EUAs), visits to clinic to monitor for adverse events throughout, and post plaque removal toxicity evaluation. EUAs, clinic visits and laboratory tests are standard of care for retinoblastoma patients.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Eligible patients must be younger than 18 years old, as retinoblastoma is a pediatric cancer and all study-related treatments are to be conducted at SickKids hospital. Eligibility is independent of gender and ethnicity. The rationale for doing a single arm dose escalation study is that Chemoplaque has never been formally tested for dose limiting toxicities in humans, and the study population should consist of patients with active retinoblastoma that has the potential to be managed by the Chemoplaque. Since the purpose of the study is to find the MTD and RP2D, the study is single armed and unblinded.

4.3 END OF STUDY DEFINITION

A participant is considered to have completed the Study Intervention if he or she has completed the Intervention and all study visits including last (**Section 1.2, Schedule of Activities (SoA))**. The duration of the Study Intervention for each individual participant will be 63 days. All surveillance EUAs and clinical exams during the Intervention Period will be at SickKids. In the follow-up period, some children may have examinations and focal treatments at other Institutions. The clinicians involved in those therapies will be included in a delegation log.

It is estimated that it will take 64 months from when the study opens to enrollment until the end of the study, the last patient being enrolled within 60 months from when the first patient was enrolled. Patients will be followed for 5 years post-treatment according to standard of care.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. *Age.* Patients must be <18 years of age.
2. *Diagnosis and Treatment.* Patients must have active residual or recurrent intraocular retinoblastoma in one eye following completion of first-line therapy (chemotherapy, systemic or intra-arterial, or brachytherapy).
3. *One eye will be the Study Eye.* When patients have two eyes with retinoblastoma, the eye with worst disease or best vision potential will be designated the Study Eye. There will only be one eye per child treated in this Phase I study, since treatment of two eyes would double the systemic dose of drug. The Non-study eye will be treated by standard of care, with only focal therapy during the Study Period, if required.
4. *Disease status*. Study eye must have vision potential and no clinical features suggestive of high risk of extraocular extension.
5. *Performance status.* Lansky play score ≥50 if <16 years of age; Karnofsky performance scale of ≥50 if ≥16 years of age (Appendix I)
6. Organ function:
    a. Adequate bone marrow function defined as absolute neutrophil count (ANC) $\geq 1x10^9$/L and platelet count $\geq 100x10^9$/L, transfusion independent, defined as not receiving platelet transfusions at least 7 days prior to CBC confirming eligibility
    b. Adequate renal function defined as serum creatinine ≤ 2x ULN for age/sex
    c. Adequate liver function defined as bilirubin (sum of conjugated and unconjugated) ≤ 3x upper limit of normal (ULN) for age and ALT ≤ 5x ULN
7. *Pregnancy prevention.* Females of reproductive potential must agree to the use of highly effective contraception during study participation and for an additional 40 days after the end of the Chemoplaque administration
8. *Informed consent.* All patients and/or their parents or legally authorized representatives must have the ability to understand and the willingness to sign a written informed consent. Assent, where appropriate, will also be obtained.

5.2 EXCLUSION CRITERIA

1. *Disease status.* Patients with any of the following are excluded:
    a. tumour involving the optic nerve rim
    b. clinical or EUA evidence of extraocular extension
    c. evidence of metastatic retinoblastoma
    d. existing neuroimaging showing suspicion of, or definitive, optic nerve invasion, trilateral retinoblastoma or extra-ocular extension
2. *Allergy*. Patients with reported allergy to topotecan, camptothecin or derivatives thereof are excluded
3. *Concomitant treatment*. Patients may not receive chemotherapy or other focal retinoblastoma therapy or any other investigational agent within 3 weeks of the placement and removal of the Chemoplaque, nor while the Chemoplaque is *in situ*.
4. *Uncontrolled intercurrent illness*. Patients with uncontrolled intercurrent illness that would limit compliance with the study requirements are not eligible
5. *Febrile illness*. Patients with clinically significant febrile illness (as determined by the investigator) within one week prior to initiation of protocol therapy are excluded.

6. *Pregnancy and lactation.* Females of reproductive potential must have a negative serum pregnancy test within 72 hours prior to initiation of protocol therapy. Due to the unknown but potential risk for adverse events (AEs) in nursing infants secondary to treatment of the mother with the study agents, breastfeeding must be discontinued if the mother is treated on study.
7. *Current smoker of tobacco user.*
8. *Current Canabis user.*
9. *Compliance*. Any condition of diagnosis that could in the opinion of the Principal Investigator or delegate interfere with the participant's ability to comply with the study instruction, might confound the interpretation of the study results, or put the participant at risk.

5.3 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened after resolution of a modifiable factor with no maximum number of times but must still meet inclusion criteria. Rescreened participants will be assigned the same participant number as for the initial screening; however, the dose may be reassigned (for which additional consent will be obtained) based on the inter-patient dose escalation schema.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

All patients treated at SickKids who meet Inclusion Criteria will be offered participation in the study after first line chemotherapy has been completed. All of the patients must be under 18 at time of enrollment, however, there are no gender, race, or ethnicity-based limitations or other requirements. The anticipated accrual rate based on 20 retrospective SickKids eligible patients between May 2015 and October 2018 is 7 patients per year who would have met the Inclusion Criteria.

