CLINICAL RESEARCH PROTOCOL

DRUG:	ONL1204 Ophthalmic Solution
STUDY NUMBER:	ONL1204-RRD-001
PROTOCOL TITLE:	A Phase 1 Open-Label, Dose Escalation Study to Assess the Safety and Tolerability of Intravitreal ONL1204 in Patients with Macula-off, Rhegmatogenous Retinal Detachment
SPONSOR:	ONL Therapeutics 1600 Huron Pkwy Building 520, Second Floor Ann Arbor, MI 48109
ORIGINAL PROTOCOL DATE:	26 November 2018
VERSION NUMBER:	v.1.6
VERSION DATE:	27 JULY 2020

Clinical Protocol Approval Form

Protocol Title: A Phase 1 Dose Escalation Study to Assess the Safety, Tolerability, Pharmacokinetics and Ocular Pharmacodynamics of Intravitreal ONL1204 in Patients with Macula-off, Rhegmatogenous Retinal Detachment.

Study No: ONL1204-RRD-001

Original Protocol Date: 26 November 2018

Protocol Version No: v1.5

Protocol Version Date: 10 May 2020

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the sponsor. The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, ICH GCP, and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Sponsor (printed) Signature

[redacted] [redacted]

[redacted]

Date: July 29, 2020

ONL1204-RRD-001

A Phase 1 Open-Label, Dose Escalation Study to Assess the Safety and Tolerability of Intravitreal ONL1204 in Patients with Macula-off, Rhegmatogenous Retinal Detachment.

Confidentiality and Investigator Statement

The information contained in this protocol and all other information relevant to ONL1204 Ophthalmic Solution are the confidential and proprietary information of ONL Therapeutics, and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of ONL Therapeutics.

I have read the protocol, including all appendices, and I agree that it contains all of the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the International Conference on Harmonisation guidelines, and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by ONL Therapeutics or specified designees. I will discuss the material with them to ensure that they are fully informed about ONL1204 Ophthalmic Solution and the study.

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

Study Summary

Title: A Phase 1 Open-Label, Dose Escalation Study to Assess the Safety and Tolerability of Intravitreal ONL1204 in Patients with Macula-off, Rhegmatogenous Retinal Detachment.

Rationale: The purpose of this study is to evaluate the safety and tolerability of ONL1204 in Patients with Macula-off, Rhegmatogenous Retinal Detachment (RRD). RRD is an acute and serious vision threatening condition in which a tear in the retina, typically resulting from a vitreous detachment, allows liquefied vitreous to enter the subretinal space, detaching the photoreceptor (PR) layer of the neurosensory retina from the retinal pigment epithelium (RPE). As the RPE is the principal source of nutritional support for the PR layer, the photoreceptors begin a cascade of inflammation and cell death. Photoreceptor cell death is the primary mechanism of vision loss after retinal detachment.

ONL1204 is a first-in-class inhibitor of Fragment Apoptosis Stimulator receptor (Fas)-mediated cell death. ONL1204 has demonstrated protection of multiple retinal cell types in numerous preclinical models of acute ocular injury.

This will be a first-in-human (FIH) study to evaluate safety and tolerability of a single-dose of ONL1204 in patients with macula-off RRD.

The standard of care for surgical repair of macula-off RRD is reattachment surgery (typically by vitrectomy with or without scleral buckling) within 7 days of the macula detaching. Patients will receive a single intravitreal injection upon enrollment in the study on the day of diagnosis. The vitrectomy procedure will remove the bulk of drug remaining in the vitreous.

Target Population: Patients who present between 1 week (7 days) to 4 weeks (28 days) of a macula-off RRD (based on patient-reported history of loss of central vision) for whom standard retinal reattachment surgery by means of a pars plana vitrectomy and gas tamponade is indicated.

Number of Patients: Approximately 16 patients will be enrolled in this study.

- 4 ascending dose groups; 4 active. The first patient in each dose group will be observed for at least 14 days post-surgery (through visit 6) prior to enrolling the remainder of the patients in that dose group.
- Patients may be replaced who do not receive an injection of study medication, or for discontinuing from the study for reasons unrelated to treatment before completing Visit 4. All patients receiving injection of study drug will be followed for safety and tolerability.

Study Visits There is a minimum of 8 scheduled study visits:

- Visit 1: Day 1 (baseline/drug injection)
- Visit 2: Day 2 (1 day post-injection*)
- Visit 3: Day of Vitrectomy (3 + days post-injection in accordance with standard of care vitrectomy)
- Visit 4: Postoperative visit (1 day post-surgery)
- Visit 5: Post-operative visit (2 weeks post-surgery and clearance of sentinel patient/cohort (14 days +4 days post-surgery))
- Visit 6: Week 6 (±7 days)
- Visit 7: Week 9 (±7 days)
- Visit 8: Week 24/Exit (±14 days)

*additional visits between visit 2 and 3 per investigator's discretion

Objectives: To evaluate safety and tolerability of a single intravitreal injection of ONL1204 in patients with macula-off, RRD.

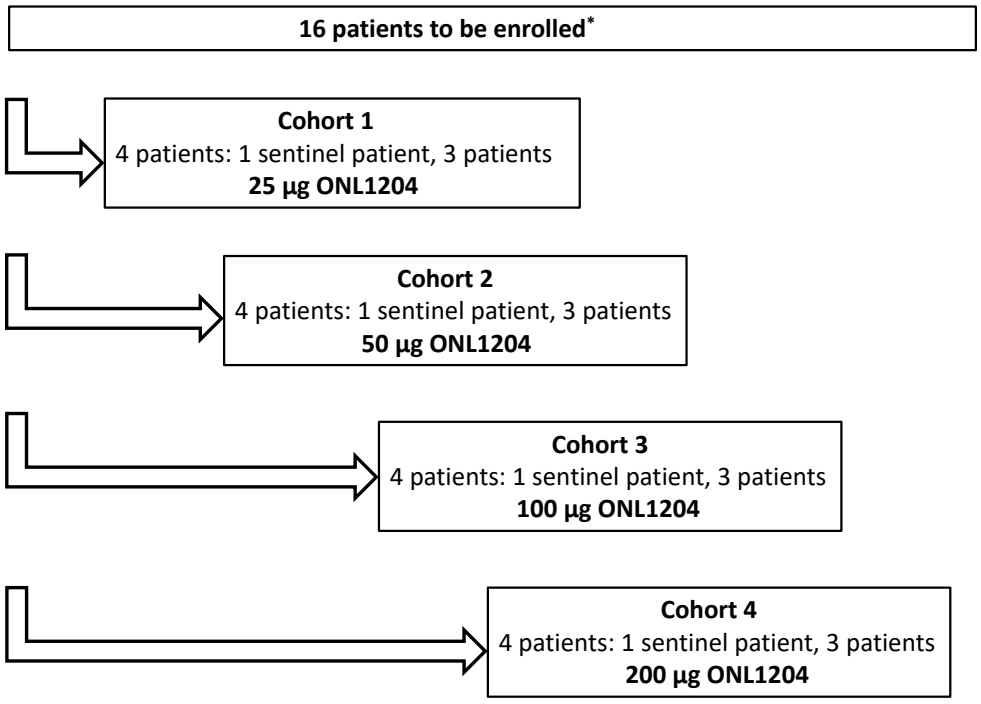
Study Design: This is a single-injection, open-label dose escalation study.