The target study sample size ranges from 4 (four) with early dose limiting toxicity terminating the study, to 24 (twenty-four) patients in the case of dose limiting. If there are no patients with no dose limiting toxicities, only 14 patients will be needed to assess all dose levels. Assuming 20% refusal rate, we estimate 5 enrolled patients per year. Accrual would be complete in approximately 5 years. Non-SickKids patients who meet the eligibility criteria may be referred and registered as SickKids patients, as is common across Canada to meet the standard of care. Because the study requires multiple visits over the course of a few months and expects 5 year follow up, patient families will be contacted regularly to encourage the continuation of participation and follow-up with further treatments by the standard of care.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention (Chemoplaque) is available in two sizes, providing a dose 0.6 mg or 0.9 mg topotecan hydrochloride. The drug component is contained in the inert silicone implant E1-050, which is contained in a P-01 container with a P-02 lid until use (see PRIMARY AND SECONDARY PACKAGING SYSTEMS). The topotecan hydrochloride drug component within the device is formulated in poly(D,L-lactide-co-glycolide) [PLGA] excipient at 50:50 monomer ratio that is a cGMP-grade FDA-approved polymer excipient that provides sustained release capability. The remainder of the Chemoplaque comprises a medical-grade silicone episcleral implant (also referred to as an episcleral reservoir) that encases the formulation consisting of the drug substance-excipient matrix. The device is non-programmable, and the duration of the one-time implant release of drug is suggested to be 50 days ± 7 days. The Chemoplaque will be removed at 42 days ± 7 days to reduce dose variability between patients.

The episcleral implant was designed to be attached to the episclera and sequester the topotecan HCl from unnecessary systemic absorption by the lymphatic/vasculature of the conjunctiva and Tenon/periocular tissues thereby preventing the topotecan HCl from systemic absorption, bypassing the eye. By blocking this route of egress, the episcleral implant enables unidirectional (one-way) drug delivery to the interior of the eye thereby enabling sustained-release ocular drug delivery otherwise unfeasible, and simultaneously greatly reducing (essentially eliminating) systemic exposure.

Chemoplaque is not currently commercially available and will be used in accordance with the current labeling. No modifications to the device will be performed for the purpose of this study. The drug product, Chemoplaque Topotecan, consists of a sustained-release formulation of topotecan hydrochloride contained within an episcleral implant at various ascending doses. The Episcleral Implant in various publications and in this protocol is referred variously as Chemoplaque, Episcleral Device, Episcleral Topotecan, Episcleral Sustained Release Topotecan, Episcleral Reservoir, Episcleral Exoplant, Episcleral Implant, and Targeted Transscleral Delivery System (TTDS).

In the current protocol we use the term **Chemoplaque**. All these terms refer to the same drug product and are interchangeable. The Chemoplaque (Episcleral Topotecan) clinical supplies will be shipped from the manufacturer (Targeted Therapy Technologies, LLC/DBA 3T Ophthalmics) ready for use and require no further manipulation before ocular placement.

6.1.2 DOSING AND ADMINISTRATION

Given that the two 0.6 mg devices used in two special access patients resulted in no detectable toxicities, a starting dose of 0.9 mg is proposed. The rolling six dose interpatient escalation schema allows for dose de-escalation should two patients experience a dose limiting toxicity within a level. The prescribed dose will escalate or de-escalate by 0.3 mg at each level, and no patient will receive more than 1.8 mg of topotecan hydrochloride due to the physical limitations if the devices available. The dose is administered **one time** on Day 1 of the study, and any drug that remains in the device on day 42 will be removed with the device. Drug administration stops as soon as the device is removed on day 42. The study participants will not self-administer the study intervention, and preparation for the insertion of the Chemoplaque is no different from preparing for a standard of care EUA. The drug product is kept cold (not frozen) between 2°C and 8°C at the pharmacy until use.

6.1.3 DOSE ESCALATION AND MODIFICATIONS

Inter-Patient Escalation in the rolling six phase 1 trial design (see appendix II: *The Rolling Six Design)* will determine Maximum Tolerated Dose (MTD) (if toxicity is observed) and Recommended Phase 2 Dose (RP2D). There will be no intra-patient dose escalation.

Dose levels

Dose level	Topotecan dose	
-1	0.6mg	1 x 0.6mg
1	0.9mg	1 x 0.9mg
2	1.2 mg	2 x 0.6mg
3	1.5 mg	0.6mg + 0.9mg
4	1.8 mg	2 x 0.9mg

Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered with pending tolerability data at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated, and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are not evaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study. At least 6 patients will be treated at the maximum tolerated dose to confirm tolerability.

The intervention is the 3T Ophthalmics Sustained-release Topotecan Episcleral Plaque (Chemoplaque) available in 0.6 mg and 0.9 mg of topotecan HCl formulation, glued to bare, dry sclera of the study eye under conjunctiva and Tenon's capsule. (Figure 4b). The planned removal is at 50 days, unless DLT is observed, in which case the plaque is removed as soon as possible.