Primary Objective: The primary objective will be to determine the Maximum Tolerated Dose (MTD) of ONL1204 and select doses for Phase 2. Determination of this will be through review of the parameters measured in the Schedule of Assessments, as well as adverse event (AE) reports.

Exploratory Objective:	During the study, ocular fluid samples will be collected at the time of study drug injection and at the time of vitrectomy. These samples will be used for pharmacokinetic and pharmacodynamic analyses, the results of which will help inform the dose selection for the Phase 2 trial(s).

STUDY SCHEMATIC

Figure 1 Study Schematic



16 patients will be enrolled and treated, starting with the lowest dose, Cohort 1. The first patient in each cohort will be observed for at least 14 days post surgery (through Visit 5) before the rest of the cohort can be enrolled. The safety review committee will review the data prior to clearing the sentinel patient and enrolling the remainder of the cohort. After all 4 patients in a cohort have completed Visit 5, the safety review committee will review available safety data to determine if dose limiting toxicity exists that prohibits enrolling the next higher dose cohort. The respective IRB's will be informed of the outcome of the SRC meetings.
If there are no safety concerns, the next cohort will start treatment.

*Patients may be replaced who do not receive an injection of study medication, or for discontinuing from the study for reasons unrelated to treatment before completing Visit 4.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BCVA	Best Corrected Visual Acuity
BUN	Blood Urea Nitrogen
°C	Degrees Centigrade
CRA	Clinical Research Associate
CRO	Contract Research Organization
CV	Coefficient of Variation
dUTP	Deoxynucleotidyl Transferase
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ETDRS	Early Treatment Diabetic Retinopathy Study
°F	Degrees Fahrenheit
Fas	Fragment Apoptosis Stimulator
FIH	First-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCT	Hematocrit
HGB	Hemoglobin
HREC	Human Research Ethics Committee
ICB	Iris-Ciliary Body
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IL	Interleukin
IOP	Introcular Pressure
ITT	Intent to Treat

IVT	Intravitreal
LLOQ	Lower Limit of Quantitation
MARS	Muenster Aging and Retina Study
mg	Milligram
mL	Milliliter
mM	Millimolar
mmHg	Millimeters Mercury
MOP	Manual of Procedures
MTD	Maximally Tolerated Dose
ng	nanogram
ONL	ONL Therapeutics
OU	Both Eyes (*oculus uterque*)
PD	Pharmacodynamic
PK	Pharmacokinetic
Post-op	Postoperative;
PR	Photoreceptor
PT	Prothrombin Time
RIPK3	Receptor Interacting Protein Kinase 3
RPE	Retinal Pigment Epithelium
RRD	Rhegmatogenous Retinal Detachment
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD OCT	Spectral Domain Optical Coherence Tomography
SE	Study Eye
SOC	Standard of Care
SRC	Safety Review Committee
SUN	Standardization of Uveitis Nomenclature
TUNEL	Terminal dUTP Nick End Labeling
UA	Urine analysis
µg	Microgram

μM	Micromolar
WBC	White Blood Cell

1 INTRODUCTION AND RATIONALE

1.1 Background

Retinal detachment is an ocular condition that involves the retina being separated from the underlying layer of cells, including the retinal pigment epithelium (RPE). This separation often results in the death of key retinal cells, including photoreceptors, which can lead to vision impairment and/or loss.

The most prevalent form of retinal detachment is rhegmatogenous retinal detachment (RRD), which involves a tear in the retina. While standard of care (SOC) surgical reattachment results in high rates of anatomic surgical success, in many cases, especially those involving the macula (central vision), patients have significant loss of vision even with successful surgery. In part, this is due to the fact that photoreceptors begin to die once the detachment takes place and cell death continues up to the time of surgery (sometimes as long as a week after the detachment).

ONL Therapeutics (ONL) is developing ONL1204, a first-in-class inhibitor of Fragment Apoptosis Stimulator (Fas)-mediated cell death that has demonstrated protection of multiple retinal cell types in numerous preclinical models of acute ocular injury. The development of ONL1204 addresses an unmet medical need: the prevention of vision loss in patients suffering from deterioration of visual function after acute retinal injury such as from macula-off RRD.

Refer to the Investigator's Brochure (IB) for more information.

1.2 ONL1204

The investigational study agent is ONL1204 Ophthalmic Solution. The drug product consists of the drug substance ONL1204 dissolved in a vehicle consisting of purified water containing mannitol, poloxamer 407, and glacial acetic acid. The pH is adjusted to pH 4.5 by sodium hydroxide solution. ONL1204 Ophthalmic Solution is provided as a sterile liquid in single-use vials stored at 2 to 8°C (36 to 46°F) and is administered by intravitreal (IVT) injection.

1.2.1 Preclinical Experience

The sponsor has observed a pharmacological effect of ONL1204 in preventing Fas-mediated cell death in 3 models of acute retinal injury – namely the rat retinal detachment model, the rabbit sodium iodate model, and the mouse microbead model of glaucoma.

ONL1204 disrupts the binding of human Fas ligand to the human Fas receptor in vitro, while ONL1204 analog Met12 has been shown to bind to Fas receptor and prevent Fas

ligand activated cell death in human Jurkat cells in vitro. The available nonclinical data from completed studies indicates that ONL1204 has efficacy towards the Fas ocular receptor based on the in vitro inhibition of caspase activity with a potency of 0.4 to 0.45 μM.

In vivo, administration of ONL1204 by IVT injection at doses of up to 10 μg/eye resulted in a reduction of terminal deoxynucleotidyl transferase (dUTP) nick end labeling (TUNEL) positive staining cells in a rat model of retinal detachment. There was an approximate 75% reduction in the percent positive staining cells across the dose range examined. The minimal, maximally effective dose for ONL1204 was 0.1 to 0.3 μg. Pharmacological activity towards the Fas receptor did not differ with different formulations of ONL1204, though poloxamer formulations appeared to have preferable pharmaceutical properties.

To study the potential role of ONL1204 in geographic atrophy, ONL conducted a sodium iodate study in rabbits. Sodium iodate is highly toxic to the retinal pigment epithelium and is a commonly used model for geographic atrophy. IVT injection of ONL1204 at 0.1 or 0.025 mg 4 days prior to sodium iodate injection preserved the RPE, suggesting that ONL1204 may also be useful in treating geographic atrophy.

In a microbead model of glaucoma, data suggest that ONL1204 can also inhibit the production of macrophage and Receptor Interacting Protein Kinase 3 (RIPK3)-dependent inflammasome activation, which exacerbates retinal detachment-induced photoreceptor cell death through the release of interleukin (IL)-1β.

In pharmacokinetic (PK) studies, ONL1204 is distributed to the retina, iris-ciliary body (ICB), and vitreous with IVT injection. Following injection, the drug is slowly eliminated from these ocular structures. The prolonged elimination of the drug is considered clinically meaningful for use in RRD where patients may not undergo surgical repair for several days following injection. However, the clinical plan for retinal detachment includes a vitrectomy within 7 days after injection, which will remove the bulk of the drug remaining in the vitreous.

Based on the pharmacodynamic (PD) and preliminary toxicity data, ONL has chosen the 4.5% mannitol, 0.4% poloxamer 407, and 10 mM acetic acid (pH 4.5) formulation to be used in further development of ONL1204. There was acceptable (minimal to mild) ocular toxicity in the rabbit with this formulation and the current drug formulation of ONL1204. Moreover, ONL1204 was undetectable in the rabbit plasma (lower limit of quantification [LLOQ]: 1 ng/mL) following a total dose equal to the planned top dose in humans resulting in no systemic toxicity after full histopathologic examination of all major organs.

Good Laboratory Practice (GLP) compliant toxicity studies using this formulation of ONL1204 are completed.

Preclinical data thus far indicate the intended clinical formulation at the top dose (200 μg) to be used in clinical trials should have an acceptable safety profile over a 14-day period following IVT injection.

Refer to the IB for detailed information on the nonclinical studies conducted using ONL1204.

1.2.2 Clinical Experience

ONL1204 has not been previously studied in humans; this will be the first-in-human (FIH) study of ONL1204. Since there are no clinical data for ONL1204, the observed findings in nonclinical studies with ONL1204 will guide the monitoring in this study.

1.3 Study Rationale

The purpose of this Phase 1 study is to collect safety information of ONL1204 in patients, establish a safe dose range, and collect PK and ocular PD information.

The study population will be patients with newly diagnosed macula-off RRD. Patients with RRD have an acute and serious vision threatening condition where a tear in the retina, typically resulting from a vitreous detachment, allows liquefied vitreous to enter the subretinal space, thereby detaching the photoreceptor (PR) layer of the neurosensory retina from the RPE. As the RPE is the principal source of nutritional support for the PR layer, the photoreceptors begin a cascade of inflammation and cell death. Nonclinical data on ONL1204 suggest that ONL1204 may inhibit the cell death pathway in RRD, preventing vision loss in patients suffering from acute retinal injury such as from macula-off RRD.

In clinical use, ONL1204 will be delivered to patients by intravitreal injection at the time of diagnosis to protect photoreceptors from death until surgery can be completed, with the hope of improving positive patient outcomes from already anatomically successful surgeries.

1.3.1 Rationale for the Proposed Doses

As described in 1.2.1 the minimal, maximally effective dose in the rat model of retinal detachment delivered by an IVT injection was 0.1 to 0.3 ug per eye. Based on scaling of this MMED from the rat eye to the human eye, the calculation is as follows: the vitreous volume of a rat eye is 13-20 microliters, while that of the human is approximately 4,400 microliters (a factor of 220-338x). With the MMED being estimated at 0.1 micrograms in the rat, this scales to a dose of 22-34 micrograms in the human eye. This dose escalation study starts at a 25 microgram dose and increases to 50 micrograms in the next

cohort, followed by a 100 microgram cohort and 200 micrograms in last dose escalation cohort.

As stated, the maximum dose planned for this trial is 200 µg. In animal studies, using Dutch Belted rabbits, this dose was intravitreally injected into one eye while the contralateral eye served as an untreated control. The findings from this study suggested the current formulation at the top dose (200 µg) to be used in GLP-compliant nonclinical studies and in clinical trials should have an acceptable safety profile over a 14-day period following IVT injection, especially given that the allometrically scaled dose in the rabbit is approximately 2-fold greater than the planned high dose intended for this initial clinical trial.

The following doses will be evaluated: 25 µg, 50 µg, 100 µg and 200 µg ONL1204. ONL1204 will be administered as a sterile liquid by intravitreal injection. Patients randomized to receive the treatment will be given one injection of the drug.

1.3.2 Rationale for Pharmacokinetic testing

Systemic PK will be evaluated following IVT administration of ONL1204. ONL1204 is not expected to be detected in the plasma and this will be confirmed in this study, which will preclude additional systemic PK evaluation in future studies.

ONL1204 will also be measured in the vitreous samples taken at the time of the vitrectomy to evaluate clearance of the drug from the vitreous.

1.3.3 Rationale for Vitreous Tap and Pharmacodynamic Analysis

A vitreous tap will be performed at the time of diagnosis/IVT injection of drug, and an undiluted vitreous sample as well as aqueous sample will be taken at time of surgery. This will allow for assessment of the cytokine profile before and several days after administration of ONL1204. This will allow for the potential identification of a biomarker for proof of principle of target engagement, via analysis of cytokines and other potential molecular biomarkers that impact visual acuity after surgical repair of retinal detachment. The described procedures are routine for retinal surgeons, with the risk of endophthalmitis thought to be similar to that of IVT injections (1 in 2000-3000 patients).

1.4 Potential Risks and Benefits

1.4.1 Potential Risks of Study Product

There could be a risk of an adverse reaction to the ONL1204 drug product or vehicle.

Although unlikely, potential risks include:

- Intraocular inflammation
- Elevated intraocular pressure
- Visual loss
- Retinal cell death
- Less favorable surgical outcome following repair
- Systemic adverse reaction

Patients will be carefully monitored after vitreous tap and intravitreal injection of ONL1204, with multiple post procedure visits with the investigator. At these visits, visual acuity will be assessed, intraocular pressure measured, the eyes examined according to assessments listed in 6.4.2, and any adverse events (AEs) reviewed. Based on these assessments, additional visits may be scheduled at investigator discretion. This close monitoring for inflammation, infection, and changes in vision will help reduce associated risks.

There is a remote risk of systemic adverse reaction in response to intravitreal injection of ONL1204. This risk is greatly mitigated by the study molecule's long half-life in vitreous (most drug stays in the eye until surgery) and extremely short half-life in plasma. Patients will undergo clinical blood testing, with assessment of complete blood count, renal function tests and hepatic function tests to monitor for any such systemic adverse reactions.

1.4.2 Potential Risk to Fetal Development

Potential risk to fetal development is unknown. Therefore, all female patients of childbearing potential must have a negative pregnancy test before being enrolled in this study, and all participants must use adequate contraceptive precautions during the study, Section 6.4.9.

1.4.3 Potential Risks of Intravitreal Injection, Vitreous Tap, Pupil Dilation and Blood Draw

Intravitreal injection and vitreous tap are common procedures, but both do carry the risk of possible adverse reaction including:

- Infection
- Inflammation
- Irritation
- Pain
- Bleeding
- Increased intraocular pressure
- Retinal holes/retinal tears
- Retinal detachments
- Cataract
- Worsened vision/vision loss/loss of eye
- Corneal abrasion

Pupil dilation is also a common procedure during an eye exam but carries a risk of possible adverse reaction including:

- Redness
- Stinging/discomfort
- Allergic reactions
- Sensitivity to light
- Blurred vision

The procedure of blood draw, even though a common procedure carries the risk of possible adverse reactions such as:

- Pain/discomfort
- Bruising
- Infection
- Fainting

Care will be taken to reduce the risk of infection at the time of the tap and intravitreal injection through antisepsis, sterile technique and expert care as these procedures will be performed by experienced retinal surgeons.

1.4.4 Potential Risks of Vitrectomy

Any surgical intervention has risk, and the risks associated with retinal detachment repair are not insignificant. Patients in this trial, however, will receive the same retinal surgery whether they participate in this trial or not so retinal surgery is not a study specific risk. Potential participants in this study have been diagnosed with macula-off, rhegmatogenous retinal detachment and will be undergoing standard retinal reattachment surgery by means of a pars plana vitrectomy (with or without scleral buckle) and gas tamponade. The surgeon will fully discuss the possible risks of this surgery with the patient prior to the surgery.

1.4.5 Potential Benefit of Study Product

There is a possibility that ONL1204 could prevent photoreceptor cell death, ultimately resulting in better visual acuity in patients treated with ONL1204; however, this is not known.

2 STUDY OBJECTIVE

2.1 Primary Objective

The primary objective will be to determine the Maximum Tolerated Dose (MTD) of ONL1204 and select doses for Phase 2. Determination of this will be through review of the parameters measured in the Schedule of Assessments, as well as adverse event (AE) reports.