Chemoplaque(s) will be applied 1 or 2 per eye, to deliver 4 escalating doses: 0.9, 1.2 [2x0.6], 1.5 [0.6+0.9] or 1.8 [2x0.9] mg. Two patients have been treated without toxicity using single 0.6 mg Chemoplaques, so will start this Phase I study at the 0.9 mg dose Chemoplaque.

Potential scenarios in terms of number of evaluable patients:

- Minimum of 4 evaluable patients:
  - 2 patients at 0.9 mg experience Dose Limiting Toxicity (DLT);
  - Dose reduce to 0.6 mg: 2 patients experience DLT;
  - Enrollment terminated with NO MTD (Trial Closed)
- Minimum of 15 evaluable patients if no DLT occurs:
  - 3 patients at lowest 3 dose levels
  - 6 patients at maximum deliverable dose (1.8 mg)
- Maximum of 24 evaluable patients if DLTs occur at every level:

- 6 patients enrolled on each dose level with a DLT
- 4 evaluable dose levels

Accrual will be suspended when MTD and RP2D determined.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

The Chemoplaques will be shipped from 3TOphthalmics directly SickKids pharmacy, where they will kept refrigerated at 2–8ºC until required.

After removal from the patient, the Chemoplaques will securely discarded in accordance with SickKids policies.

Supplier/Distributor
Targeted Therapy Technologies, LLC (DBA: 3T Ophthalmics, 5 Jenner Suite 150, Irvine, California 92618) will supply the Chemoplaques for this clinical trial) will supply the Chemoplaques for this clinical trial.

IND number assigned: 112785. See package insert for further information.

6.2.2 ACCOUNTABILITY AND DESTRUCTION OF CHEMOPLAQUE

The principal Investigator (or an authorized designee) will maintain a careful record of the inventory of Topotecan Chemoplaques using the Drug Accountability Form.

6.2.3 FORMULATION, APPEARANCE, PACKING AND LABELING

3T Ophthalmics will supply the Chemoplaques in the format described in the Product Brochure (above and Appendix IV)

6.2.3.1 FORMULATION OF THE EPISCLERAL TOPOTECAN CHEMOPLAQUE PRODUCT

Sustained release topotecan is delivered from an episcleral implant (Chemoplaque). Topotecan (drug product) consists of topotecan hydrochloride (drug substance), formulated in poly(D,L-lactide-co-glycolide) [PLGA] excipient at 50:50 monomer ratio that is a cGMP-grade FDA-approved polymer excipient that provides sustained release capability, and a medical-grade silicone episcleral implant (also referred to as an episcleral reservoir) that encases the formulation consisting of the drug substance-excipient matrix.

The Chemoplaque is prepared by formulating the drug substance, topotecan HCl, and PLGA, in a suitable solvent following precision dispensing into the episcleral silicone reservoirs, after which the whole system is lyophilized, thereby removing the process solvents. Episcleral reservoirs containing the formulation matrix are then packaged in primary and secondary packaging systems.

6.2.3.2 PRIMARY AND SECONDARY PACKAGING SYSTEMS

Primary packaging of Episcleral Topotecan, consists of P-01 container and P-02 lid (Figure 6a).

Figure 6a. Episcleral Topotecan inside P-01 container with its corresponding P-02 lid: Episcleral Topotecan 0.6 mg using E1-050 inert silicone implant.

Secondary packaging chevron foil pouch with product unit with primary packaging inside (Figure 6b) includes label and sterilization detector that changes from light yellow/orange to dark red following terminal sterilization. The chevron foil pouch limits exposure to humidity, light, particulate matter, and maintains sterility.

Figure 6b. Complete package of Episcleral Topotecan with affixed product label and irradiation sterilization indicator.

6.2.4 PRODUCT STORAGE AND STABILITY

The Chemoplaque is stored at 2-8º C in its unopened sterile package until it is opened in the OR for insertion.

6.2.4.1 STABILITY OF THE TOPOTECAN CHEMOPLAQUE PRODUCT

The formulated topotecan is stable when exposed to temperature and pH conditions similar to those expected in the treated conditions and topotecan is released over time from the matrix-drug formulation in both lactone and carboxylate forms. The pH media where the drug is released ultimately determines which form is prevalent. Both forms of topotecan—lactone and carboxylate—are adequately present throughout the release period indicating that the matrix preserves the “yet-to-be released” topotecan while in the reservoir. Topotecan undergoes a pH-dependent reversible hydrolysis from the lactone form to the biologically inactive carboxylate form. The lactone form is predominant at lower pH (i.e. < 4) while the carboxylate form is mostly favored at higher pH (i.e. > 9). At physiological pH, both forms are present.

Prior to use the Chemoplaque will be stored at 2-8º C (36-46ºF).

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND MASKING

This Phase I study will not include randomization or masking.