2.2 Exploratory Objective

During the study, ocular fluid samples will be collected at the time of study drug injection and at the time of vitrectomy. These samples will be used for pharmacokinetic and pharmacodynamic analyses, the results of which will help inform the dose selection for the Phase 2 trial(s).

3 STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoints will be the safety profile demonstrated in this study, including:

- Adverse event reporting
- Clinical evaluations including BCVA
- Clinical laboratory evaluation

3.2 Exploratory Endpoints

The exploratory endpoints will be the pharmacokinetic and pharmacodynamic analyses performed in this study, including:

- Measurement of ONL1204 drug levels in plasma and vitreous fluid for PK analysis
- Cytokine and other potential molecular biomarker measurement in aqueous and vitreous samples, taken by vitreous tap, and at vitrectomy

4 STUDY DESIGN

This proposed study is a single-injection, open-label, dose escalation study to assess the use of intravitreal ONL1204 in patients with macula-off RRD. Approximately 16 patients with RDD will be enrolled. The expected duration of patient participation in the study is approximately 24 weeks (treatment, then 24 weeks of follow-up).

4.1 Overview of Study Design

Sixteen patients will be enrolled in 4 ascending dose groups.

After signing informed consent and meeting all eligibility criteria, patients will undergo a vitreous tap for cytokine and other potential molecular biomarker analysis followed by a single intravitreal injection of ONL1204. This will occur on the day of diagnosis (Day 1). Safety visits will be conducted 1 day post-injection and per Investigator's discretion until Visit 3. At Visit 3 (3+ days post-injection, in accordance with standard of care) patients will undergo surgical repair of their retinal detachment with vitrectomy (with or without scleral buckling) and gas or oil tamponade. At the time of surgery, an undiluted vitreous sample will be collected for pharmacokinetic and pharmacodynamics analyses, and an aqueous sample will be collected for pharmacodynamic analysis. Additional safety visits will be conducted 1 day post-surgery, 14 (+4 days) days post-surgery, Weeks 6, 9 (±7 days each), and Week 24 (±14 days; study exit).

As this is a first-in-human safety study of ONL1204, the first patient in the first cohort will receive the lowest dose of ONL1204. After this patient completes Visit 5 (14 +4 days post-surgery) and a safety review committee reviews the data, the remainder of the patients in that cohort will be enrolled. After all patients in the cohort have completed Visit 5, the SRC will review the available safety data to determine if dose

limiting toxicity exists that prohibits enrolling the next higher dose cohort. This process will be repeated until escalating to the top dose.

The following doses will be evaluated: 25 µg, 50 µg, 100 µg, and 200 µg ONL1204. ONL1204 is available in vials with concentrations of 0.5 mg/mL and 2 mg/mL. Therefore, a volume of 0.05 or 0.1 mL will be injected into the study eye.

Patient participation will be approximately 24 weeks (6 months): a single injection treatment and 24 weeks of follow-up.

4.1.1 Treatment Masking

This is an open-label study and all patients will be receiving study drug.

4.2 Dose Limiting Criteria and Maximum Tolerated Dose

4.2.1 Dose Limiting Criteria

Dose limiting toxicity, if observed, will be declared by the SRC, based on their review of the relevant clinical information.

Determination of dose limiting toxicity will include consideration of the following events:

1. Ocular inflammation increases by 2 units from pre-injection on the Standardization of Uveitis Nomenclature (SUN) grading scale for aqueous cell or vitreous haze, secondary to inflammation and not the drug formulation itself, identified post-injection of ONL1204 and prior to retinal reattachment surgery;

2. Sustained elevation of IOP characterized as > 30 mmHg for 3 consecutive days, post-injection of ONL1204 and prior to retinal reattachment surgery, despite pharmacologic therapy;

3. Reduction in visual acuity from baseline after injection of ONL1204 and prior to retinal reattachment surgery, that in the opinion of the investigator is likely due to the investigational product and results in a:

    a) Decrease in visual acuity from 20/200 or 20/400 to light perception without progression of the underlying retinal detachment; or

    b) Decrease in visual acuity from baseline to no light perception.

4. Any serious adverse event (SAE) that occurs within the first 14 days following ONL1204 injection that, in the opinion of the investigator, is related to ONL1204.

4.2.2 Dose Escalation Decisions

Dose escalation decisions include the following:

1. To begin enrolling the next cohort at the planned dose or an adjusted dose.

2. To delay opening the next cohort in order to collect additional safety on the current cohort, or to enrol additional patients in the current cohort if safety concerns are identified.

3. To stop the cohort escalation if unacceptable toxicities are noted.

If, in the opinion of SRC, dose limiting toxicity is reached, the previous, lower dose will be considered the Maximum Tolerated Dose (MTD).

4.3 Schedule of Assessments

Table 4-1 Schedule of Study Procedures and Assessments

Study Visit	**Visit 1 Day 1**			**Visit 2 Day 2 ([1],**	**Visit 3 (Day 4 +)**	**Visit 4**	**Visit 5**	**Visits 6, 7**	**Visit 8**	**Unscheduled Visit(s)**
	Baseline[2]/ Injection			**1 day Post-Injection**	**3 + days Post-Injection) Day of Surgery (Vitrectomy)[3]**	**1 Day Post-Surgery**	**14 Days (±4 days) Post-Surgery**	**Weeks 6, 9 (±7 days)**	**Week 24 (±14 days) Exit or early termination**	
Assessment	**Pre-Injection**	**Study Drug IVT**	**Post-Injection**							
Informed Consent	**X**									
Medical History	**X**									
Demographics	**X**									

Note: Screening procedures are in red.
Abbreviations: AE = Adverse event; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = Intraocular pressure; PK = Pharmacokinetic; Post-op = Postoperative; OU = Both eyes; SD OCT = Spectral Domain Optical Coherence Tomography; SE = Study eye; UA = Urine analysis.
[1] IOP > 30 mmHg requires consecutive daily visits until resolved or vitrectomy. Visits between visit 2 and 3 may be added per investigator's discretion.
[2] All baseline procedures to be done before injection, except blood draw for ONL1204 levels and PK sample (may be drawn with clinical laboratory evaluations, and 1 hour [±15 minutes] after injection), and AE reporting, (pre- and post-injection). If injection is scheduled for early morning, baseline procedures can be done the day before surgery.
[3] All Visit 3 procedures are to be performed before vitrectomy.

Study Visit	**Visit 1 Day 1**			**Visit 2 Day 2 ([1],**	**Visit 3 (Day 4 +)**	**Visit 4**	**Visit 5**	**Visits 6, 7**	**Visit 8**	**Unscheduled Visit(s)**
	Baseline[2]/ Injection			**1 day Post-Injection**	**3 + days Post-Injection) Day of Surgery (Vitrectomy)[3]**	**1 Day Post-Surgery**	**14 Days (±4 days) Post-Surgery**	**Weeks 6, 9 (±7 days)**	**Week 24 (±14 days) Exit or early termination**	
Assessment	**Pre-Injection**	**Study Drug IVT**	**Post-Injection**							
Concomitant Medications	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Vital Signs	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**
Height and weight	**X**									
Pregnancy Test (UA) (females only)	**X**								**X**	
ETDRS Best Corrected Visual Acuity	**OU**			**OU**				**OU**	**OU**	**SE[4]**
Clinical Laboratory Evaluation	**X**		**X**		**X**				**X**	

Note: Screening procedures are in red
Abbreviations: AE = Adverse event; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = Intraocular pressure; PK = Pharmacokinetic; Post-op = Postoperative; OU = Both eyes; SD OCT = Spectral Domain Optical Coherence Tomography; SE = Study eye; UA = Urine analysis.
[4] OU if clinically indicated.

Study Visit	**Visit 1 Day 1**			**Visit 2 Day 2 ([1],**	**Visit 3 (Day 4 +)**	**Visit 4**	**Visit 5**	**Visits 6, 7**	**Visit 8**	**Unscheduled Visit(s)**
	Baseline[2]/ Injection			**1 day Post-Injection**	**3 + days Post-Injection) Day of Surgery (Vitrectomy)[3]**	**1 Day Post-Surgery**	**14 Days (±4 days) Post-Surgery**	**Weeks 6, 9 (±7 days)**	**Week 24 (±14 days) Exit or early termination**	
Assessment	**Pre-Injection**	**Study Drug IVT**	**Post-Injection**							
Blood Sampling for Plasma ONL1204 PK			**X[5]**	**X**	**X**		**X**	**X[6]**	**X**	
Study Drug IVT		**X**								
Pin Hole Visual Acuity						**OU**				
Low Luminance ETDRS Best Corrected Visual Acuity								**OU**	**OU**	
Low Contrast ETDRS Best Corrected Visual Acuity								**OU**	**OU**	
Contrast Sensitivity Testing								**OU**	**OU**	
Farnsworth D15 Color vision test									**OU**	

[5] Post-injection blood sample for plasma PK to be drawn 1 hour (± 15 minutes) after study drug IVT.
[6] Blood sample for plasma PK to be drawn only on Visit 7 (week 9)

Study Visit	**Visit 1 Day 1**			**Visit 2 Day 2 ([1],**	**Visit 3 (Day 4 +)**	**Visit 4**	**Visit 5**	**Visits 6, 7**	**Visit 8**	**Unscheduled Visit(s)**
	Baseline[2]/ Injection			**1 day Post-Injection**	**3 + days Post-Injection) Day of Surgery (Vitrectomy)[3]**	**1 Day Post-Surgery**	**14 Days (±4 days) Post-Surgery**	**Weeks 6, 9 (±7 days)**	**Week 24 (±14 days) Exit or early termination**	
Assessment	**Pre-Injection**	**Study Drug IVT**	**Post-Injection**							
Intraocular Pressure[7]	**OU**			**OU**	**SE**	**OU**	**OU**	**OU**	**OU**	**SE[4]**
Slit Lamp Biomicroscopy	**OU**			**OU**		**OU**	**SE**	**OU**	**OU**	**SE[4]**
Indirect Ophthalmoscopy	**OU**			**OU**		**OU**	**SE**	**OU**	**OU**	**SE[4]**
Fundus Photography	**OU**								**OU**	
ONL1204 Fundus Autofluorescence									**OU**	
B Scan Ultrasonography (optional)	**SE**									
SD OCT	**OU**							**SE**	**OU**	**SE**

Note: Screening procedures are in red
Abbreviations: AE = Adverse event; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = Intraocular pressure; PK = Pharmacokinetic; Post-op = Postoperative; OU = Both eyes; SD OCT = Spectral Domain Optical Coherence Tomography; SE = Study eye; UA = Urine analysis.
[7] iCare Tonometry and Tonopen methods of measurement are acceptable.

Study Visit	**Visit 1 Day 1**			**Visit 2 Day 2 ([1],**	**Visit 3 (Day 4 +)**	**Visit 4**	**Visit 5**	**Visits 6, 7**	**Visit 8**	**Unscheduled Visit(s)**
	Baseline[2]/ Injection			**1 day Post-Injection**	**3 + days Post-Injection) Day of Surgery (Vitrectomy)[3]**	**1 Day Post-Surgery**	**14 Days (±4 days) Post-Surgery**	**Weeks 6, 9 (±7 days)**	**Week 24 (±14 days) Exit or early termination**	
Assessment	**Pre-Injection**	**Study Drug IVT**	**Post-Injection**							
Vitreous Tap for Cytokine / Biomarker Analysis	**SE**									
Undiluted Vitreous Collection for Cytokine / Biomarker Analysis and ONL1204 Drug Levels					**SE**					
Anterior Chamber Tap for Cytokine / Biomarker Analysis					**SE**					
Adverse Events	**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

Note: Screening procedures are in red
Abbreviations: AE = Adverse event; ETDRS = Early Treatment Diabetic Retinopathy Study; IOP = Intraocular pressure; PK = Pharmacokinetic; Post-op = Postoperative; OU = Both eyes; SD OCT = Spectral Domain Optical Coherence Tomography; SE = Study eye; UA = Urine analysis.

5 STUDY POPULATION

5.1 Number of Patients

The study population includes approximately 16 patients to be enrolled at 2 primary sites in Australia. Additional sites will be available, if enrollment at the primary sites does not meet timeline goals.

5.2 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Males and females, ≥ 18 to 80 years old

2. Able to give informed consent and comply with all study visits and procedures

3. Patients who:

    a) Present between 1 week (7 days) and 4 weeks (28 days) of a macula-off RRD (based on patient-reported history of loss of central vision)

    b) For whom standard retinal reattachment surgery by means of a pars plana vitrectomy (with or without scleral buckle) and gas or oil tamponade is indicated, and

    c) In the opinion of the investigator, can safely undergo all study procedures.

4. Best corrected Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity of 20/100 to hand motion in the study eye

5. Best corrected ETDRS visual acuity in the fellow eye of 20/60 or better

5.3 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Presence of giant retinal tear defined as greater than 3 clock hours or other type of complex retinal detachment in the study eye

2. Presence of vitreous hemorrhage in the study eye

3. Presence of ocular or periocular infection or intraocular inflammation in either eye

4. Intraocular Pressure > 22 mmHg in the study eye

5. Any other significant ocular disease in the study eye including media opacity that, in the opinion of the investigator, would preclude a visual acuity of at least 20/25 following successful vitrectomy or limit adequate visibility of the retina

6. Any other ocular pathology in the study eye requiring treatment with topical ophthalmic drops or intravitreal injection

7. History of previous ocular surgery in the study eye other than uncomplicated cataract surgery with posterior chamber intraocular lens and intact posterior capsule or a refractive surgery (surgery must have occurred at least 3 months prior to the baseline visit)

8. Participation in other clinical trials or use of any other investigational drugs or devices within 3 months prior to study participation

9. Females who are pregnant or lactating and women of childbearing potential who are not using adequate contraceptive precautions (e.g., intrauterine device, oral contraceptives, barrier method, or other contraception deemed adequate by the investigator)

10. Known retinopathy, known hepatic disease (or history of significant chronic liver disease), or known renal disease. Patients with diabetes and no known retinopathy may be enrolled

11. History of uncontrolled hypertension

12. History of stroke, transient ischemic attack, or major cardiac surgery within 3 months prior to study, or current treatment for systemic infection

13. Any ocular or systemic condition that in the opinion of the investigator could compromise the safety of the patient, or may interfere with the safety and tolerability assessments or study procedures of the trial

6 STUDY CONDUCT

This trial will be conducted in compliance with the study protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

6.1 Study Personnel and Organizations

A full list of investigators is available in the sponsor's investigator database.

6.2 Treatment Assignment

All patients will receive study drug in 1 of 4 treatment cohorts.

6.3 Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians.