6.4 STUDY INTERVENTION COMPLIANCE

Adherence to the protocol (e.g., surgical timing and technique of placement) will be recorded in the participant drug log, a trial-specific OR checklist and the operative note including relevant details of placement of a Chemoplaque, which will be used to calculate study intervention compliance.

All violations or deviations will be reported to the site's REB (as per REB guidelines and local regulations). All REB correspondence will to be forwarded to 3TOphthalmics.

6.5 CONCOMITANT THERAPY

There is no specific required concomitant therapy. Standard supportive care for symptomatic relief of any toxicity will be used.

Supportive care will be administered as needed in accordance with SickKids standard clinical practices. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements from 14 days before baseline until 21 days after the final dose of the study intervention (i.e. removal of the Chemoplaque). Participants will be instructed to contact the study team prior to initiating any new medications if possible and to inform the study team of any medications they have taken at each study visit.

No other anti-cancer therapies or other experimental therapeutic agents will be permitted while on study. There are no other specific restricted concomitant medications.

7 DISCONTINUATION AND WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

The Chemoplaque will be removed earlier than the timeline proposed in the SOA in the following situations:

- Toxicity (adverse event) defined as grade 3 systemic or local except Grade 3 conjunctival response in the quadrant containing the Chemoplaque
- Tumour progression endangering tumour spread

Discontinuation from Chemoplaque does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the PI or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an Adverse Event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Reason for discontinuation
- Evidence of toxicities

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An Investigator may discontinue or withdraw a participant from the study for the following reasons:

- Withdrawal of informed consent (participant or parent/guardian withdraw for any reason)
- If any clinical Adverse Event (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
- Significant study intervention non-compliance
- Disease progression which requires discontinuation of the study intervention
- Requirement of prohibited concomitant medication(s) that requires discontinuation of the study intervention
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Pregnancy

The reason for participant discontinuation or withdrawal from the study will be recorded in the study file eCRF. Participants who sign the informed consent form but do not receive the study intervention or withdraw (for reasons other than toxicity) before completion of the toxicity evaluation period may be replaced. The data from participants who are withdrawn or discontinued from the study will be used in the analysis unless the participant requests otherwise.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ASSESSMENTS

The standard of care for retinoblastoma is outlined in section 2.2. The following procedures and evaluations are study specific, and are not considered standard of care:

- Initial screening for eligibility
- Enrollment
- eCRF forms
- Chemoplaque insertion/removal

Of note, all disease evaluations, clinical laboratory tests and anaesthetic procedures (EUAs) required for Chemoplaque insertion and removal are consider standard of care.

8.2 DEFINITION OF DOSE-LIMITING TOXICITY (DLT)

Dose-limiting toxicity will be defined as any of the following events that are at least possibly, probably or definitely attributable to the Chemoplaque. The observation period for the purposes of dose-escalation will be 63 days (i.e. 21 days following Chemoplaque removal on day 42).

Systemic DLT: any Grade 3 or greater toxicity that is that are at least possibly, probably or definitely attributable to the Chemoplaque

Ocular DLT: any of the following that are that are at least possibly, probably or definitely attributable to the Chemoplaque

- Grade 2 or greater scleral necrosis (may be detected after Chemoplaque removal)
- Grade 2 or greater eye pain
- Grade 3 ocular toxicities with the specific exception of Grade 3 conjunctival response in the quadrant containing the Chemoplaque and localized Grade 3 retinal detachment (specifically serous retinal detachment which is not given in CTCAE), which are expected and not considered an ocular DLT

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An Adverse Event (AE) is any untoward medical occurrence associated with the use of an intervention in a study participant, which does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the intervention, whether or not considered related to the investigational intervention.

Stable chronic conditions which are present prior to entry in the study and do not worsen are not considered AEs after administration of the study product unless they reoccur after the subject has recovered from the pre-existing condition or they represent an exacerbation in intensity or frequency. These pre-existing conditions will be documented in the participant's medical history.

Only laboratory test abnormalities that are considered clinically relevant (e.g. causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations) or judged relevant by the Investigator should be reported as an adverse event.

As part of good patient care, unscheduled visits and procedures are allowed in this protocol. Any unscheduled visits will be documented on the site source document and, as necessary, captured in the CRF.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A Serious Adverse Event is any AE that is:

- fatal;
- life-threatening;
- requires or prolongs inpatient hospital stay;
- results in persistent or significant disability or incapacity;
- is an important medical event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (example: intensive treatment in an emergency room or at home for bronchospasm, convulsions that do not result in hospitalization);
- Medical and scientific judgment will be exercised in deciding whether some events should be considered as serious because their quick reporting to the sponsor may be of interest for the overall conduct of the study;
- suspected transmission of an infectious agent by the Chemoplaque;
- an important medical event.

Life-threatening: The term “life-threatening” in the definition of “serious” refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an AE that hypothetically might have caused death if it were more severe.

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions are met:

- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study).

OR

- The admission is not associated with an adverse event.

OR

- The admission results in a hospital stay of less than 12 hours.

However, it should be noted that invasive treatment during any hospitalization may fulfill the criteria of ‘medically important’ and as such may be reportable as a SAE dependent on clinical judgment.