6.4 Study Procedures and Assessments

6.4.1 Study Visits

There is a minimum of 10 scheduled study visits:

- Visit 1: Day 1 (baseline/injection)
- Visit 2: Day 2 (1day post-injection)
- Visit 3: Day of Vitrectomy (3 + days post-injection in accordance with standard of care)
- Visit 4: Postoperative visit (1 day post-surgery)
- Visit 5: Clearance of sentinel patient/cohort Day 14 (+4 days) post-surgery
- Visit 6: Week 6 (±7 days)
- Visit 7: Week 9 (±7 days)
- Visit 8: Week 24/Exit (±14 days)

Patients may return for a non-scheduled visit at any time if deemed appropriate by the investigator.

6.4.2 Study Procedures

Refer to the Schedule of Assessments (Table 4-1) for the timing of procedures. Additional details are provided as necessary in the manual of procedures (MOP), and in the sections that follow. A list of study procedures for this study is below:

- Vital signs
- Height and weight
- Clinical laboratory evaluation
- ETDRS BCVA at 3 meters
- Pin Hole Visual Acuity
- Low Luminance BCVA at 3 meters
- Low Contrast BCVA (2.5%)
- Contrast Sensitivity using the Muenster Aging and Retina Study (MARS) system
- Farnsworth D15 Color Vision Test
- Intraocular Pressure
- Slit Lamp Biomicroscopy
- Indirect Ophthalmoscopy
- Fundus photography
- Fundus autofluorescence
- Spectral Domain Optical Coherence Tomography (SD OCT)
- B scan ultrasonography of the affected eye with measurement of the height of detachment at the macula (this assessment is optional)
- Plasma ONL1204 levels
- Vitreous tap for inflammatory cytokine and other potential molecular biomarker analysis at baseline (post-injection) and vitreous sampling (non-diluted) for cytokine

and other potential molecular biomarker analysis and ONL 1204 levels at time of vitrectomy

- Anterior chamber fluid (tap) for cytokine and other potential molecular biomarker analysis, and ONL1204 levels at baseline and at the time of vitrectomy
- Injection of ONL1204
- Urine pregnancy test (females of childbearing potential only)

Additional Procedure:

- Standard of care vitrectomy (with or without scleral buckling) with gas tamponade

6.4.3 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

6.4.4 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded at baseline.

6.4.5 Medical History and Prior Medications

During baseline, a complete medical history will be compiled for each patient. In addition, medications taken by the patient 30 days prior to the IVT injection and throughout the study will be recorded.

6.4.6 Patient Height and Weight

Height and weights will be measured only during baseline visit.

6.4.7 Vital Signs

Vital signs will be assessed at the times specified in the Schedule of Assessments (Table 4-1). Vital signs will consist of sitting blood pressure, heart rate, respiratory rate, and body temperature.

6.4.8 Pregnancy Test

A urine pregnancy test will be performed for women of childbearing potential at Visit 1, pre-injection. Negative results must be available before the study drug is administered. A urine pregnancy test will also be repeated at the exit visit.

6.4.9 Contraception and Pregnancy Avoidance Measures

Due to the unknown effects of ONL1204 on sperm and the developing fetus, female patients of childbearing potential (i.e., non-sterilized, premenopausal female patients) and male patients must agree to use double barrier contraception methods throughout the study and for at least 30 days after the dose of study drug. Double barrier contraception is defined as a condom and one other form of the following: a) Birth control pills (The Pill), b) Depot or injectable birth control, c) IUD (Intrauterine Device), d) Birth control patch (e.g. Ortho Evra), e) NuvaRingR, f) Documented evidence of surgical sterilization at least 6 months prior to the study drug injection, i.e., tubal ligation or hysterectomy for women or vasectomy for men. Rhythm methods during the study and for at least 30 days after the dose of study drug will not be acceptable.

Male patients must not donate sperm for at least 24 weeks post-dose of the last study treatment. Male partners of female patients and female partners of male patients must also use contraception, if they are of childbearing potential.

6.4.10 Clinical Laboratory Tests

The following clinical laboratory tests will be performed, according to the Schedule of Assessments (Table 4-1):

- Complete blood count, including: white blood cell (WBC) count with differential, hemoglobin (hgb), hematocrit (hct), and platelet count.

- Renal function tests, including: albumin, blood urea nitrogen (BUN), bicarbonate, calcium, chloride, creatinine, eGFR, glucose, phosphorus, potassium, and sodium.

- Hepatic function tests, including: alanine transaminase (ALT), alkaline phosphatase (ALP), albumin and total protein, aspartate transaminase (AST), bilirubin, and prothrombin time (PT).

6.4.11 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the electronic Case Report Form (eCRF) from 30 days before treatment with study drug through the 24-week follow-up period of the study, or study exit.

6.5 Pharmacokinetics

Systemic PK will be evaluated following IVT administration of ONL1204. ONL1204 will also be measured in the vitreous samples taken at the time of the vitrectomy. Samples will be shipped for PK analysis when available for each dose escalation cohort. Refer to the MOP for instructions.

6.6 Ocular Pharmacodynamics

Exploratory ocular PD will be assessed by cytokine and other potential molecular biomarker analysis of aqueous and vitreous samples taken at baseline (by vitreous tap) and at vitrectomy. Samples will be shipped for cytokine analysis when available for each dose escalation cohort. Refer to the MOP for instructions.

6.7 Protocol Deviations

Deviations from this protocol, regulatory requirements, and/or GCP must be recorded and reported to the sponsor prior to database lock. If needed, corrective and preventive action should be identified, implemented, and documented within the study records.

6.8 Premature Discontinuation

Patients may discontinue the study if they desire at any time. The primary reason for discontinuation should be recorded in the eCRF. The procedures outlined in the Schedule of Assessments (Table 4-1) for exit/early termination should be completed if possible.

Patients who exit from the study for reasons unrelated to treatment before completing Visit 4, may be replaced.

7 STUDY DRUG

7.1 Description

ONL1204 is provided as a sterile liquid in single-use vials stored at 2 to 8°C (36 to 46°F) and is administered by intravitreal injection.

7.2 Formulation

Study drug is available at concentration of 0.5 mg/mL or 2.0 mg/mL in 4.5% mannitol, 0.4% poloxamer 407 and 10 mM acetate buffer pH 4.5.

7.3 Storage

Upon receipt at the investigative site, ONL1204 vials should be stored at 2 to 8°C (36 to 46°F). All investigational supplies must be stored in a secure area with controlled access. All ONL1204 supplies should be used before the expiry date.

7.4 Packaging and Shipment

ONL Therapeutics will provide the study material to the investigative sites. ONL1204 single-use vials will be packaged and labeled in accordance with all applicable regulations.

7.5 Route, Dose and Administration

ONL1204 is administered via IVT injection, so the drug can be distributed to the retina, ICB, and vitreous.

The following doses will be evaluated: 25 µg, 50 µg, 100 µg and 200 µg. Patients will receive one intravitreal injection of ONL1204 to the one affected eye. The study vial contains either a 0.5 mg/mL or 2 mg/mL concentration of ONL1204 and a volume of 0.05 or 0.1 ml is injected into the eye to deliver the desired dose (as described in MOP).

7.6 Permitted Concomitant Therapy

Standard and necessary concomitant medications (such as drops) are permitted as indicated.

7.7 Prohibited Concomitant Therapy

None.

7.8 Potential for Drug-Drug Interactions

No pharmacokinetic interaction studies for ONL1204 have been conducted.

7.9 Accountability

A drug dispensing log, including records of drug received from the sponsor and drug dispensed to the patients, will be provided and kept at the study sites. The sponsor CRA will reconcile the study drug for that cohort.

Proper drug accountability includes, but is not limited to:

- Monitoring expiration dates if expiry date or retest date is provided to the Investigator.
- Verifying that actual inventory matches documented inventory.
- Verifying that the master drug log is completed for all study medication received at the site and that all required fields are complete, accurate, and legible.
- Review of temperature log, and assure that the study medication is stored under locked, access-controlled conditions.
- Verifying the patient individual drug accountability log is completed for each patient and that all required fields (units dispensed, returned, used, etc.) are complete, accurate, and legible.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately. At the end of the study, the Investigator will retain all the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor.

7.10 Compliance

Study drug will be administered only to eligible patients under the supervision of the principal investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

7.11 Documenting Adverse Events

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation or other diagnostic procedures will be recorded on the appropriate page of the eCRF. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. This includes changes in ocular assessments, such as a decrease in visual acuity or a persistent increase in IOP. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

8 ADVERSE EVENTS

8.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence before administration of any study medication or study procedure in a patient or subject who has signed informed consent to participate in a study; it does not necessarily have to have a causal relationship with study participation.

8.2 Adverse Event Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product or undergoing a study procedure; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product or study procedure whether or not it is related to the medicinal product or study procedure. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug or study procedure.

8.3 Assessment of Intensity

For both serious and non-serious AEs, the investigator must determine both the intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

8.4 Assessment of Causality

Relationship to study drug administration will be determined by the investigator with the following options to choose from: Definitely related – Probably related – Possibly related – Unlikely/Remotely related – Not related – Unknown.

8.5 Clinical Laboratory Changes

Blood samples for clinical laboratory evaluation, and urine for pregnancy test will be obtained as specified in the Schedule of Assessments (Table 4-1). Any clinically significant or concerning laboratory results will be documented as an adverse event.

8.6 Adverse Event Follow-up

All AEs, both non-serious and serious, will be monitored throughout the study until the exit visit, or 30 days after use of the study drug, whichever is longer. Serious AEs will be followed to resolution or stabilization or until 30 days after subject completes the study.

8.7 Serious Adverse Events

8.8 Serious Adverse Event Definition

A SAE is any event that meets any of the following criteria:

- Death
- Life-threatening
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a patient who received ONL1204
- Other: Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or

surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are:

- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in inpatient hospitalization
- Development of drug dependency or drug abuse
- Study specific: No study specific serious adverse events are expected

Definition of Terms

Life-threatening: An AE is life-threatening if the patient was at immediate risk of death from the event as it occurred; i.e., it does not include a reaction that if it had occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug induced hepatitis can be fatal.

Hospitalization: AEs requiring overnight hospitalization should be considered SAEs. Hospitalization for elective surgery or routine clinical procedures that are not the result of AE (e.g., elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'non-serious' according to the usual criteria.

In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.

Disability/incapacitating: An AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the patient's ability to carry out normal life functions.

8.9 Reporting Serious Adverse Events

Regardless of causality, upon signing the ICF, SAEs and serious pretreatment events must be reported by the investigator to the medical monitor and contract research organization (CRO) (contact information provided below), and if required, the investigator’s own Human Research Ethics Committee (HREC). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form will be provided to each clinical study site. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information:

Novotech Pharmacovigilance Department,

Email: safety@novotech-cro.com

8.10 Overdose

Any instance of overdose (suspected or confirmed of ONL1204, including any study dose higher than that which was assigned to the patient) must be reported to the medical monitor and CRO, and if required, the Investigator's own HREC. This must be done within 24 hours and be fully documented as an SAE. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

9 STATISTICS

One database will be created after all patients in all cohorts have either completed the study or prematurely discontinued the study. A detailed statistical analysis plan (SAP) will be approved prior to database lock.

9.1 Statistical Design

9.1.1 Statistical Hypotheses

No hypothesis will be formally tested in this study.

9.1.2 Sample Size

The number of patients to be enrolled has been selected to provide information for this Phase 1 study. No formal sample size calculation is provided given the pilot nature of this study.

9.1.3 Analysis Populations

9.1.3.1 ITT population

All patients will be included in the intent to treat ITT Population.

Safety Population: All patients will be included in the Safety Population. Patient data will be summarized according to the dose they received.

9.1.3.2 Ocular PK Population

The ocular PK Population will comprise all patients in the Safety Population who provide adequate ocular PK samples to calculate the PK parameters. Patients with protocol violations will be assessed on a patient-by-patient basis for inclusion in the ocular PK Population. The PK analysis will be conducted using the ocular PK Population.

For the pharmacokinetic data, per cohort and per protocol analyses will be performed. Each cohort population is defined as all patients within a dose cohort who received their assigned treatment and includes all those with no major protocol deviations. The per protocol population is defined as all patients who received their assigned treatment and includes all those with no major protocol deviations. These populations will be determined well before database lock. If patients withdraw from the study, their plasma concentration data may be included in the pharmacokinetic analysis provided there are no significant protocol noncompliance issues.

9.2 Study Endpoints

9.2.1 Primary Endpoints

The primary endpoints will be the safety profile demonstrated in this study, including:

- Adverse event reporting. AEs will be split into study eye, non-study (fellow) eye, and systemic events
- Clinical evaluations including BCVA
- Clinical laboratory evaluations

9.2.2 Exploratory Endpoints

- Measurement of ONL1204 drug levels in plasma and vitreous for PK analysis
- Cytokine and other potential molecular biomarker measurement in aqueous and vitreous samples, taken by vitreous tap, and at vitrectomy.

9.3 Statistical Methods

A statistical analysis plan will be developed and finalized before database lock and will describe the patient populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary, and exploratory endpoints.

In general, continuous variables will be summarized by descriptive statistics including sample size, mean, standard deviation, median, minimum, and maximum. Geometric

mean and CV% will be presented for PK parameters. Categorical variables will be summarized by frequency and percentage. Data for ONL1204 treated patients will be summarized at each time point by cohort.

9.3.1 Safety Analyses

All safety analyses will be based on the Safety Population. Safety will be assessed through adverse event reporting, clinical evaluations including BCVA, ophthalmic imaging, and clinical laboratory evaluation.

9.3.1.1 Adverse Events

Adverse events will be coded to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ classification. The occurrence of treatment-emergent AEs will be summarized using MedDRA preferred terms, system organ classifications, and severity. TEAEs are defined as adverse events that occurred or worsened following the first administration of study medication. Separate summaries of treatment-emergent SAEs and TEAEs considered related to study treatment and AEs leading to study treatment discontinuation will be generated. All AEs will be listed for individual patients showing both verbatim and preferred terms.

Ocular and systemic AEs will be reported separately. Ocular AEs will be split into study eye and fellow eye events. Events reported in 'both' eyes will be counted in the study and fellow analysis. Separate causality analyses will be performed for the study eye events (related to drug and related to procedure); for fellow eye and systemic events, causality will be assessed based on study drug alone.

9.3.1.2 Clinical Laboratory Results

The clinical laboratory results (continuous parameters) will be presented by summary statistics for each laboratory parameter within the specific test panel. In addition, summaries will include the change from baseline values at each scheduled post-baseline visit. Laboratory values will be compared to normal range of the laboratory and values that fall outside of the normal ranges will be flagged as: H (High) and L (Low) in the data listings.