Disability means a substantial disruption of a person’s ability to conduct normal life’s functions.

Important medical event: Any AE may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the participant and may require intervention to prevent one of the other serious outcomes noted above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

The SAE reporting period begins at insertion of the Chemoplaque. For the SAEs that have been deemed by the investigator as unrelated to protocol treatment, the SAE reporting period ends 21 days after removal of the Chemoplaque. For the SAEs that have been deemed by the investigator as at least possibly related to protocol treatment, the SAE must be reported even if this occurs past 21 days after removal of the Chemoplaque.

All SAEs must be recorded on eCRFs. In addition, all serious adverse events are subject to reporting using the SAE form and must be submitted within 24 hours of becoming aware of the event.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

The severity of an AE is assessed by a qualified physician who is part of the study team, who should use the following definitions when assessing the intensity of an AE:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All Adverse Events (AEs) must have their relationship to the study intervention assessed by a qualified physician who is part of the study team based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below. For all AEs, relationship to study drug will be reported on the appropriate AE eCRF page. The Investigator must judge whether the Chemoplaque caused or contributed to the AE in which case it is considered to be an Adverse Drug Reaction, and report it as either:

- **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 study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals, or there is a plausible biological mechanism through which study drug may have caused or contributed to the AE. The response to withdrawal of the study intervention should be clinically plausible.
- **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 study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship

improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments), or another cause of the AE is evident and most plausible.

- **Unrelated** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology, or the temporal sequence is inconsistent between the onset of the AE and study drug administration; a causal relationship is considered biologically implausible.

8.3.3.3 EXPECTEDNESS

Expected adverse reactions are AEs that are known to occur for the study intervention being studied. Expectedness is assessed based on the awareness of AEs previously observed (listed in product monograph, IB, package inserts, or device manual), not on the basis of what might be anticipated from the properties of the study intervention.
[A qualified physician who is part of the study team will be responsible for determining whether an Adverse Event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.]

- Grade 3 conjunctival response in the quadrant containing the Chemoplaque is expected and not considered an ocular DLT

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

All Adverse Events (AEs) or Serious Adverse Events (SAEs) with start dates occurring any time during or after receiving the study intervention until 7 days (for non-serious AEs) or 21 days (for SAEs) after the last day of study intervention will be documented. SAEs thought to be at least possibly related to the study treatment will be recorded whenever they occur. The occurrence of an AE or SAE may be detected during study tests (e.g. clinically significant laboratory results), spontaneously reported by the participant/parent or guardian to the research team, elicited by appropriate questioning during clinical evaluations or gathered during telephone follow-up calls. At each study visit, the participant will be asked about any change in their health since the last visit and for any changes to AE and SAEs that were ongoing at the last visit or telephone contact.

All AEs and SAEs occurring while on study must be documented regardless of relationship. Information to be collected includes event description, date and time (if possible) of onset, date and time (if possible) of resolution/stabilization of the event, outcome, and the assessment of seriousness, expectedness, relationship to study intervention and severity by a delegated qualified physician.

Any baseline condition recorded in the medical history that deteriorates at any time during the study, will be recorded as an AE or SAE.

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.

Events will be followed for outcome information until resolution or in the opinion of the PI or qualified physician delegate, the participant is stable and does not require further follow-up, or the participant is deemed lost to follow-up.

8.3.5 ADVERSE EVENT REPORTING

AE will be reported to The Hospital for Sick Children Research Ethics Board according to The Hospital for Sick Children's Adverse Event Reporting Requirements.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

All Serious Adverse Events (SAE) must be reported to Dr. Brenda L. Gallie and to a member of the clinical research (CRA) staff within 24 hours of becoming aware of the SAE. The initial report should contain as much information as available, at a minimum, the report must contain:

- Participant Identification Code,
- Adverse Event Term,
- Study Drug Dose and Start/Stop Dates

On the next working day email to CRA and REB completed trial-specific Serious Adverse Event form or Council for International Organizations of Medical Sciences (CIOMS) form.

Only adverse drug reactions that are *both* serious and unexpected are subject to expedited reporting to Health Canada. Expedited reporting of reactions which are serious but expected is not required. Expedited reporting is also inappropriate for serious events from clinical investigations that are considered unrelated to the study product, whether or not the event is expected.

During a clinical trial the Sponsor is required to inform Health Canada of any serious, unexpected adverse drug reaction (SUADR) that has occurred inside or outside Canada:

a. where it is neither fatal nor life-threatening, within 15 days after becoming aware of the information;
b. where it is fatal or life-threatening, immediately where possible and, within 7 days after becoming aware of the information; and
c. within 8 days after having informed Health Canada of the SUADR, submit as complete a report as possible which includes an assessment of the importance and implication of any findings. Final reports of fatal or life-threatening reactions must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar drugs.

Each SUADR which is subject to expedited reporting should be reported individually in accordance with the data element(s) specified in the Health Canada / ICH Guidance Document *E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*.

In situations when causality assessment and determination of expectedness is not straightforward, the report should be submitted in the expedited manner and the relevant issues addressed in a cover letter.