9.3.1.3 Vital Signs

All vital signs parameters will be summarized using descriptive statistics for each treatment group for all timepoints assessed, including change from baseline for all post-treatment assessments.

9.3.1.4 BCVA

BCVA will be summarized using descriptive statistics for each treatment group for all time points assessed, including change from baseline for all post-treatment assessments. BCVA assessment will be split between the study eye and fellow eye.

9.3.1.5 Ophthalmic Imaging

Ophthalmic imaging will be conducted at the last study visit (exit/early termination), and these results will be measures of interest. Parameters will be summarized using descriptive statistics by treatment group. Ophthalmic Imaging assessments will be split between the study eye and fellow eye.

9.3.1.6 Intraocular Pressure

IOP will be summarized using descriptive statistics for each treatment group for all time points assessed, including change from baseline for all post-treatment assessments. BCVA assessment will be split between the study eye and fellow eye.

9.3.1.7 Systemic PK

The amount of study drug present in the patient plasma will be summarized at each time point. ONL1204 concentrations that are below the quantitation limit (BQL) will be set to 0 if before the first quantifiable concentration and to 0 thereafter for all descriptive analyses of ONL1204. For the calculation of geometric mean and geometric CV%, all BQL values will be set to missing. The number of BQL values at each time point will be summarized through frequency counts and percentages.

9.3.1.8 Other Parameters

Other safety data will be listed by treatment group and may be further evaluated through descriptive summaries. Concomitant medications will be coded using the World Health Organization drug dictionary and summarized by treatment group.

9.3.2 Ocular PK Analyses

Ocular PK will be analyzed per treatment group as well as per protocol across all treatment groups. Concentration data from the bioanalysis of the ocular fluid samples will be reported in summary tables. Pharmacokinetic parameters (e.g., Tmax, Cmax, terminal t1/2, AUC0-last, and AUC0-infinity) may be calculated based on the concentration data from the bioanalysis of the collected samples, if appropriate.

9.3.3 PD Analyses

Pharmacodynamic statistical analyses will be conducted based on the proteomic analysis of cytokine biomarkers in ocular fluids.

Vitreous and aqueous humor sample results and changes from baseline will be summarized by treatment group. Treatment effect will be assessed within and between treatment groups using an appropriate statistical method. The analysis will be based on log-transformed data if required.

Measurements below or above the limits of detection will be censored at the laboratory reported lower or upper limit of detection. Analytes will not be included in the analyses if more than half of the measurements in a treatment group are below the limit of detection.

Further exploratory analyses may be performed to evaluate potential dose-related measures.

9.3.4 Demographic and Baseline Characteristics

Demographic information (age, sex, ethnicity, race) will be summarized by treatment arm based on the ITT population.

9.4 Interim Analysis

There are no plans to conduct an interim analysis for this study.

10 ETHICS AND RESPONSIBILITIES

10.1 Good Clinical Practice

The study will be conducted in accordance with the ICH GCP and the appropriate regulatory requirements. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

10.2 Safety Review Committee

A safety review committee (SRC) comprising of relevant site investigators, the medical monitor, and sponsor representative will oversee safety, sentinel patient clearance, cohort evaluation, and dose escalation for the study. A formal charter will be established to include the rules, meeting frequency, and scope of responsibilities of the SRC for the conduct of the SRC. The respective IRB's will be informed of the outcome of the SRC meetings.

The decision to dose-escalate to the next cohort will include evaluation of potential dose limiting toxicities as detailed in Section 4.2.1 as well as adverse events, clinical laboratory evaluations and ophthalmologic imaging data. Applicable sections of the Common Terminology Criteria for Adverse Events (CTCAE) version 5, 17Nov2017 will be used to grade adverse events.

10.3 Human Research Ethics Committee

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The HREC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where HREC approval has been obtained. The protocol, IB, informed consent form, advertisements (if applicable), written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the HREC by the investigator or the sponsor, as allowed by local regulations.

10.4 Informed Consent

After the study has been fully explained, written informed consent will be obtained from the patient before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH GCP and all applicable regulatory requirements.

10.5 Records Management

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated, web-based electronic data capture (EDC) application. ONL Therapeutics will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

10.6 Source Documentation

The study sites will be provided with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

eCRFs will be completed for each patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF within 5 business days of visit.

10.7 Study Files and Record Retention

The investigator will maintain all study records according to the ICH GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and ONL Therapeutics must be notified.

11 AUDITING AND MONITORING

Monitoring and auditing procedures developed or approved by ONL Therapeutics will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. Study monitors will visit the sites throughout the study to review and confirm that information in the eCRF corresponds with source documents for the patient. They will also assess drug accountability and ensure that the study is being conducted according to pertinent regulatory requirements. The review of all patient data will be performed in a manner that ensures patient confidentiality is maintained.

12 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by ONL Therapeutics. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the HREC is notified within 5 days.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the HREC and the investigator must await approval before implementing the changes. ONL Therapeutics will submit protocol amendments to the appropriate regulatory authorities for approval.

If in the judgment of the HREC, the investigator, and/or ONL Therapeutics, the amendment to the protocol substantially changes the study design and/or increases the

potential risk to the patient and/or has an impact on the patient's involvement as a study participant, the currently approved written informed consent form will require similar modification. In such cases, informed consent will be renewed for patients enrolled in the study before continued participation.

13 STUDY REPORT AND PUBLICATIONS

ONL Therapeutic is responsible for preparing and providing the appropriate regulatory authorities with clinical study reports according to the applicable regulatory requirements.

The publication policy of ONL Therapeutics is discussed in the investigator's Clinical Research Agreement.

14 STUDY DISCONTINUATION

Both ONL Therapeutics and the Principal Investigator reserve the right to terminate the study at the investigator's site at any time. Should this be necessary, ONL Therapeutics or a specified designee will inform the appropriate regulatory authorities of the termination of the study and the reasons for its termination, and the Principal Investigator will inform the HREC of the same. In terminating the study, ONL Therapeutics and the Principal Investigator will assure that adequate consideration is given to the protection of the patients' interests.

15 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from ONL Therapeutics. However, authorized regulatory officials, HREC personnel, ONL Therapeutics, and its authorized representatives are allowed full access to the records.

Identification of patients and Case Report Forms shall be by initials, screening, and treatment numbers only. If required, the patient's full name may be made known to an authorized regulatory agency or other authorized official.

16 APPENDICES

16.1 APPENDIX I – Sponsor Contact Information

Sponsor:	ONL Therapeutics 1600 Huron Pkwy Building 520, Second Floor Ann Arbor, MI 48109
Clinical Research Organizations:	Novotech Level 3, 325 Pyrmont Street Pyrmont, NSW 2009 Australia

16.2 APPENDIX II – Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects,
Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my subject will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the subject's interest when providing medical care which might have the effect of weakening the physical and mental condition of the subject."

Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best-proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research, and for those for whom the research is combined with care.

Research investigators should be aware of the ethical, legal, and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal, or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a subject of the research, even though the subject has given consent.

Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project.

The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the subject's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study, and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of

funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic, or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the subjects who are research subjects.

The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

At the conclusion of the study, every subject entered into the study should be assured of access to the best-proven prophylactic, diagnostic, and therapeutic methods identified by the study.

The physician should fully inform the subject which aspects of the care are related to the research. The refusal of a subject to participate in a study must never interfere with the subject-physician relationship.

In the treatment of a subject, where proven prophylactic, diagnostic, and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the subject, must be free to use unproven or new prophylactic, diagnostic, and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health, or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.