There are situations in addition to the above that may necessitate rapid communication to Health Canada, and appropriate scientific and medical judgment should be applied to each situation. For example, information that might influence the risk-benefit assessment of a drug, or that would be sufficient to consider changes in drug administration, or in the overall conduct of a clinical trial, represent such situations; including:

a. for an "expected" serious Adverse Drug Reaction (ADR), an increase in the rate of occurrence which is judged clinically important;
b. a significant hazard to the patient population, such as lack of efficacy with a drug used in treating a life-threatening disease; and
c. a major safety finding from a newly completed animal study.

Adverse events will be reported to The Hospital for Sick Children Research Ethics Board according to The Hospital for Sick Children's Adverse Event Reporting Requirements.

The PI will notify all Investigators of all Serious Adverse Events that are reportable to regulatory authorities in Canada from this trial as described above. Investigators must notify their Research Ethics Boards (REBs) according to institutional requirements and file the report and acknowledgement from the REB (e.g. letter from the REB acknowledging receipt, stamp from the REB, signed and dated by REB chair or delegate, acknowledging receipt) with their Investigator Site File.

Expedited Serious Adverse Events occurring within a center should also be reported to local REBs according to institutional requirements.

The Data Safety Monitoring Board (DSMB) will be notified of all unexpected Adverse Events within 7 days and serious, unexpected Adverse Events within 48 hours.

The Health Canada Medical Devices Regulations require adverse incidents or problems experienced with medical devices that meet the criteria of an SAE within Canada to be reported to the Health Product and Food Branch Inspectorate in the following manner:

- Where it is neither fatal nor life threatening, within 30 days after becoming aware of the information;

Where the device has caused a fatal outcome or deterioration in the health of a research participant, user, or another person, reporting should be immediate where possible, and, in any event within 10 days after becoming aware of the information.

Adverse Events will be reported to The Hospital for Sick Children Research Ethics Board according to The Hospital for Sick Children's Adverse Event Reporting Requirements.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

Participants and/or their parent/legal guardian will be informed in a timely manner of any new information, including safety information, that is relevant to that participant's willingness to continue participation. The communication of this information will be documented through a revised REB approved Informed Consent Form, where possible, based on the timeliness of the information.

In the event that a study procedure detects a new clinically important secondary finding/incidental finding, the qualified physician will notify the Most Responsible Physician (MRP) physician at SickKids (if the participant is being treated at SickKids) or request the participant's family doctor's name and contact information in order to arrange medical follow-up to interpret the significance of the findings.

8.3.8 EVENTS OF SPECIAL INTEREST

Any death (regardless of cause) that occurs from the time of insertion of the Chemoplaque until 21 days after removal of the Chemoplaque, and any death occurring after this time that is judged at least possibly related to prior treatment with the Chemoplaque, will be promptly reported.

8.3.9 REPORTING OF PREGNANCY

If a participant becomes pregnant, the study will continue and the participant will complete the evaluations/procedures. Pregnancy will be documented in the study file and any unexpected complications during the pregnancy will be documented as an AE. If the outcome of the pregnancy meets the criteria for classification as a SAE, (e.g., ectopic pregnancy, spontaneous abortion, stillbirth, neonatal death or congenital anomaly) this will be documented and reported accordingly.

9 STATISTICAL CONSIDERATIONS

STEP-RB will implement the Rolling Six dose escalation scheme in order to determine the MTD and RP2D and follow the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 in grading adverse events.

9.1 SAMPLE SIZE DETERMINATION

The concepts of type I error and power do not play a role in determining sample size for dose-escalation studies. The number of patients enrolled will depend on the observed number of DLTs and the enrolment rate and will be between 2 and 24. Only 2 patients will be enrolled if the first 2 patients on the lowest dose experience a DLT. A maximum of 24 patients will be enrolled if 6 patients are enrolled on each dose, with no more than 1 DLT on any particular dose. Six patients can be enrolled on a dose if the 6th patient is enrolled prior to knowing the DLT status of the first 3 patients on that dose.

9.2 POPULATIONS FOR ANALYSES

The following study populations are defined and will be analyzed as specified below. All evaluable patients fit into the *Safety dataset*, among other datasets:

The Intent to Treat (ITT) dataset: the total population of patients registered in the study.

Safety dataset: all registered participants who received at least one Chemoplaque study intervention.

Efficacy population: all enrolled patients who completed 42 days with at least one Chemoplaque and had adequate assessment of disease progression.

Any patient who is registered on to this trial but never receives study treatment will be described, including the reason(s) for non-participation.

All patients that receive a study dose will be included in all analyses.

Any patient who is registered but never receives study treatment will be described, including the reason(s) for non-participation.

9.3 STATISTICAL ANALYSES

9.3.1 GENERAL APPROACH

A general descriptive approach will be taken.

9.3.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The measured effects of the Chemoplaque are primarily toxicity and secondarily disease response which are both measured on an ordinal scale. The MTD and RP2D are determined using the Rolling Six dose escalation design.

The populations for which the analysis will be conducted will include the Safety Population, as only patients who receive the Chemoplaque may be screened for toxicity. The number and proportion of patients with a DLT will be tabulated by dose level.

9.3.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For the purposes of designing a phase 2 trial, a Swimmers Plot will be used to display the extent that a patient experiences either a CR or VGPR.

9.3.4 SAFETY ANALYSES

Primary endpoints will be measured by scoring heme/onc and ocular toxicities using the CTCAE Version 5.0. The Rolling Six dose escalation scheme will be used to determine the MTD and the RP2D during treatment. All registered participants who received at least one Chemoplaque study intervention will be analysed for safety.

9.3.5 BASELINE DESCRIPTIVE STATISTICS

Summary statistics will be used to describe baseline characteristics. Categorical variables will be summarized using proportions and frequencies. Continuous variables will be summarized using the mean, median, range or standard deviations.

9.3.6 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed by measure and time point when necessary to address unique cases. A description of all DLTs and disease response will be listed per patient.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 STUDY DISCONTINUATION AND CLOSURE

When a study is prematurely terminated, refer to **Section 7, Discontinuation and Withdrawal**, for handling of enrolled study participants.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, Investigator, funding agency, Sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the REB and Sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

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

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant discontinuing the trial
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, REB, DSMB, and/or regulatory agency.]

The Sponsor reserves the right to discontinue the trial for any reason but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigators must contact all participating patients immediately after notification. Standard therapy and follow-up for subjects will be assured and, where required by the applicable regulatory requirement(s), the relevant regulatory authority(ies) will be informed.

The REB or IRB/EC will be informed promptly and provided with a detailed written explanation for the termination or suspension.

As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

10.1.2 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating Investigators, their staff, and the Sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

Any research information obtained about the patient in this study will be kept confidential. A patient will not be identified by name, only by unique study ID number. The patient's name or any identifying information will not appear in any reports published as a result of this study. All identifying information will be kept behind 2 security measures or as per equivalent institutional policy, under the supervision of the study/site PI and will not be transferred outside of the hospital.

Information obtained from individual subject's participation in the study may be disclosed with his/her consent to the health care providers for the purpose of obtaining appropriate medical care. The subject's medical records/charts, and tests will be made available to 3T Ophthalmics, the Hospital for Sick Children its potential eventual partners, the Canadian HPFB/TPD, the REB/IRB and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A subject's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind locked doors, under the supervision of the study Principal Investigator and will not be transferred outside of the hospital.

A subject may take away his/her permission to collect, use and share information about him/her at any time. If this situation occurs, the subject will not be able to remain in the study. No new information that identifies the subject will be gathered after that date. However, the information about the subject that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

The study monitor, auditor and other authorized representatives of the Sponsor, representatives of the Research Ethics Board (REB), regulatory agencies or 3T Ophthalmics supplying study product (if contractually required) may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Data generated as a result of this study are to be available for inspection on request by local health authority auditors, the Sponsor's Study Monitors and other personnel (as appropriate) and by the IRB/EC. The Investigator shall permit sponsor, authorized agents of the sponsor, CRO and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect all source documents. The protocol and other study documents contain confidential information and should not be shared or distributed without the prior written permission of sponsor.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the SickKids. 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 used by SickKids research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the SickKids.

The Research Site will retain these records for 25 years after study close-out as required by Canadian regulations or as specified in the Clinical Trial Agreement, whichever is longer.
Under no situation is identified information to be released to third parties.

10.1.3 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the SickKids. After the study is completed, the de-identified, archived data will be transmitted to and stored at the SickKids, for use by other researchers including those outside of the study. Permission to transmit data to the SickKids will be included in the informed consent. Biological samples will not be stored.
During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the SickKids.

10.1.4 KEY ROLES AND STUDY GOVERNANCE

The study will be overseen by a study committee comprising Dr Gallie (Staff Ophthalmologist, PI and sponsor) and colleagues.

Safety Oversight

Safety oversight will be under the direction of an independent Data Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semi-annually to assess safety and efficacy data. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined.

10.1.5 STUDY MONITORING

Monitoring of the trial will be performed to verify that:

- The rights and well-being of participants are protected;
- The reported trial data are accurate, complete, and verifiable from source documents; and
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), ICH GCP, and local regulations and requirements.

The Sponsor will be responsible for all monitoring activities. Any trial-related duty or function transferred to and assumed by a third party, including monitoring and auditing, will be specified in a clinical trial agreement and oversight provided by the Sponsor.

The monitoring plan for the trial will be documented prior to the activation of the study and include the following;

- Follow risk-based practices,
- Document the rationale for the chosen monitoring strategy,
- Reference the Sponsor’s process that will be followed to address situations of non-compliance,
- Describe the monitoring responsibilities of all the parties involved, and
- Outline the data and processes to be monitored.

The site Investigator(s)/delegate(s) will allow direct access to source data/documents for the purposes of monitoring by the Sponsor, and inspection by regulatory authorities, both domestic and foreign (if applicable). It is important that the Sponsor, site Investigator and site personnel are available during monitoring visits and inspections, and that sufficient time is devoted to the process.

Monitoring procedures will be implemented beginning with the data entry system and data 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.

Monitoring reports will be issued after each monitoring visit for review and follow up by the Sponsor, site Investigator, and appropriate management and personnel responsible for trial and site oversight.

10.1.6 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Auditing of the trial will be performed independently from monitoring to evaluate trial conduct and compliance with the protocol/amendment(s), SOP, ICH GCP and local regulations and requirements.

The Sponsor will be responsible for all auditing activities. Any trial-related duty or function transferred to and assumed by a third party, including auditing, will be specified in a clinical trial agreement and oversight provided by the Sponsor.

The site Investigator(s)/delegate(s) will allow direct access to source data/documents for the purposes of auditing by the Sponsor, and inspection by regulatory authorities, both domestic and foreign (if applicable). It is important that the Sponsor, site Investigator and site personnel are available during audits and inspections, and that sufficient time is devoted to the process.

Auditing reports will be issued after each audit for review and follow up by the Sponsor, site Investigator, and appropriate management and personnel responsible for trial and site oversight.

As per the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), the sponsor will be responsible for implementing and maintaining quality assurance and quality control systems.

3TOphthalmics may additionally organize on-site monitoring of this study at their discretion and subject to appropriate contractual agreement with the Sponsor.

10.1.7 DATA HANDLING AND RECORD KEEPING

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Where the source data is not collected as part of the participant's medical record, hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Study data will be entered into paper or electronic ICFs, the latter utilizing clinical-trial appropriate electronic systems. Any electronic data collected specifically for the study will be maintained on secure servers provided by The Hospital for Sick Children.

10.1.7.2 STUDY RECORDS RETENTION

To enable evaluations and/or audits from Health Canada and/or the Sponsor, the Principal Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition in a secure location for a minimum of 25 years.

If the Principal Investigator relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

10.1.7.3 PROTOCOL DEVIATIONS

A protocol deviation is any non-compliance with the clinical trial protocol or Manual of Procedures (MOP) requirements, if applicable. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Sponsor and documented approval from the Research Ethics Board (REB), except where necessary to eliminate an immediate hazard(s) to the trial participants. The non-compliance 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. All protocol deviations will be documented; the Principal Investigator will assess each protocol deviation to determine the impact to the patient's rights, safety or welfare, study efficacy and data integrity. If there is any uncertainty regarding the impact of the protocol deviation, the Principal Investigator will consult with the Medical Monitor.

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents and reported to the Sponsor. Protocol deviations must be sent to the reviewing REB in accordance with their policies. The Principal Investigator is responsible for knowing and adhering to the reviewing REB requirements.

10.1.8 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The Hospital for Sick Children has established policies and procedures to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS

ADR	Adverse Drug Reaction

AE	Adverse Event
TNMH	Tumour Node Metastasis Heritability AJCC Cancer Staging 8th Edition
ANCOVA	Analysis of Covariance
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DLT	Dose limiting toxicity
DRE	Disease-Related Event
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
ES	Overall Eye Salvage
EUA	Examination under anesthetic
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
IAC	Intra-arterial chemotherapy
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IOP	Intraocular pressure
ISM	Independent Safety Monitor
ISO	International Organization for Standardization

ITT	Intention-To-Treat
IVitC	Intravitreal chemotherapy
LLOQ	Lower limit of quantification
LSMEANS	Least-squares Means
MOP	Manual of Procedures
MRP	Most Responsible Physician
MSDS	Material Safety Data Sheet
MTD	Maximum tolderated dose
NCT	National Clinical Trial
OD	Left eye
OS	Right eye or Overall Survival
PR	Partial response
PHIPA	Personal Health Information Protection Act
PI	Principal Investigator
PLGA	Poly Lactic-co-Glycolic Acid
PFS	Progression-free survival
PD	Progressive disease
QA	Quality Assurance
QC	Quality Control
REB	Research Ethics Board
RP2D	Recommended phase II dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan or Special Access Program
SMC	Safety Monitoring Committee
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SD	Stable Disease
SUADR	Serious unexpected adverse drug reaction
TNMH	Tumour Node Metastasis Heritability AJCC Cancer Staging 8th edition for retinoblastoma

TPT	Topotecan Hydrochloride
VGPR	Very good partial response

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12 APPENDICES

APPENDIX I: Performance status scales/scores

PERFORMANCE STATUS CRITERIA Karnofsky and Lansky performance scores are intended to be multiples of 10			
Karnofsky		**Lansky**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

Appendix II. Dose escalation chart

The following table provides the decision rules for enrolling a patient at (i) the current dose level, (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

# Patients enrolled	# Patients with DLT	# Patients without DLT	# Patients with data pending	Decision
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥2	0, 1, or 2	0, 1, or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate**
6	0	0, 1, 2, 3 or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3, 4 or 5	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

*If six patients already entered at next lower dose level, the MTD has been defined. If the lowest dose level is not tolerated, the study will close to accrual

** If final dose level has been reached, the recommended dose has been reached

If <6 patients have been treated at maximum tolerated dose (or RP2D if final dose level is reached), dose level will be expanded to ensure than 6 patients are treated at this dose level